ABSTRACT

Title of Dissertation: NECK CIRCUMFERENCE AS A NEW ANTHROPOMETRIC INDICATOR FOR PREDICTION OF CARDIOMETABOLIC RISKS IN SAUDI POPULATION

Reem Sulaiman Albassam, Doctor of Philosophy, 2016

Dissertation directed By: Professor David K.Y. Lei
Department of Nutrition & Food Sciences

Background: Recent studies have associated neck circumference (NC) with metabolic and cardiovascular disease risk factors. No studies designed to examine NC as a measure of cardiometabolic risks have been performed in Saudi Arabia (KSA).

Objective: This study aimed to analyze the association between NC and several cardiometabolic risk factors, and to determine the cut-off point value of NC for predicting women at increased risk of metabolic syndrome (MetS).

Methods: This cross-sectional study comprised of 700 participants (623 women and 77 men aged 18–70). Study performed in Riyadh city, KSA. International Diabetes Federation (IDF) guidelines were used to diagnose MetS among the subjects. The main indicators studied were NC, waist circumference (WC), body mass index (BMI), body fat %, blood pressure, plasma glucose, total cholesterol, lipoproteins, triglycerides, and homeostasis model assessment-estimated insulin resistance (HOMA-IR) levels.

Covariance, and logistic regression analyses were used to evaluate the association of NC to cardiometabolic risk factors separately by genders. Receivers operating characteristic (ROC) curves analyses were used to determine the optimal cutoffs.

Results: NC is associated with BMI and WC in men and women. In women, it is associated with cardiometabolic risk factors beyond other anthropometric indices. NC is independently associated with all cardiometabolic risk factors except LDL ($P < 0.001$). Fully adjusted OR (95% CI) values for incremental increases in NC for women were 1.70 (1.48–2.94) for raised fasting glucose; 1.29 (1.15–1.45) for raised blood pressure; 1.25 (1.13–1.38) for high triglycerides; 1.20 (1.02–1.40) for insulin resistance; and 1.14 (1.02–1.40) for low HDLc. Women in the largest NC quartile were 13 times more likely [OR (95% CI): 13.39 (6.35 - 28.23)] to have MetS compared to the lowest NC quartile after adjustments for possible confounders (all $P < 0.01$). Finally, our results indicated that the appropriate NC to predict three or more metabolic risk factors in Saudi women is 35.5 cm. This cutoff value was associated with a much greater risk of MetS in participants with both high and normal BMI and WC values.

Conclusion: NC is significantly and independently associated with cardiometabolic risk factors in adult Saudi women.

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By

Reem Sulaiman Albassam

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Advisory Committee:
Professor David Lei, Chair
Assistant Professor Hee-Jung Song
Associate Professor Hong Jiao
Assistant Professor Shaik Rahaman
Professor Jiuzhou Song

Dedication

This dissertation is dedicated to my husband, Waleed Alshubaili, who has given me more love, support, and guidance than anyone could ever ask for.

Waleed, your words and encouragement always put things in perspective and give me motivation to continue moving forward, even during frustrating times. I could not have done it without you.

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Table of Contents

List of Tables

List of Figures

List of Abbreviations

ADA	American Dietetic Association
AHA	American Heart Association
BMI	The body mass index
BIA	Bioelectrical impedance analysis
CAD	Coronary artery disease
CCR	Creatinine clearance rate
CHD	Coronary heart disease
CI	Confidence interval
CT	Computed Tomography
CVDs	Cardiovascular diseases
DEXA	Dual-energy X-ray absorptiometry
DM	Diabetes mellitus
eGFRCG	Estimated according to the Cockcroft-Gault formula
FDA	Food and Drug Administration
FFA	Free fatty acid
g/dL	Grams per Deciliter
HDL	High density lipoprotein
hsCRP	High-sensitivity C-reactive protein
HOMA-IR	Homeostasis model assessment-estimated insulin resistance
Ibs	Pounds
IDF	International Diabetic Federation

IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
in^2	Square Inch
IAS	International Atherosclerosis Society
IOTF	International Obesity Task Force
IASO	International Association for the Study of Obesity
kg	Kilogram
KKUH	King Khalid university hospital
KSA	Kingdom of Saudi Arabia
LDL	Low density lipoprotein
M^2	Square meter
MetS	Metabolic syndrome
Mg	Milligram
mmol/L	Millimole per Liter
MRI	Magnetic resonance imaging
NC	Neck circumference
NCEP ATPIII	National Cholesterol Education Program-Third Adult Treatment Panel
NHLBI	National Institution of Health, National Heart, Lung and Blood Institute
OSAS	Obstructive sleep apnea syndrome
PAI-1	Plasminogen Activator Inhibitor
PCOS	Polycystic Ovarian Syndrome

RDHS	RENO Diet-Heart Study
ROC	Receiver operating characteristic
RR	Relative risk
SAT	Subcutaneous adipose tissue
SD	Standard Deviations
SF	Subcutaneous fat
SPSS	Statistical Package for Social Sciences
T2DM	Type 2 diabetes mellitus.
TG	Triglyceride
HTN	Hypertension
TOBEC	Total body electrical conductivity
TOPS	Take Off Pounds Sensibly
VAT	Visceral adipose tissue
VF	Visceral fat
WC	Waist circumference
WHF	World Heart Federation
WHO	World Health Organization
WHR	Waist Hip Ratio
Wt	Weight

Chapter 1: Introduction

The Kingdom of Saudi Arabia has undergone a remarkable and rapid economic development over the past two decades (1, 2). The discovery of oil in huge quantities generated sudden wealth, and the average family income increased sharply. The increase in income was found to be accompanied by a rise in cardiometabolic diseases, which were previously reported to be associated with the more economically developed countries. Of these, overweight and obesity are the most prominent and influential due to increased risk of morbidity and mortality. Obesity accounts for over 600 million deaths every year (3). The prevalence of overweight and obesity is rising to epidemic proportions at an alarming rate in both developed "Westernized" and developing countries around the world (4, 5, 6). Obesity will probably trade cigarette smoking as the main killer of Americans in the next century (7). The prevalence of obesity has increased by about 10-40% in the majority of European countries in the last ten years (8). Over the same period, the prevalence of obesity in the Gulf region found to be among the highest in the world (9). The prevalence of overweight and obesity among Saudi nation found to be around 55% (10). Obesity-related diseases include type 2 diabetes, heart disease, stroke, and certain types of cancer, some of the leading causes of preventable death.

Obesity epidemiology is the impetus for proper obesity care and appropriate allocation of resources for its control (11). Considering the great economic and human costs associated with obesity, prevention of this disease is an urgent need. Management of obesity is identical with prevention of cardiometabolic disease, and must be a priority. For intervention, prevention is vital to protect the long-term health of patients (12). There

are several methods of assessing overweight and obesity, such as bioelectrical impedance, dual-energy x-ray absorptiometry, and total body water, which are used for measuring body fat (13). Some methods are more applicable to primary clinics, such as height, weight, waist and hip circumferences are used for measuring body mass index (BMI), and waist/hip ratio (WHR). The most widely used assessment is the BMI. The BMI is a mathematical calculation used for determining the whole body adiposity, and is calculated by dividing a person's body weight in kilograms by the square of height in meters (14). BMI is not a sensitive indicator of either the amount or the distribution of body fat (15). Body fat distribution is verified through numerous methods, as waist circumference (WC), waist/hip ratio (WHR), and neck circumference (NC). WC is corresponded to abdominal visceral fat (VF), which is shown to have a major role in cardiometabolic risk (16, 17). On the other hand, upper body subcutaneous fat (SF) relates to cardiometabolic risk as much as abdominal VF (18). Besides, the free fatty acid release from upper body subcutaneous fat was found to be larger than that from lower body subcutaneous fat (19), a further fact that strengthens the significance of measuring upper-body subcutaneous adipose tissue depots. The neck circumference is an index of upper body SF that correlates with whole body adiposity (BMI) (20), abdominal adiposity (WC and waist-to-hip ratio) (21), abdominal VF (18) and components of the metabolic syndrome (MetS), such as systolic and diastolic blood pressures, triglycerides, total cholesterol, fasting glucose and insulin resistance (IR) (22, 23, 24). Despite the popular use of the WC in the evaluation of cardiometabolic risk, it has some limitations (25). Whereas, different clinical studies have been using different anatomical sites in measuring WC. However, specific site used to measure the WC influences the absolute

WC value that is obtained (26). In addition, WC is subject to variations during the day and under health conditions (e.g. severe obesity, lipoabdominoplasty, Ascites). Finally, it might not be practical for large population studies or primary care clinics, especially in cold weather and heavy clothing. Measuring the neck circumference is easier than measuring the WC, which reveals a large variability in its procedure. Furthermore, the neck circumference measurements can be useful in clinical screenings for persons with an increased risk of cardiometabolic diseases (27).

This is the first study that aids in establishment of neck circumference measurement as an accurate assessment tool for overweight and obesity for Saudi population. The main goals are to examine whether neck circumference can be used to identify overweight, obesity and to test its application in predicting the cardiometabolic risk factors in Saudi adult population in the city of Riyadh. The data generated will provide standardized assessment tools to determine accurate prevalence, treatment protocols, and achieve control of obesity among Saudi population. Moreover, findings will contribute in preventing the epidemic of obesity and its complications in Saudi Arabia and the entire Arabian Gulf.

Objectives

1) To evaluate the ability of neck circumference in diagnosing overweight and obesity in study subjects or (adults).

2) To specify the cardiometabolic risk factors that correlate with neck circumference; and examine whether neck circumference is associated with these cardiometabolic risk factors independently.

3) To determine the optimal cutoff point value of neck circumference for predicting women at increased risk of metabolic syndrome.

Research Questions

Question 1: What is the association between overall obesity (as measured by BMI) and upper-body adiposity (as measured by nick circumference or by waist circumference) in Saudi adult?

Question 2: What is the ability of neck circumference in predicting overweight and obesity in patients?

Question 3: What are the cardiometabolic risk factors (central obesity, hypertriglyceridemia, reduced high density lipoprotein cholesterol (HDLc), elevated low density lipoprotein cholesterol (LDLc), hyperglycemia, hypertension, and insulin resistance (IR)) that correlate most closely with elevated neck circumference?

Question 4: What are the cardiometabolic risk factors central obesity, hypertriglyceridemia, reduced HDLc, elevated LDLc, hyperglycemia, hypertension and metabolic syndrome, and IR) that correlate most closely with elevated WC?

Question 5: Is neck circumference associated with these cardiometabolic risk factors independently?

Question 6: What are the odds ratios for the development of the cardiometabolic risk factors (central obesity, hypertriglyceridemia, low HDLc, IR, hyperglycemia, hypertension and metabolic syndrome) in subjects with elevated neck circumference?

Question 7: What are the optimal gender specific BMI cutoff values for the diagnosis of adiposity in Saudi adults that predict increased risk of the cardiometabolic risk factors?

Question 8: What are the optimal gender specific WC cutoff values for the diagnosis of adiposity in Saudi adults that predict increased risk of the cardiometabolic risk factors?

Question 9: What are the optimal gender specific neck circumference cutoff values for the diagnosis of adiposity in Saudi adults that predict increased risk of the cardiometabolic risk factors?

Question 10: What is the prevalence of Saudi adults at risk of cardiometabolic factors using BMI ($\geq$30kg/m^2), WC (male > 94cm, and female > 80cm), and neck circumference determined in question 9?

Question 11: Is there a synergistic effect for the joint levels of neck circumference and BMI or WC on the metabolic syndrome?

Literature Review

Cardiometabolic risks or diseases

Obesity

Obesity is defined medically as a state of increased adipose tissue of sufficient magnitude to produce adverse health consequences and is associated with increased morbidity and mortality (28, 29). The main risk factors that lead to obesity, poor nutrition and inactivity combined, are the second leading cause of preventable death after tobacco. The morbidity and mortality risk from being overweight is proportional to its degree. Obesity is associated with significant increases in risk for Type2 diabetes mellitus, hyperlipidemia, high cholesterol, coronary artery disease, gallbladder disease, osteoarthritis, and degenerative joint disease. Colon, rectum and prostate cancer are more prevalent in obese men. Whereas, in women, uterus, biliary tract, breast and ovary cancer are highly prevalent (30).

Obesity is a disease that affects nearly one-third of the American adult population (34.9% or approximately 79 million). The number of overweight and obese Americans has continued to increase since 1960, a trend that is not slowing down. Today, 78.6 percent of adult Americans are categorized as being overweight or obese. Each year, obesity causes at least 300,000 excess deaths in the U.S., and healthcare costs of American adults with obesity amount to approximately $147 billion (American Obesity Association, 2015) (31).

Hypertension (HTN)

Hypertension is a medical condition in which the blood pressure is chronically elevated. Blood pressure is the force of blood pressing against the walls of the arteries. High blood pressure raises the heart's workload and can cause serious damage to the arteries. Persistent hypertension is one of the risk factors for strokes, heart attacks, heart failure and can cause chronic renal failure. Hypertension is classified as essential (primary) or secondary. In essential hypertension, no specific medical cause can explain a patient's condition. It may be due to family history or lifestyle. Most people with elevated blood pressure have essential hypertension. Secondary hypertension, on the other hand, is less common and is the result of using certain medicines or presence of another condition, such as kidney disease or adrenal gland tumor (32, 33). Elevated blood pressure is associated with obesity and glucose intolerance and insulin resistance. The strength of this relation varies in different populations (34, 35). Globally, high blood pressure is estimated to cause 7.5 million deaths, about 12.8% of the total of all deaths (36).

Diabetes mellitus (DM)

Diabetes mellitus is a metabolic disorder of impaired carbohydrate, fat, and protein metabolism either by lack of insulin secretion (Type1 diabetes) or by decrease in sensitivity of tissues to insulin (Type2 diabetes), or both (37). Diabetes mellitus characterized by hyperglycemia. Hyperglycemia is defined as impaired fasting glucose IFG (as defined by the American Diabetes Association), impaired glucose tolerance IGT or diabetes (38).

Diabetes was estimated to affect 415 million adults (20–79 years of age) worldwide in 2015. According to International Diabetes Federation (IDF), the number of people with diabetes in the world will reach 642 million by 2040 (39). More than 90% of diabetes cases are Type2 diabetes, a progressive disease that leads to dysfunction and failure of various organs and the emergence of retinopathy, neuropathy, and nephropathy (40). Type 2 diabetes increases the risk of heart disease, stroke, and all-cause mortality by 1.4–4.5 times (41, 42).

Dyslipidemia

The dyslipidemia is a condition marked by abnormality in lipid or lipoprotein concentrations in the blood. A typical feature of obesity, insulin resistance, Type2 diabetes, and metabolic syndrome, atherogenic dyslipidemia has emerged as an important risk factor for cardiovascular disease (CVD) and stroke. It characterized by increased total cholesterol, low-density lipoprotein (LDL) cholesterol, apolipoprotein B, and triglyceride, and decrease high-density lipoprotein (HDL) cholesterol concentration in the blood. The lipid abnormalities are due to the interaction of genetic factors with environmental influences including diet, physical activity and stress (43, 44, 45). Dyslipidemia in obesity or metabolic syndrome are related to insulin resistance and some mediators like hepatic lipase, lipoprotein lipase and cholesterol ester transfer protein (46, 47).

Insulin resistance (IR)

Insulin resistance is the condition in which liver, skeletal muscle and adipose tissue cells become less sensitive and eventually resistant to insulin. Insulin resistance in fat cells results in suppressing lipogenesis while promotes lipolysis of stored triglycerides and hence increases of free fatty acids in the blood. In muscle, insulin resistance reduces whole body glucose uptake by 60-70% whereas in liver it reduces glucose storage, both would cause an increase in blood glucose (48, 49). Insulin resistance is present in most obese people. The insulin resistance seen in obesity is believed to involve primarily muscle and liver. Several studies have shown that upper body adiposity is strongly associated with insulin resistance. Excess upper body fat can be accumulated as subcutaneous (truncal) or intraperitoneal (visceral) fat. Results from numerous studies suggest that excess visceral fat is more strongly correlated with insulin resistance than any other adipose tissue compartment (50, 51); other researchers claim that excess subcutaneous upper body fat has a significant association with insulin resistance (52, 53). In general, the pattern of upper body adiposity correlates more strongly with insulin resistance and lipid abnormality than lower body obesity. Elevated circulating free fatty acids are key factor that links upper body adiposity and insulin resistance (54, 55).

The insulin resistance syndrome, which is synonymous to metabolic syndrome, defines the cluster of abnormalities that occur more frequently in insulin resistant individuals. These include glucose intolerance, dyslipidemia, endothelial dysfunction and elevated procoagulant factors, elevated inflammatory markers, abnormal uric acid metabolism, sleep-disordered breathing and increased ovarian testosterone secretion (56). Clinical syndromes associated with insulin resistance include type 2 diabetes,

essential hypertension, cardiovascular disease, non-alcoholic fatty liver disease, polycystic ovary syndrome, and certain forms of cancer and sleep apnea (49, 56).

Ultimately, raised level of circulating free fatty acids is a chief factor that links obesity, dyslipidemia and insulin resistance (58, 59). The enlarging adipose tissue discharges high levels of FFA into the portal and systemic circulation (55, 60); this will result in accumulation of lipid in areas other than adipose tissue and the ectopic fat storage syndrome could occur. In muscles and liver, increased FFAs will promote insulin resistance (61, 62) and dyslipidemia (63). These FFAs decrease insulin sensitivity in muscle by inhibiting insulin signaling, glucose phosphorylation, glycogen synthase and pyruvate dehydrogenase (64, 58). Whereas, increases in free fatty acid flux to the liver will increase hepatic triglyceride synthesis. As a result of hypertriglyceridemia, a decrease in the cholesterol content of HDLc results from decreases in the cholesteryl ester content of the lipoprotein core (65). In addition, LDL composition will be altered to a small dense LDL resulting in increase of very low lipoproteins (VLDL) (66). This change in LDL composition is attributable to relative depletion of unesterified and esterified cholesterol, and phospholipids, with either no change or an increase in LDL triglycerides (67).

Metabolic syndrome (MetS)

The IDF considers the obesity epidemic to be one of the main drivers of the high prevalence of the MetS (45). Metabolic syndrome (MetS) is the name for a group of risk factors that increases the development of cardiovascular disease and Type2 diabetes mellitus (38). The metabolic risk factors including central obesity, atherogenic dyslipidemia, elevated plasma glucose, elevated blood pressure, prothrombotic and a proinflammatory state. In the effort of finding diagnostic tool for the metabolic syndrome (MetS) in clinical practice, several different sets of criteria have been recommended by different organizations for identifying patients with MetS. The more accepted of these definitions has been proposed by World Health Organization (WHO), the European Group for the Study of Insulin Resistance (EGIR), the American Association of Clinical Endocrinologists (AACE), the National Cholesterol Education Program- Adult Treatment Panel III (NECP ATP III), and International Diabetes Federation (IDF) (45, 68).

The World Health Organization (WHO) definition considers insulin resistance as the major causal risk factor and requires its indicators [impaired glucose tolerance (IGT), impaired fasting glucose (IFG), type 2 diabetes mellitus, or impaired disposal of glucose under hyperinsulinemic, euglycemic conditions] for diagnosis. The presence of one of the several markers of insulin resistance and at least two of the following risk factors; obesity, hypertension, high triglycerides, reduced HDL cholesterol and microalbuminuria constitutes a diagnosis of metabolic syndrome. Patients with type 2 diabetes mellitus are at higher risk for cardiovascular disease (46). Therefore, the WHO group indicates the

term metabolic syndrome to be used in patients with Type2 diabetes who met the requirements for this syndrome (69).

In 1999 the European Group for the Study of Insulin Resistance (EGIR) defined the syndrome in non-diabetic individuals who have hyperinsulinemia. They proposed to use fasting insulin levels to estimate insulin resistance, whereas plasma insulin levels in the upper quartile of the population will define insulin resistance. By their criteria, elevated fasting plasma insulin plus 2 other factors including abdominal obesity, hypertension, increased triglycerides, decreased HDL cholesterol and increased fasting plasma glucose will define metabolic syndrome. And if subjects were receiving treatment for hypertension or dyslipidemia they were considered to have the risk factor (70).

The other important criteria came from the National Cholesterol Education Program (NCEP), Adult Treatment Panel III (ATP III) in 2001. These criteria do not include any measure of insulin resistance, which makes them more practical to use in epidemiological studies and clinical practice. In addition, these criteria do not emphasize a single cause and include waist circumference as the measure of obesity. The definition is based on the WHO criteria and requires the presence of at least three of five components including elevated triglycerides, reduced HDL cholesterol, hypertension, elevated fasting glucose and central obesity (71). Few years later, in 2005, the ATP III stated some modifications in metabolic syndrome definition including using lower waist circumference, including the medication use for high triglycerides, low HDLc and high blood pressure as the risk factor for these conditions even when their values are normal, and reducing the blood glucose thresholds for hyperglycemia from 110 mg/dL to 100 mg/dL (72).

In 2003, the American Association of Clinical Endocrinologists (AACE) announced a position statement on *insulin resistance syndrome.* Major factors for identifying the insulin resistance syndrome are raised blood pressure, raised triglycerides, reduced HDLc cholesterol, raised fasting and post load glucose, and obesity. The diagnosis for the insulin resistance syndrome is based on clinical judgment. The AACE statement does not provide a specific number of factors for definition of this syndrome. Other factors used to decide the clinical judgment are: family history of CVD or type 2 diabetes mellitus, polycystic ovary syndrome and hyperuricemia. By this definition the term "insulin resistance syndrome" can be applied after the person is diagnosed with Type 2 diabetes (68).

In 2005, the International Diabetes Federation (IDF) proposed new criteria that modify ATP III definition. This definition requires the presence of abdominal obesity for diagnosis of syndrome. The justification for this requirement is that abdominal obesity is highly correlated with insulin resistance and other components of the syndrome. And it is a simple diagnostic tool to be use in clinical practice and research worldwide (67).

Recently (2009), IDF and AHA/NHLBI representatives held discussions to attempt to resolve the remaining variations between definitions of metabolic syndrome. The establishment of a set of criteria, to be used worldwide is crucial, with agreed-upon cut points for different ethnic groups and sexes. This is crucial for international comparisons and to facilitate the etiology worldwide. Both sides agreed that abdominal obesity should not be a prerequisite for metabolic syndrome diagnosis. Instead abdominal obesity will be 1 of 5 criteria. Hence, the presence of any 3 of 5 risk factors constitutes a diagnosis of metabolic syndrome. All definitions agree on the key elements of the MetS

including obesity, insulin resistance, hypertension and dyslipidemia. However they provide different criteria and cut points to define this condition. The different criteria proposed for clinical diagnosis of metabolic syndrome are summarized in Table 1.

IDF and AHA/NHLBI representatives believe that defining thresholds for abdominal obesity is complicated, in part as a result of differences in the relation of abdominal obesity to other metabolic risk factors in different ethnic groups. Moreover, predictive values for different levels of abdominal obesity for cardiovascular disease and diabetes could differ. Consequently, they demanded long-term prospective studies to reach more reliable waist circumference cut points for different ethnic groups, particularly for women (73). Table 2 lists current international recommendations projected by the IDF for thresholds of abdominal obesity to be used as 1 component of the metabolic syndrome.

Table 1. Criteria for clinical diagnosis of metabolic syndrome

	WHO (1999) [74]	EGIR (1999) [75]	NCEP ATP III (2001) [71]	AACE (2003) [68]	IDF (2005) [67]	NCEP ATP III (2005) [72]	Harmonizing[73] (2009)**
MetS definition	GT, IFG, T2DM and/or insulin resistance Plus 2 or more of the following	Fasting plasma insulin > 75 percentile for non-diabetic individuals Plus 2 or more of the following	Three or more following	IGT or IFG Plus any of the following based on clinical judgment	Central obesity defined as WC with ethnic specific cutoffs plus 2 or more of the following	Three or more following	Three or more following
Central obesity	Men: WHR>0.90 Women: WHR>0.85 And/or BMI>30kg/m2	Men: WC ≥94 cm Women: WC ≥80 cm	Men: WC ≥102 cm Women: WC ≥88 cm	BMI ≥25 kg/m2	Defined as WC with ethnic specific cutoffs	Men: WC ≥90 cm Women: WC ≥80 cm	Defined as WC with ethnic specific cutoffs
Triglycerides	TG ≥150 mg/dL (1.7 mmol/L)	TG >180 mg/dL and/or medication use for dyslipidemia	TG ≥150 mg/dL (1.7 mmol/L)	TG ≥150 mg/dL (1.7 mmol/L)	TG ≥150 mg/dL (1.7 mmol/L) or specific treatment for dyslipidemia	TG ≥150 mg/dL (1.7 mmol/L) or medication use for dyslipidemia	TG ≥150 mg/dL (1.7 mmol/L) or specific treatment for dyslipidemia
HDLc	Men: <35 mg/dL (<0.9 mmol/L) Women: <39 mg/dl (<1.0mmol/L)	HDLc <39 mg/dL (<1.0mmol/L) and/or medication use for dyslipidemia	Men: <40 mg/dL (<1.03 mmol/L) Women: <50 mg/dl (<1.29 mmol/L)	Men: <40 mg/dL (<1.03 mmol/L) Women: <50 mg/dl (<1.29 mmol/L)	Men: <40 mg/dL Women: <50 mg/dl (<1.29 mmol/L) or specific treatment for dyslipidemia	Men: <40 mg/dL (<1.03 mmol/L) Women: <50 mg/dl (<1.29 mmol/L) or medication use for dyslipidemia	Men: <40 mg/dL Women: <50 mg/dl (<1.29 mmol/L) or specific treatment for dyslipidemia
Fasting glucose	IFG, IGT*, or T2DM	≥ 110 mg/dL(≥6.1 mmol/L)	≥ 110 mg/dL(≥6.1 mmol/L)	IGT or IFG (Not diabetes)	≥ 100 mg/dL or previously diagnosed with T2DM	≥ 100 mg/dL (≥5.6 mmol/L)	≥ 100 mg/dL (≥5.6 mmol/L)
Blood pressure	≥ 140/90 mmHg	≥ 140/90 mmHg or treatment for hypertension	≥ 130/85 mmHg	≥ 130/85 mmHg	≥ 130/85 mmHg or treatment for hypertension	≥ 130/85 mmHg or treatment for hypertension	≥ 130/85 mmHg or treatment for hypertension
Other	Microalbuminuria (urinary albumin excretion rate ≥ 20mg/min or albumin:creatinin e ratio ≥ 30 mg/g)			Family history of CVD or T2DM, poly cystic Ovary syndrome and hyperuricemia			

BMI, body mass index; CVD, cardiovascular disease; HDLc, high density lipoprotein cholesterol; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; T2DM, type 2 diabetes mellitus; WHR, waist to hip ratio; WC, waist circumference.

* IFG: fasting plasma glucose >=6.1 mmol/L (110 mg/dL) and <7 mmol/L (126 mg/dL) per WHO 1999 criteria. (ADA has chosen a lower cutoff of 5.6mmol/L or 100mg/dL); IGT: fasting plasma glucose (if available) <7.0 mmol/L (126 mg/dL) AND 2 hour post 75g glucose drink of >= 7.8 mmol/L (140 mg/dL) and <11.1 mmol/L (200 mg/dL).

** The Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity.

Table 2. Current recommended waist circumference thresholds for abdominal obesity by organizations

Population	Organization	Recommended Waist Circumference Threshold for Abdominal Obesity	
		Men	Women
Europoid	IDF [72]	≥94cm	≥ 80 cm
Caucasian	WHO [14]	≥ 94 cm (increased risk) ≥ 102 cm (still higher risk)	≥ 80 cm (increased risk) ≥ 88 cm (still higher risk)
United States	AHA/NHLBI (ATPIII)* [76]	≥102 cm	≥ 88 cm
Canada	Health Canada [77, 78]	≥102 cm	≥ 88 cm
European	European Cardiovascular Societies [79]	≥102 cm	≥ 88 cm
Asian (including Japanese)	IDF [72]	≥ 90 cm	≥ 80 cm
Asian	WHO [80]	≥ 90 cm	≥ 80 cm
Japanese	Japanese Obesity Society [81]	≥ 85 cm	≥ 90 cm
China	Cooperative Task Force [82]	≥ 85 cm	≥ 80 cm
Middle East Mediterranean	IDF [72]	≥ 94 cm	≥ 80 cm
Sub-Saharan African	IDF [72]	≥ 94 cm	≥ 80 cm
Ethnic Central and South American	IDF [72]	≥ 94 cm	≥ 80 cm

*Recent AHA/NHLBI guidelines for metabolic syndrome recognize an increased risk for CVD and diabetes at waist-circumference thresholds of ≥94 cm in men and ≥80 cm in women and identify these as optional cut points for individuals or populations with increased insulin resistance.

The pathogenesis of metabolic syndrome and its components is multifarious and remains to challenge the professionals. The underlying risk factors for developing metabolic syndrome appear to be changeable such as, abdominal obesity (57, 83) physical inactivity (83, 84) and insulin resistance (85). Other related risk factors are genetic profile (72, 86), aging (87), and hormonal imbalance (88).

Obesity and related cardiometabolic diseases in Saudi Arabia

The Kingdom of Saudi Arabia (KSA) has witnessed a significant lifestyle shift over the last 60 years. The rapid modernization with the invasion of new lifestyle habits has resulted in rapid and progressive increase in the prevalence of obesity. KSA is ranked among the top 10 countries with regard to the prevalence of obesity (89). The IDF believes the obesity epidemic to be one of the key drivers of the high prevalence of the MetS. Obesity contributes to hypertension, hyperglycemia, high serum TGs, low HDL cholesterol and insulin resistance, and is associated with higher CVD risk (45).

Overweight and obesity are emerging as major public health concerns in Saudi Arabia. The Saudi population seems to be the next victim of obesity since it has reached alarming level. The prevalence of obesity in Saudi Arabia has been reported to be about 14% in children up to 83% in adult. This wide variation due to the differences in criteria used to define obesity and due to the differences in age, sex, and health status of subjects in each study (90). According to recent national prevalence data of Saudis aged 15 years or older, around two thirds of adult women are either overweight (28.0%) or obese (33.5%). In contrast, 33.4% of the men are overweight and 24.1% are obese (10).

Diabetes mellitus (DM) is highly prevalent in Saudi adults. In 2004, 23.7% of Saudi adult were found to be diabetic according to a national representative data (91). In 2013, Saudi Arabia has the 7th highest national diabetes prevalence (20.2%) world-wide (92). From recent data, in a nationally representative sample of more than 10 million Saudis aged 15 years or older, the prevalence of diabetes has been found to be 13.4 %. Interestingly, large percentage (43.6 %) of diabetic individuals were undiagnosed (93)

Hypertension (HTN) and borderline hypertension were highly prevalent in Saudi Arabia. 15% Saudis aged 15 years or older had hypertension and 40.6%, or 5,222,051, had borderline hypertension. Besides, the data revealed high rates of undiagnosed hypertension (57.8%) (94).

Cardiovascular diseases (CVDs) were the major cause of death (27%) for Saudi nation in 2002 (95). Recent data revealed that, among Saudis aged 15 years or older, 5.4% reported that they were previously diagnosed with hypercholesterolemia. And 8.5% had hypercholesterolemia as measured by research's laboratory tests with blood cholesterol level greater or equal to 6.2 mmol/L. However, 65.1% were undiagnosed or unaware of their condition. 19.6% of Saudis had borderline hypercholesterolemia with measured blood cholesterol levels between 5.18 and 6.2 mmol/L (96).

Metabolic syndrome (MetS) according to the National Cholesterol Education Program-Third Adult Treatment Panel (NCEP ATP III) was 35.3% (CI 33.5–37.01). Low HDL cholesterol was the most common MetS component with almost 9 out of 10 (88.6%) of subjects affected followed by hypertriglyceridemia with a prevalence of 34%. MetS prevalence increased with age, whereas individuals aged 50–55 years had MetS in almost 6 out of 10 adults. (97). Another recent data used International Diabetes Federation (IDF) definition, reported MetS prevalence as 28.3% (98).

High Prevalence of undiagnosed diseases is shocking in a country with free medical care and high resources. Indeed, these data call for action to control the burden of cardiometabolic diseases in the kingdom. A national plan to increase awareness, early detection, and control of cardiometabolic diseases is urgently needed (89).

Obesity Assessment tools

Obesity is mainly diagnosed through calculating body mass index and sometimes through measuring body fat distribution; skinfolds, waist to hip circumference ratio, and waist circumference. Many studies have demonstrated that Neck circumference (NC) is a good predictor for obesity and cardiovascular disease in adults (20, 99, 100, 22). Other techniques, such as bioelectrical impedance, dual-energy x-ray absorptiometry, and total body water, can also be used for measuring body fat (13, 101).

Body mass index (BMI)

BMI is usually considered a surrogate marker of excess adiposity in terms of overweight and obesity (102, 103). The body mass index is a mathematical calculation used for determining whether a patient is overweight or obese, and is calculated by dividing a person's body weight in kilograms by the square of height in meter or by using the conversion with pounds (lbs) and inches (in) squared as shown below. Overweight is defined as a body mass index (BMI) between 25 and 29.9 kg/m^2. Obesity is defined as a BMI of 30 kg/m^2 or higher (14) as in Table 3.

BMI = weight (kg) ÷ Height (M^2) or

BMI = Weight (Ibs) ÷ Height (in^2) X 704.5

Table 3. Classification of BMI according to the WHO study group (2000)

Obesity classifications	BMI (kg/m^2)
Under weight	<18.5
Normal weight	18.5 – 24.9
Over weight	25 – 29.9
Obese class I	30 – 34.9
Obese class II	35 – 39.9
Obese class III	> 40

This equation is fairly accurate for all individuals. However, BMI has some limitations as a measure of total body fat since its formula depends only upon weight and height, and it does not depict the true body composition. BMI may overestimates body fat in lean persons who are very muscular, in contrary under-estimates body fat in persons who have less muscle mass (15). BMI has been shown to be associated with cardiovascular diseases, diabetes and hypertension in Caucasians (104, 105, 106). Nevertheless, Caucasian people in the USA generally have a lower percentage of body fat for the same BMI than those in Europe (107). Also, Asians generally have a higher percentage of body fat than Caucasian people of the same age, sex, and BMI. Therefore, if the US prediction formula (108) is applied to these populations, the percentage of body fat is underestimated (109). In the same vein, a recent study in Saudi Arabia illustrated a significant limitation in using BMI alone to diagnosing obesity and its relative metabolic risk factors in the Saudi population. This study found an increased risk of hypertension and diabetes relative to BMI, starting at a BMI as low as 21 kg/m^2, but overall there is no cutoff BMI level with high predictive value for the development of these chronic diseases, including the WHO definition of obesity at BMI of 30 kg/m^2. The optimal BMI

cut-off points for overweight ranged from 28.50 to 29.50 for males and from 30.50 to 31.50 for females depending on the risk factor being studied. These values are higher in general but, much higher in females than, BMI ≥25kg/m^2, the values suggested by WHO (table 3). The authors stated several reasons for the failing of BMI as a tool to classify obesity; BMI does not reflect fatness uniformly in different populations and ethnic groups (110, 111, 112, 113) and Saudi women have short stature with a mean height of 1.54 m which could be the second reason for limiting the usefulness of BMI in this population (113).

Waist-to-hip ratio (WHR)

Historically, the waist-to-hip ratio is the most studied and well-established measurement of fat distribution (114). The cardiometabolic risks related to an increase in body weight and obesity are not limited to just increases in body fat mass but are also associated with body fat distribution. A specific area of interest is the upper-body fat mass relative to lower-body fat mass. This is generally assessed by a comparison of waist and hip circumference measurements and is expressed as the waist-to-hip ratio (WHR). Health risk increases with increase in upper-body fat (13). Waist-to-hip ratio (WHR) showed relatively strong correlations with total cholesterol, LDL-cholesterol and triacylglyceride concentration in both men and women (115). Bouchard (1991)(116) categorized obesity into four-types:

Type 1 is characterized by a uniform body fat distribution; adipose tissue is not highly localized in any given region of the body.

Type 2 or android obesity is expressed as high accumulation of body fat in the trunk, primarily in the subcutaneous tissue regions.

Type 3 represents individuals with excessive body fat in the abdominal viscera.

Type 4 or gynoid shows localization of stores in the gluteofemoral region.

Including the four categories, Types 2 and 4 represent the two most well known expressions of obesity. Type 2 or android obesity is often designated as the "apple", due to the excess accumulation of adipose tissue in the upper body (trunk/ abdomen), giving the subject rounded appearance much like an apple. In contrast, type 4 or gynoid is known as the "pear", with regional fat distribution on the lower body (hips, pelvis and lower extremities). WHR higher than 0.8 for women and 0.95 for men is defined as android obesity (117, 118, 119). Android obesity has been shown to be significant predictors of coronary heart disease (CHD) (120). In addition, Rebuffe et al (1990) considered that the android phenotype prone to high release of free fatty acids from intra-abdominal depots, thus leading to altered metabolic functioning (121).

Waist circumference (WC)

In 1998 (122), the National Heart, Lung, and Blood Institute (NHLBI) in cooperation with the National Institute of Diabetes and Digestive and Kidney Diseases have determined that waist circumference alone without hip measurement correlates better with biomarkers of health risk (e.g., hyperlipidemia, hyperglycemia, hypertension) and health outcomes (actual disease and mortality). Central adiposity increases the risk for cardiovascular and other diseases independent of obesity. Clinicians may use the WC

as a measure of central adiposity. The waist circumference cut-offs established by the NIH to identify those at increased risk were

Men:	>102 cm (>40 in.)
Women:	>88 cm (>35 in.)

WHO agreed to the same cutoff points pronounced by NHLBI and considered them the most effective technique for assessing abdominal fat (14). According to WHO, a person will have: lower risk if WC is ≤ 79cm in women, ≤ 93cm in men; increased risk if WC is 80-87cm in women, 94-101cm in men; and substantially increased risk if WC is ≥ 88cm in women, ≥102cm in men (14). The waist circumference thresholds are not reliable for patients with a BMI greater than 35 kg/m^2 (123). Whereas, International Diabetes Federation established different cut-off points for different ethnic groups categorize as; a WC of > 97cm (37 in) for males, and >80 cm (34 in) for female Europids population; as well as WC of > 90cm (37 in) for males, and >80 cm (34 in) for female South Asians, Chinese and Japanese population (124) (table 2). European Cardiovascular Societies and Health Canada recommended that the threshold for waist circumference to define abdominal obesity should be higher as presented in Table 2 (77, 78, 79). Recent study in the Middle East showed that optimal WC cut-off point 85 cm for both sex in Tunisian population (125). Other studies at the Arabian Gulf region indicated that WC and WHR predict MetS risk better than BMI. The optimal WC cut-off points are 80.0 cm for men and 84.5 cm for women among Omani population (126). WC cutoff points for Iranian were (90 cm for men and 90.3 cm for women) and for Iraqi were (97 cm for men and 99 cm for women) (127, 128). Beside, in Qatar, men WC at a cut-off 99.5 cm resulted in the highest sensitivity (81.6%) and specificity (63.9%). In women, WC at a

cut-off 91 cm resulted in the highest sensitivity and specificity of 86.5% and 64.7%, respectively (129).

WC is reported as a cardiometabolic predictor in literature, yet it has some drawbacks. For individuals with a BMI $\geq$ 35, waist circumference adds little to the predictive power of the disease risk classification of BMI (130). The risk prediction of WC is influenced by the anatomic location of measurement, especially in women. Accordingly, the choice of measurement protocol may bias research findings and influence clinical decision-making. Mason and Katzmarzyk (131), emphasized that until a uniform approach to the measurement of WC is widely agreed, the location of measurement should be an important consideration in the interpretation of WC measurements (131, 26). Waist circumference accuracy is limited in some situations, including pregnancy, medical conditions where there is distension of the abdomen, such as ascitic, or reduction of the abdomen, such as abdominal liposuction or tummy tuck (Abdominoplasty) (27). The main limitation of the WC measure is the huge inter-ethnic variability that arises for certain ethnic groups and for children and young people. Special threshold for WC is being recommended in several different populations and ethnic groups (presented in table 2). Whereas, the risk associated with a particular WC will differ in different populations. This is especially relevant in a country without local cut off levels, such as Saudi Arabia.

Neck Circumference as an indicator of cardiometabolic risk factors

Obesity is well known to cause metabolic abnormalities. The distribution of excess adipose tissue may be considered to be more important than total fat in conferring metabolic and cardiovascular risk (132). Upper-body obesity is more associated with glucose intolerance, insulin resistance, diabetes, hypertriglyceridemia, and uric calculous disease than is lower-body obesity (20). Visceral adipose tissue (VAT) is acknowledged as a unique pathogenic fat depot. Elevated VAT may indicate metabolic risk over assessments provided by standard anthropometric measures, such as body mass index (BMI) and waist circumference (WC) (133). Large amount of VAT increases risk of certain obesity related complications, such as insulin resistance, type 2 diabetes, and atherosclerosis (134, 135). Nevertheless, some studies showed that VAT accounts for only modest correlations with cardiometabolic risk factors, implying that other mechanisms, or other fat depots, may also contribute to the development of cardiovascular disease (CVD) risk factors (18, 133). Upper body fat distribution has long been recognized as correlated to increased cardiovascular disease risk, where neck skinfold (117) or neck circumference (NC) (136, 137) has been used as an index for such an adverse risk profile. Moreover, free fatty acid release from upper body subcutaneous fat depots (SAT) was reported to be larger than that from lower body subcutaneous fat or from visceral adipose tissue, suggesting that this fat depot may play a considerable role in risk factor pathogenesis (138, 53). Raised free fatty acid concentrations have been associated with insulin resistance, increased very low density lipoprotein cholesterol production, and endothelial cell dysfunction (139). The strong correlation between SAT and cardiometabolic risk factors may be determined by the results from some (140, 141,

142) but not all studies (143, 144). Neck circumference is a proxy measure for upper body subcutaneous fat depots (SAT), and the association has been examined. Among 258 men from the control group of the Fat Redistribution and Metabolic Change in HIV Infection study, upper body section fat was found to be independently associated with insulin resistance even after adjustment for VAT (145). In another study of 145 control participants from the Fat Redistribution and Metabolic study revealed that increased levels of upper-body section fat were positively associated with LDL cholesterol and inversely associated with HDL cholesterol levels, after adjustment for demographic and lifestyle factors (146). According to the Framingham Heart Study, neck circumference is a proxy of upper-body section fat, and is a novel, discrete, and pathogenic fat depot both independent of and synergistic with VAT (18). While the adjustment for VAT diminishes the association between neck circumference and cardiometabolic risk factors, it is essential to note that most associations remained statistically significant (18). Neck circumference is correlated with body mass index (BMI) and cardiovascular risk factors (147, 21). Some studies have demonstrated that neck circumference may be an independent correlate of metabolic risk factors even above and beyond BMI and waist circumference (148, 21). While other presented the neck circumference as a simple, time-saving and cost effective measure to assess overweight and obesity, especially during winter and in busy primary care practice (20). Several studies have examined the association between neck circumference and cardiometabolic risk factors. Neck circumference has been compared directly with VAT with respect to their association with cardiometabolic risk factors. Neck circumference is considered an index of upper body obesity and associates positively with changes in systolic and diastolic blood

pressure and other components of the metabolic syndrome (22). Neck circumference has been found to be a good clinical predictor of insulin resistance, menstrual irregularity, infertility, hirsutism, and the Polycystic Ovarian Syndrome (PCOS) (100). A cross-sectional study among 1912 Turkish adults, estimated neck circumference as an indicator of central obesity. And even with the adjustment for sex- and age, neck circumference was significantly associated with metabolic syndrome (MetS) and obstructive sleep apnea syndrome (OSAS) in both genders. WC has higher independent association with MetS. While both neck circumference and WC were reported to share significant independence of association with OSAS whereby neck circumference appeared to be a superior marker in men and WC in women (21). In contrast, another study found a greater association of neck circumference with cardiometabolic risk factors in women as compared with men. According to a cross-sectional analysis of 541 Finnish individuals, neck circumference in the highest quintile was associated with nearly a 5-fold increased risk of impaired fasting glucose in women after adjustment for BMI. No association was seen for men. Neck circumference was also found to be associated with approximately a 3-fold increase of hypertension, after adjustment for BMI, in both men and women (100). A cross-sectional study of 4053 Chinese subjects reported neck circumference is independently correlated with Fatty liver disease (FLD). The participants with FLD had significantly higher neck circumference levels and other anthropometric measures (body weight, WC, HC, BMI and WHR) in both men and women compared with non-FLD participants. Consistently, the FLD participants had higher fasting blood glucose, blood pressure, blood uric acid, triglycerides, total cholesterol, apolipoprotein B, and apolipoprotein E, as well as alanine transaminase (ALT), aspartate transaminase (AST) and γ-glutamyl transpeptidase (GGT).

Moreover, even after adjusting for age, logistic regression analysis presented a strong positive association between neck circumference and FLD in both men and women. Whereas, after additional adjusting for BMI and WC, the corresponding ORs were attenuated to 1.94–2.53 (P <0.001) in women and 1.45–2.08 (P <0.001) in men. And neck circumference cut off points of 38 cm in men and 34 cm in women had the optimal sensitivity and specificity to predict subjects with FLD (149).

The available up to date cut-off points of neck circumference for determining subjects with overweight, obesity, and metabolic and cardiovascular disease risks are presented in the following table.

Table 4. Current recommended neck circumference cutoff points for overweight, obesity, and metabolic syndrome risks by literature.

Study	Year	Country	n.	Male				Female			
				Over-wt	Obese	Abd-obesity	MetS risk	Over-wt	Obese	Abd-obesity	MetS risk
Ben-Noun et al. [20]	2001	Israel	253	≥ 37cm	≥ 39.5cm			≥ 34cm	≥ 36.5cm		
Onat et al. [21]	2009	Turkey	1912			38.5cm	39cm			34.5cm	35cm
Yang et al. [147]	2010	China	3182	≥ 38cm			≥ 39cm	≥ 35cm			≥ 35cm
Hingorjo et al. [150]	2012	Pakistan	155	> 35.5cm	> 37.5cm			> 32cm	> 33.5cm		
Kumar et al. [151]	2012	India	203				>37cm				>34cm
Zhou et al. [152]	2013	China	4201				>37cm				>33cm
Stabe et al. [27]	2013	Brazil	1053				>40cm				>36.1cm
El Din et al. [153]	2013	Egypt	6718	≥ 38cm	≥40.25cm			≥ 36cm	≥37.25cm		
Aswathappa et al. [154]	2013	India	1351	>36cm		>38cm		>32cm		>34cm	
Kumar et al. [155]	2014	India	431				>37cm				>34cm
Yan et al. [156]	2014	China	2092		>38cm		>38cm		>35cm		>35cm
Limpawattana et al. [157]	2016	Thailand	589				>39cm				>33cm

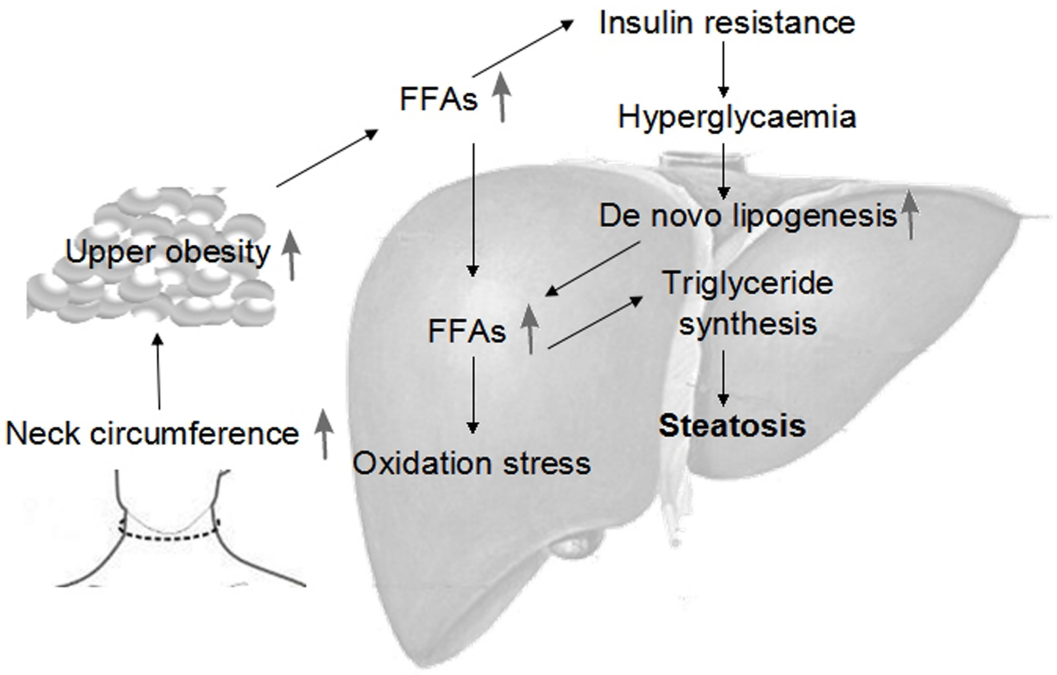
Over-wt: Overweight; MetS risk: metabolic syndrome; Abd-obesity: Abdominal obesity

Possible biological mechanisms

Obesity is no longer viewed as a single disease, but rather as a complex condition manifested in multiple expressions or phenotypic forms. For example, two obese individuals, though similar in height, age and weight, may not appear exactly alike. One individual may carry more weight on his upper body (trunk/ or abdominal), while his counterpart exhibits a heavier weight distribution in the lower extremities. This has led researchers to establish a classification scheme, to determine how these various expressions may alter a patient's disease and mortality profile (114). Whereas, the android phenotype prone to high release of free fatty acids that lead to altered metabolic functioning. Literatures strongly suggest that free fatty acids are an important link between obesity and insulin resistance. Some studies have reported that is due to upper body/visceral adipose tissue (144), while others have established that upper body/subcutaneous fat is responsible for higher release of free fatty acids (140, 141, 142, 158). The excess free fatty acid release, associated with upper body/subcutaneous fat, has been suggested to be one mechanism that clarifies the association between cardiometabolic risks and neck circumference (18). The inability of insulin to adequately suppress FFA release from upper body subcutaneous fat is the major defect in upper body obesity (158, 159) and Type2 diabetes (160). It is well recognized, however, that high levels of FFA can mediate insulin resistance in muscle (161, 162) and liver (163, 164). As a result of the failure to suppress FFA, inhibition of carbohydrate oxidation and glycogen synthesis in muscle during hyperinsulinemia (165), reduction in the clearance of insulin by the liver (166), and elevation in VLDL-triglyceride production (167) will occur. The other potential mechanism might be related to upper body fat (168, 169),

which could be estimated by the neck circumference (170, 18). The excess FFAs increase oxidative stress, thereby triggering the inflammatory response and progressive liver damage. Stojiljkovic et al. (171) reported that an acute raise in plasma lipids increased the concentration of the oxidative stress biomarker F2-isoprostanes and raised the possibility of the cardiovascular risk factor cluster. These observations might illuminate the mechanism by which an elevated neck circumference independently increases the risk of cardiometabolic risks and the developing fatty liver disease. (Fig. 1)

Figure 1. Mechanisms linking a hypertrophic neck with the development of fatty liver disease



FFAs: Free Fatty Acids

- *Source:* Huang BX et al. (149)

Chapter 2: Methods

Study Design

A cross-sectional survey was conducted in King Khalid University Hospital (KKUH) primary health care centers in Riyadh city, Kingdom of Saudi Arabia, during September 2014 - April 2016, using a total of 700 adults aged 18-70 years.

Study setting

The study was conducted in the city of Riyadh. Riyadh is the capital and largest city of Saudi Arabia, with a population of approximately 5 million. Whereas, 65% are Saudi and 35% are non-Saudi. The city is located in the center of the Kingdom of Saudi Arabia (Riyadh Principality). The study setting consisted of primary health care center of King Khalid University Hospital (KKUH) in Riyadh city. This setting was selected for carrying out the study as a surrogate for a population-based study that would be ideal for the recruitment of study subjects, but was challenging given the limited time and resources. The attendants of KKUH setting actually represented the Saudi population in Riyadh since any Saudi was eligible for getting primary care services at this center regardless of any personal or socio-demographic, or economic factors. Moreover, the attendants were a mix of healthy (coming for preventive services) as well as unhealthy individuals.

Study population

The target population for this study consisted of all Saudi men and women aged 18-70 years who attended KKUH primary health care center in Riyadh city during the time of the study. Inference from the sampling to the target population might be possible if we can assume that Saudi men and women who attended primary health care center were not different from other Saudi population living in Riyadh, whether they used primary health care center services or not. This assumption may need to be evaluated through comparing the basic socio-demographic characteristics in the study sample with the corresponding national indicators. If statistically significant differences were revealed, the study findings would only be inferred to men and women in the sampling population.

A written consent was obtained from each of the clients about their willingness to participate, after explaining the purpose of the study, to assure that information would be kept confidential and used strictly for research purpose.

Eligibility criteria

This study enrolled subjects with the following criteria: Saudi men and women aged 18-70 years old.

Subjects with the conditions below were excluded from the study:

- Pregnant and lactating women.
- Having thyroid nodule.
- Having serious diseases (i.e. Organ Failure, Transplant, Cancer)
- Having impaired-decision capacity or mental illness.

Sample size calculations

Power: In order to determine the appropriate sample size for the study, an analysis of statistical power was performed (172). Statistical power is the probability that the Null Hypothesis, when the null hypothesis is false, will be rejected. For a specific statistical procedure, the likelihood of rejecting the Null Hypothesis is a function of: a) the alpha level for testing the Null Hypothesis; b) the effect size for the independent variable or variables being tested; and c) the sample size. By fixing the alpha level and effect size, the sample size needed to attain a desired power level could be determined. Sample size computations for the present study assumed that the statistical tests would be conducted at alpha = 0.05, and that the independent variable had a moderate effect size (equivalent to a correlation of .3) (175). Sample sizes were computed to attain a more lenient level of power (Beta = 0.80) as well as a more stringent one (Beta = 0.95). A power level of 0.80 is considered acceptable for an exploratory study. At this power level, there is an 80% probability of rejecting the Null Hypothesis when the assumed effect size is true. A power level of 0.95 is considered necessary for a more definitive study in which the costs of retaining a false Null Hypothesis are greater. With a power level of 0.95, there is a 95% probability of rejecting the Null Hypothesis if the assumed effect size is true.

In this study, the computations of the sample sizes needed to attain the 0.80 and 0.95 levels of statistical power were performed using the G*Power3 software package (173). For the analyses involving partial correlations, there was a need for between 84 and 138 subjects for each gender. For analyses within a multiple regression framework with ten predictors, there was a need for between 172 and 245 subjects for each

gender. For the logistic regression analyses, we needed between 600 and 1200 subjects for each gender.

As for the discrimination between normal and subject at cardiometabolic risk, the sample size was calculated based on the accuracy of a test calculation. It depended on the following (174):

- Type I error - alpha: (α-level, two-sided)
- Type II error - (β-level)
- Area under ROC curve: the hypothesized Area under the ROC curve (the AUC expected to be found in the study).
- Null hypothesis value: the null hypothesis AUC.
- Ratio of sample sizes in negative / positive groups. In this work, the negative is the normal subject and the subject with cardiometabolic risk is the positive.

The following table presents the sensitivity analysis for sample size calculations for ROC curve using the MedCalc® Version 12.5.0.0 statistical software package

Alpha	Beta	ROC area (HA)	ROC area (Ho)	Ratio (-ve/+ve)	Sample size	
					-ve	+ve
0.05	0.2	0.8	0.5	3/1	9	27
0.05	0.1	0.8	0.5	3/1	12	36
0.05	0.2	0.75	0.5	3/1	14	42
0.05	0.1	0.75	0.5	3/1	18	54
0.05	**0.2**	**0.7**	**0.5**	**3/1**	**22**	**66**
0.05	0.1	0.7	0.5	3/1	29	87
0.05	0.2	0.65	0.5	3/1	39	117
0.05	0.1	0.65	0.5	3/1	52	156
0.05	0.2	0.6	0.5	3/1	86	264
0.05	0.1	0.6	0.5	3/1	118	354

ROC curve area of 0.7 was determined to be 88 (n=22+66).

Eventually, based on the primary outcome measure of differences in cardiometabolic risks on neck circumference, the sample size of 600, for each gender, was determined to have 80% power with two-tailed significance level of 5% to detect a moderate effect size. The sample sizes was estimated to be large enough for the regression analysis with 10 or more independent variables according to Hsieh et al., 1998 (176). The calculation was performed using the G*Power3 software package (173), and MedCalc® Version 12.5.0.0 statistical software package.

Sampling technique

Ideally, subjects should be selected by systematic random sampling from the patients' registers in KKUH primary health care center. A sampling frame would thus be constructed (separate by gender) according to the eligibility criteria, and then a systematic random sample is recruited with the periodicity of selection determined by dividing the total eligible population by the required sample size. Then, the selected persons would be contacted and invited to participate. We found that this process is not feasible in a conservative community, and would lead to considerable selection bias due to non-response. Therefore, the sampling frame was constructed from the daily booking logs of the center. Names and file numbers of all Saudi men and women ages 18-70 years were obtained first in the morning. Then, the systematic random sampling technique was used to select participants from these frames. We used the following formula for systematic sampling: $K \leq N/n$. whereas; the population size (N) is the number of total eligible population (Saudi males and females aged 18-70 years) and the required sample

size (n) was chosen based on the power calculation. Therefore, n=700, and the total eligible population were N=4,167. The formula then became $5.9 \leq 4167/700$. In order for systematic sampling to be valid, the first item was randomly selected from the first K items in the daily booking logs until the target sample size of 700 was achieved. We then looked at every 6^{th} subject from KKUH primary health care center.

In the case of rejection or if participant did not meet the study criteria, the next adjacent participant was selected. This has been done for all 5-days of the week in each center to avoid any bias related to the days of the week. At the end of each day, the list form (personal identifier) was destroyed. Yet, we do keep a list of the participants file numbers only to avoid taking or selecting them again in the future.

Then, researchers rescreened the selected persons for eligibility using the screening tool (**Appendix** 1; 1A-Arabic version and 1B-English version). If eligibility criteria were met, the participants were invited to participate, provided with informed written consent (**Appendix** 2), and asked to answer questions, on a volunteer basis, with estimated time of 10-15 minutes in order to complete the survey (**Appendix** 3; 3A-Arabic version and 3B-English version). The selected subjects were asked to participate one time only. All procedures and required data were fully explained. They were assured that they would not be identified and the information would strictly be used for the purpose of this research study.

Data Collection

This work have been done in collaborative work with Biomarkers Research Program(BRP), King Saud University, Riyadh (KSA), data collection was carried out by

the researcher and her team over a period of 18 months from September 2014 to April 2016. The Ethics Committee of the King Saud University, Riyadh, Kingdom of Saudi Arabia and University of Maryland College Park Institutional Review Board (IRB) approved the study (**Appendix** 4).

The data collection tools included an interview questionnaire, anthropometric measurement, clinical assessment, and blood biochemical tests.

I. Interview Questionnaire

For collecting data for the study, a pre-coded interview questionnaire was designed. Since Arabic is the primary language among Saudi people, the questionnaire has been designed in Arabic then translated into English language. Prior to using the Arabic questionnaire, the researcher carried out a pilot study in the waiting area of the same primary health care center. The aim was to test the clarity of the questions and the time needed for the interview. The pilot consisted of a convenience sample of 26 clients (11 Men and 15 women) aged 18 to 51 years. All those invited to participate gave their oral consent. Based on the participant responses and the clients' ability to understand, some questions were modified, excluded and added to the questionnaire. The time spent in the interview averaged 15 minutes. The pilot sample was not included as a part of the actual study sample.

The questionnaire was judged for its face validity through review by experts in nutrition and behavior sciences, students in the Master's and PhD programs in Nutrition and Food Science department at University of Maryland College Park, USA, as well as the research supervisors. The questionnaire is entitled "Overweight and obesity

assessment tool." The questionnaire consists of five parts: socio-demographic data, medical history, dietary habit and practices, physical activity and lifestyle as well as anthropometric measurements and blood test results (**Appendix** 3; A-Arabic versions and B-English versions). Each subject who agreed to participate will be interviewed in an empty room to provide an atmosphere of comfort and trust.

a) Socio-demographic data

Socio-demographic variables including age, gender, education level, marital status, number of children, occupation, average monthly income level, smoking statues, and previous participation in research study were assessed using "Overweight and obesity assessment tool" questionnaire (**Appendix** 3).

Education levels was categorized as illiterate, read and write, elementary, intermediate, secondary, graduate, post- graduate and further categorized to five strata: illiterate, less than high school (including read and write, elementary, intermediate), completed high school or diploma (secondary), bachelor degree and higher education. **Marital status** was categorized as unmarried, married, separated, divorced, widowed and further divided into two categories as married (including living as married), and unmarried (including being widowed, divorced, separated, or never married). While, **the occupation** was categorized as unemployed (housewife), student, teacher, office work, business, medical doctor, nurse, millenarian, and retired. **The economic status** was assessed by total monthly family (household) income (less than 1,999; 2,000 SR - 4,999 SR; 5,000 SR – 7.999 SR; 8,000 SR -10,999 SR; 11,000 SR - 13,999 SR; 14,000 SR -16,999 SR; 17,000 SR - 19.999 SR; More than 20.000

SR; and unknown). And further categorized to four strata: less than 9,999 SR; 10,000 SR to 19,999 SR; more than 20,000 SR*; and unknown. **Smoking** (cigar, pipe, shisha [water pipe or flavored tobacco]) was categorized as never smoked (if they had smoked <100 cigarettes in their lifetime), former smoker (≥100 lifetime cigarettes, not currently smoking), and current some day smoker (≤100 lifetime cigarettes, currently some day smoking), and current every day smoker (≥100 lifetime cigarettes, currently very day smoking). And further categorized to two strata: non smoker (if they had smoked <100 cigarettes in their lifetime) and smoker (≥100 lifetime cigarettes in their lifetime) (177)

b) Family Medical History / Health History Data

Family history of chronic diseases and conditions: Subjects were considered to have a family history of chronic diseases or condition if any of their biological (blood) relatives, living or deceased, including grandparents, parents, brothers, and sisters had obesity; diabetes; hypercholesterolemia; hypertension; or cardiovascular diseases. Subjects with a previous diagnosis of diabetes, hypercholesterolemia, hypertension, or cardiovascular diseases were determined. Treatment for previously diagnosed hypertriglyceridemia, hypercholesterolemia, and diabetes were identified. For female, the age of the first menstrual cycle, menopausal, and hormonal therapy were specified. Females were also asked if they ever used hormone or hormone therapy (yes vs. no). Menopausal status was categorized as last month (regular mensuration), within the past 12 months (irregular mensuration), stopped for at least

* 1 US $ = 3.75RS

12 consecutive months and further defined as: premenopause if menses had occurred in the past 12 months; postmenopause if menses had stopped for at least 12 months (178, 179).

c) Dietary habit and practices

Data about subjects dietary habits and practices were ascertained by 15 questions about regularity of daily meals, meal skipping, snacks intake, snack of different types and at different times, fruits and vegetable consumption, use of sweeteners, fats, dairy products, food preparation, and consumption of fast foods. The questions in section were modified after existing reliable questionnaires (180, 181, 182). Eleven dietary practice questions were scored from 1 to 3 with higher score for more healthy practices.

The total dietary habit and practice scores ranged from 11 - 33, and only in the descriptive table, were leveled as follows:

Good practices	26- 33
Fair practices	18-25
Poor practices	11-17

Alpha reliability coefficient (Cronbach's alpha) for dietary habit and practice instrument or scale was 0.54. We improved the consistency by removing the lowest correlated variable. And the finale Cronbach's alpha was 0.72.

d) Physical activity and life style

A special physical activity assessment questionnaire (Activity Records) was modified after RENO Diet-Heart Study (RDHS) quoted from (Harrington, 1997) and

used for assessing participants, physical activity practices about regularity and intensity (183). Four questions were included about physical activity types, times per week, session's time per minutes, and sedentary leisure time during the last entire year were scored as follows.

- The total score was calculated by summing the regularity score, intensity score, and lifestyle score.

Scoring the regularity of physical activities:

Sedentary (Never)	1
Irregularly Active (Some time)	2
Regularly Active (Always)	3

Scoring of physical activities at differing intensity levels per week (183,184):

Light	1	Walking less than 150 minutes
Moderate	2	150 -279 minutes of walking Less than 60 minutes of running, swimming, cycling, aerobic, and resistance exercise
Hard	3	More than280 minutes of Walking More than 60 minutes of running, swimming, cycling, aerobic, and resistance exercise

- Scoring of daily activities (lifestyle) at differing levels (180, 184):

Very Sedentary	1	Typing, reading, and watching TV
Sedentary	2	Cleaning, shopping
Moderate Active	3	Hard job
Very Active	4	Swimming, cycling

The total score was ranged from 2 - 10 and, only in the descriptive table, was divided into tertiles, where the lowest one will be referred to as “sedentary physical activity level”; the medium one, referred to as “partially moderate physical activity level”; and the highest one, referred to as “active physical level” (185).

Alpha reliability coefficient (Cronbach’s alpha) for Physical activity and life style levels instrument or scale was 0.740.

II. Anthropometric Measurements

The anthropometric measurements have been conducted according to the Anthropometry Procedures Manual proposed by the National Health and Nutrition Examination Survey 2002 (186). Six variables were selected for anthropometric measurements, height, weight, body mass index (BMI), neck circumference (NC), waist circumference (WC), hip circumference, waist-hip ratio (WHR) and body fat (%). All anthropometric measurements were taken by a well-trained health care provider (clinic in charge nurse), who was instructed to use the same technique of weight and height measurements for all subjects of the study sample.

The height was recorded to the nearest 0.5 cm, by using a height scale measurement, with the subject standing upright barefooted or in thin socks and bareheaded. **The weight** was recorded to the nearest 0.1 Kg, with appropriate international standards scales, by using standardized beam weight scales (Detecto scale, Cardinal Scale Mfg. Co., USA). A 5 kg standard weight was used daily for assessing and adjusting the scales (scale calibration). Weight was taken without shoes and with light clothing. **Body mass index (BMI)** was calculated by the equation: BMI = Weight in Kg /

(Height in meters)². According to the World Health Organization's BMI additional cut-off points categorization, participants were classified into: normal weight (≤24.99 kg/m^2), over-weight (25 kg/m^2 to 29.99 kg/m^2), and obese (≥30 kg/m^2) (109).

A Gulick II® fiberglass tape measure, (Country Technology, Gays Mills, WI) model # 67020, was used to measure neck circumference (NC), waist circumference (WC), hip circumference. **Neck circumference** was measured to the nearest 0.1 cm, with the participants standing erect and their head positioned in the Frankfort horizontal line (facing forward). The tape measure was then placed horizontally at the midway of the neck between mid-cervical spine and mid-anterior neck, just below the laryngeal prominence (Adam's apple) (18, 20). Waist and hip circumferences were measured, with the participants in the standing position and in light clothing (social reason), to the nearest 0.5 cm by using a flexible measure tape. The reading was taken to the nearest 0.1 cm with the tape ensured to be snug, but not compressing the skin. **Waist circumference (cm)** was measured at mid-point between bottom of the rib cage and above the top of iliac crest. **Hip circumference (cm)** was measured at widest point of the buttocks. **Waist-to-hip ratio (WHR)** was calculated by dividing the waist circumference (cm) by the hip circumference (cm). WHO and IDF recommended that different WC cutoff points should be used to define central obesity among different ethnic groups, and that the Europid standards should be used in our Eastern Mediterranean region until specific national data become available (45, 73). WC cut-off points are currently categorized as: a WC of > 97 cm (37 in) for males, and >80 cm (34 in) for females for Europids population (70, 72, 124).

Body fat percentage (%) was assessed by using a dual-energy X-ray absorptiometry (DEXA) device (model: Prodigy Advance, GE healthcare). DEXA is a scanning technique that measures bone mineral, fat tissue, and fat-free soft tissue. Subjects must lie completely still on the DEXA machine platform while X-rays at a high and low energy levels are passed over the body (187, 188). After completing the doctor visit, the subject was asked to visit the radiology department within the same center. Well-trained radiologic technologists performed the DEXA scan, with estimated time of 15-20 minutes in order to be completed. This procedure was not painful, but there could be some minor discomfort from lying in the same position. This discomfort was minimized by keeping the time involved in making the measurements as short as possible, and by allowing the subject a break if necessary.

III. Clinical & Biochemical Parameters

The parameters determined were: fasting plasma level of glucose (FPG), insulin, triglycerides (TG), total cholesterol (TC), HDL cholesterol (HDLc), and LDL cholesterol (LDLc); as well as blood pressure.

- **Blood Pressure Measurement:** before starting the measurement, subjects were seated quietly for a five-minute period. The subjects were not allowed to smoke or drink coffee during the examination since these could affect the blood pressure. If the subject has had any coffee, or cigarettes thirty minutes before the examination, this was recorded on the form but the measurements were still taken. The right arm was used for standardization and consistency. Measurement was taken using standardized mercury sphygmomanometers (Diplomat Presameter 660-360 manufactured by

Riester GMBH, Germany). Blood pressure was considered normal if systolic BP < 130 mm Hg and diastolic BP < 85 mm Hg (38).

- The agreed to participate subjects were scheduled for a second visit to the laboratory in the same clinic within one week. They were informed to attend after fasting for 10-12hrs. Samples were analysed and stored in the Biomarkers Research Program (BRP), College of Science, King Saud University (KSU), Riyadh, Saudi Arabia. In brief, all blood and serum samples were placed in plain polystyrene tubes, delivered on the same day to BRP and stored at −20°C. Fasting blood glucose and lipids (total cholesterol, triglycerides and HDL cholesterol) were measured using a standard chemical analyzer (hexokinase and colorimetric methods, respectively) (Konelab, Vantaa, Finland) under strict conditions. The analyser was recalibrated frequently according to manufacturer's instructions. LDL-cholesterol was estimated by using the Friedewald equation = [Total Cholesterol] - [HDL cholesterol] - ([Triglycerides]/2.2) (189). Insulin concentrations were determined by electro-chemiluminescence method (COBAS-E-411; Roche Diagnostics, Mannheim, Germany). Homeostasis model assessment for insulin resistance (HOMA-IR) was then calculated for all patients using the HOMA formula: HOMA-IR= fasting insulin (μU/mL) × fasting plasma glucose (mmol/L) /22.5. (190, 191)

Variables of Interest

The variables of interest were grouped as described earlier into the following categories: socio-demographic including age, gender, education level, marital status, number of children, occupation, average monthly income level, smoking statues; dietary habit; Physical activity; anthropometric; biochemical; and cardiometabolic risk factors.

Cardiometabolic risk factors

Biomarkers of cardiometabolic diseases (cardiometabolic risk factors) are defined according to the International Diabetes Federation IDF definition guidelines (38) as follow: central obesity (94 cm ≥ for men, 80 cm ≥ for women), hypertriglyceridemia (triglycerides ≥1·7 mmol/L), low HDL cholesterol (<1·03 mmol/L for men and 1·29 mmol/L for women or specific treatment for this lipid abnormality), hyperglycemia (fasting plasma glucose ≥5·6 mmol/L or previously diagnosed type 2 diabetes), and hypertension (systolic BP ≥ 130 mm Hg, diastolic BP≥ 85 mm Hg or treatment for previously diagnosed hypertension). Metabolic syndrome are defined as per (IDF, NHLBI, AHA, IAS, IASO) harmonized definition guidelines (73) with the presence of any three or more of the following risk factors: raised triglycerides (≥1·7 mmol/L), reduced HDL cholesterol (<1·03 mmol/L for men and 1·29 mmol/L for women or specific treatment for this lipid abnormality), raised fasting plasma glucose (≥5·6 mmol/L or previously diagnosed type 2 diabetes), raised blood pressure (systolic BP ≥ 130 mm Hg, diastolic BP≥ 85 mm Hg) or treatment for previously diagnosed hypertension. Insulin resistance was assessed by using a homeostasis model assessment (HOMA-IR) [fasting glucose (mmol/l) X fasting insulin (μmol/mL)/ 22.5] (190).

Assessment of Covariates

The information on covariates and potential confounders such as: age (y), smoking habit [non smoker (if they had smoked <100 cigarettes in their lifetime) and smoker (≥100 lifetime cigarettes in their lifetime) (173)], physical activity (sedentary physical activity level, partially moderate physical activity level, active physical level)(185), menopausal status [premenopause if menses had occurred in the past 12

months; postmenopause if menses had stopped for at least 12 months (177, 179)], current estrogen use (no vs. yes), treatment for previously diagnosed hypertriglyceridemia (no vs. yes), hypercholesterolemia (no vs. yes), and diabetes (no vs. yes) were included in the analysis.

Statistical Analysis

Descriptive statistics was applied for all variables. Continuous data were presented as mean ± standard deviation (SD) and Median (25^{th} -75^{th}) percentiles for variable following Gaussian and Non Gaussian variables. Categorical variables were presented as frequencies (n) and percentages (%). All Continuous variables were checked for normality using graphs, Kolmogorov-Smirnov test, as well as Skewness and Kurtoses (≤0.8). If they were not normal, the continuous variables were transformed to log or SQRT transformation, where it was appropriate. The frequency distribution of each variable at baseline was compared in men and women by using chi-square (χ^2) or Fisher exact tests, as suitable for categorical variables. Student t-test and Mann-Whitney U test were used for Gaussian and Non Gaussian variables. All analyses involving insulin measures (insulin, and HOMA-IR) were restricted to participants without diabetes. Relationships among variables were sought by Partial correlations and performed between the study variables. The findings were expressed as correlation coefficients and P-Value, after controlling for: age in men. And controlling for: age; menopausal status (premenopausal vs. postmenopausal); and current estrogen use (no vs. yes) for women. Analyses were performed separately for each gender. Regression and ROC curve analyses were performed for women only, because of the low sample size in men. Neck circumference, WC, BMI, and fat% were standardized in women to a mean of zero and a SD of one to facilitate the comparisons of the regression coefficients. Linear regression analysis was performed, considering the cardiometabolic risk factors (Log Fasting glucose, SQRT Insulin, SQRT HOMA-IR, SQRT Triglycerides, HDLc, LDLc, SBP,

DBP) as dependent variables, as well as considering neck, body mass index, waist circumference, and body fat percentage as independent variables.

Multiple binary logistic regression analysis was performed, with the consideration of the cardiometabolic risk factors: central obesity (present/absent), hypertriglyceridemia (present/absent), low HDLc (present/absent), high LDLc (present/absent), hyperglycemia (present/absent) and hypertension (present/absent), HOMA-IR >75th (present/absent), the presence of two or more of the risks, metabolic syndrome as per the harmonized criteria (the presence of three or more of the risks), metabolic syndrome as per the IDF criteria (the presence of abdominal obesity and two or more of the risks) as dependent variables and the neck circumference as independent variables and control for covariates. Then participants were classified into quartiles (Q1–Q4), with Q1 (<25th percentile) as the reference. Multivariate logistic regression analysis was used to calculate odds ratios (ORs) and 95% confidence intervals (CI) for cardiometabolic risks according to the neck circumference quartiles after adjusting for covariates. Multicollinearity among independent variables and between confounders was tested in regression model by examining variance inflation factor (VIF) and tolerance. No variable with VIF greater than 10 or tolerance less than 0.01 was detected.

Receiver operating characteristic (ROC) curves were used to determine the efficacy of neck circumference as screening measure for correctly identifying subjects with cardio metabolic risks and to select appropriate sex-specific cut-off points for neck circumference (192). The optimal cut-off points for women were determined using the Youden index (J), and calculated as: J = maximum (sensitivity + specificity -1) and the shortest distance between any point on the curve and the top left corner on the y-axis. The

distance on ROC curve values were calculated as the square root of [(1-sensitivity)^2 + (1-specificity)^2] (192).

The additive interaction between neck circumference and other anthropometric measurements was evaluated using logistic regression analysis, as suggested by Rothman et al. (147, 193,194, 195), with 3 indices: the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP) and the synergy index (S) with 95% CI. If there was no additive interaction, 95% CI of RERI and AP were equal to 0, and S equal to 1 (Appendix 5).

Statistical analyses were performed using SPSS 22 (IBM Corp., Armonk, NY, USA). All tests were 2-sided, and levels of statistical significance were set at p-values of < 0.05.

Chapter 3: Results

Participants

The study was carried out at the King Khalid University Hospital (KKUH) primary heath care center. Participants were Saudi men and women between 18–70 years of age. Of the 922 subjects initially identified for study inclusion, 66 declined to participate, as being too busy or not interested. Seventy-one (71) subjects were excluded for one of the following reasons: age, pregnancy, or lactating. In addition, 85 subjects were excluded because they did not show up for their blood tests. Seven hundred (700) subjects, 18 years of age or older, with no known major medical issues, were enrolled in the study. The study sample consisted of 623 women and 77 men.

Socioeconomic and behavioral characteristics of the study subjects

The results of **Table 5** show that only 3% of the participants were <25 years of age, 9% were between 25–34 years of age, 19% were between 35–44 years of age, 43.3% were between 45–54 years of age, and 25.6% were ≥55 years of age. The mean ages of men and women were significantly different as 53±8.7 and 47±10.7 years old, respectively. As compared to the men, 26.3% of female participants were illiterate and 17.5% had graduate and post-graduate qualifications. While in men, 41.5% were at least high school educated, 45.5% had a bachelor's degree, and 10.4% had graduate and post-graduate qualifications.

The majority of the sample, amounting to 71.2% (*n*=497), reported being married, while 6% were single, 9.8% were separated or divorced, and 13% were widowed. The

data for the women showed that 41.4% had more than six children, 31.8% had four to six children, 14.7% had three children or less, while 12.1% had no children. A considerable proportion of the women (31.2%) were unemployed. Most of the participants, amounting to 22.4% and 25.9% of men and women, respectively, were office workers. In addition, 28.9% of men and 14.5% of women were retired. Most of the men did not respond to the income question (86.8%), and 40.6% of female participants had less than a 10,000 Saudi Riyal (SR) monthly income. Only 6.5% of the women had more than a 20,000 SR monthly income*.

Data presented in **Table 5** shows that nearly 40.3% of men and 63.5% of women had fair dietary habits and practices. Only 0.4% of the subjects had a good dietary habits and practices. The total physical activity score showed that 72.7% of men and 55.5% of women had a poor physical activity and lifestyle level. In addition, 15.6% of men and 34.7% of women had a fair physical activity and lifestyle level. However, only 10% of the subjects had a good physical activity and lifestyle level.

* 1 US $ = 3.75RS

Clinical and biochemical characteristics of the study subjects

The participants' clinical and biochemical characteristics by gender are shown in **Table 6**. The average body mass index (BMI), hip circumference (HC), and body fat percentage were higher for the women ($P<0.00$). Men were taller, heavier, and had larger waist circumference (WC), waist hip ratio, and neck circumference (NC) values (all $P<0.05$). The differences in weight and WC seem to be due to age rather than gender differences (not significant after age adjustment).

The cardiometabolic biomarkers data indicate that men had greater values for blood pressure, fasting blood glucose ($P<0.001$), triglycerides (TG), as well as HOMA-IR and insulin ($P<0.05$), and lower high density lipoprotein cholesterol (HDLc) ($P<0.001$), as compared to women. Consistently, after the age adjustment, systolic blood pressure (SBP) and triglycerides no longer showed a significant difference **(Table 6)**.

The prevalence of cardiometabolic risk factors and medical history of the study population are summarized in **Table 7**. Cardiometabolic risk factors (high blood pressure, high fasting glucose, high triglycerides, and being in HOMA-IR $\geq 75^{th}$ percentile) were found to be significantly higher in men as compared to women ($P<0.01$). However, abdominal obesity, and low HDLc were more prevalent in women ($P=0.001$). More than seventy percent (70.9%) of the population had metabolic syndrome. The prevalence according to the harmonized definition (84.4% in men and 69.3% in women, $P<0.01$) was higher than the IDF definition in both genders. Nearly half of the population (44.8%) had hypertension. In contrast, only 14.3% had reported that they had been previously diagnosed with hypertension. Family history of diabetes mellitus was more prevalent in

men (P=0.01) (**Table 7**).

Neck circumference and the other obesity indices

Scatter plot matrixes in **Figures 3** and **4** show fair to moderate positive linear correlation between neck circumference and BMI, and WC, in both genders. The scatter around the line is quite small, except for body fat percentage.

As shown in **Table 8**, the partial correlation coefficient was used to examine the correlation of neck circumference with body fat percentage, BMI, and WC after controlling for the effects of age. BMI showed the highest correlation with WC, as compared to its correlations with other clinical indices (r=0.676, n=584 in whole sample; r=0.765, n=70 in men; r=0.697, n=514 in women; all p<0.001). Neck circumference and WC were highly correlated in both men and women (r=0.537 in men and r=0.607 in women; P<0.001 for both). All correlation coefficients of neck circumference and WC with the clinical indices were highly significant among men and women (P<0.01).

The men were also divided into subgroups based on their BMI. The BMI cutoffs, as per WHO criteria (109) were normal weight (≤24.99 kg/m^2), over-weight (25 kg/m^2 to 29.99 kg/m^2), and obese (≥30 kg/m^2). Correlation coefficients of neck circumference and WC with the clinical indices were varied in the subgroups **(Table 9)**. Each BMI subgroup was further divided into three subgroups based on 25th, 25–75th, and 75th percentiles of WC. Neck circumference data showed increases from the lower WC subgroups to the higher WC subgroups within each BMI subgroup. The only exception was in the over-weight groups, where the neck circumference value for the WC>75th percentile was not different than that of the WC 25th–75th percentile group **(Figure 5)**. No man in the obesity

subgroup was below the 25th percentile for WC. Although the sample size for men is low, this figure was presented for reference.

After further adjustment for postmenopausal status and hormone use in women, all women were divided into subgroups based on their BMI. Neck circumference and WC were significantly correlated in the overall sample (r=0.605) and in the three BMI subgroups (r=0.511, r=0.410, r=0.514) (all P<0.01) **(Table 10)**. Each BMI subgroup was further divided into three subgroups based on 25th, 25–75th, and 75th percentiles of WC. In women, neck circumference significantly increased from the lower WC subgroups to the higher WC subgroups within each BMI subgroup **(Figure 6)**. Interestingly, no woman in the normal weight subgroup was above the 75th percentile of WC.

Neck circumference and cardiometabolic risk indicators in women

Table 11 presents the age, menopausal status, and hormone use adjusted correlation coefficient between all anthropometric indices and cardiometabolic risk factors used in this study for the whole sample and per BMI. With the exception of body fat percentage, all other indices were correlated with systolic blood pressure (SBP), diastolic blood pressure (DBP), high density lipoprotein (HDL), triglycerides (TG), insulin, and HOMA-IR. For the whole sample, neck circumference was positively correlated with all cardiometabolic risk factors except for total cholesterol and low density lipoprotein (LDL) (P<0.001). Moreover, compared to body fat percentage, BMI, and WC, neck circumference has the highest correlation with all cardiometabolic risk factors for the whole sample and in the overweight and obese groups, but not in the normal group (**Table 11**).

After controlling for the effects of age, menopausal status, hormone use, dietary habits and practices, as well as physical activity and lifestyle in women, multivariate regression analyses were used to examine the independent association of neck circumference with cardiometabolic risk factors. **Table 12** illustrates the results of the multivariate regression analyses conducted by using separately each cardiometabolic risk factor as the dependent variable, while all listed covariates were entered in first block of the model. In the second block, the independent variable (neck circumference) was added to the model. Neck circumference was associated with all risk factors, except for LDL cholesterol (Models 1). After further adjustment for BMI (Models 2), R-squared changes were slightly increased for fasting glucose and total cholesterol (0.041, 0.016, respectively). On the other hand, the R-squared changes were attenuated for SBP, DBP, HDLc, insulin, and HOMA-IR, but still remained significantly associated with all risk factors. For example, among women, an incremental increase in neck circumference of 1 standard deviation (SD) was associated with a 4.87 mm Hg increase (P<0.001) in SBP in the primary model. Upon further adjustment for BMI (Models 2), the increase in SBP became 4.33 mm Hg (P<0.001) per 1 SD incremental increase in neck circumference. In Models 3, which adjusted for WC, the neck circumference β-coefficients were also increased for DBP, fasting glucose, and total cholesterol. The R-squared changes were attenuated for SBP, DBP, triglycerides, HDLc, insulin, and HOMA-IR, but remained highly statistically significant for all risk factors (all P<0.001 except for TC and HDLc, P<0.05). In Models 4, which adjusted for BMI and WC, the R-squared changes showed the same trend as the previous models 3 and 4 (that adjusted for BMI or WC). In Models 5, which adjusted for BMI, WC, and body fat percentage, the predictive power, as

adjusted R-squares, for these models were the highest. However, the R-squared change increased only for fasting glucose (R^2 *change*=0.048, P<0.001) **(Table 12)**. Moreover, in **Table 13,** regression models were constructed by considering cardiometabolic risk factors separately as dependent variable, and BMI, WC, NC, and body fat percentage were the four independent variables (entered in the second block). All confounders (age, postmenopausal status, hormone use, dietary habits and practices, physical activity and lifestyle, and the medications intake) were controlled (entered in the first block). Neck circumference showed the highest β-coefficients for all risk factors except for HDLc and LDL cholesterols (P<0001 for all, P<0.01 for total cholesterol).

Figures 7 to **13**, present an analysis of the interaction between tertiles of neck circumference and BMI subgroups (normal, overweight, and obese) on cardiometabolic risk factor levels in women. Within each subgroup of BMI, there was a stepwise increase in risk factor levels by tertiles of neck circumference. There was no significant interaction between neck circumference and BMI for cardiometabolic risk factors except for insulin (P=0.015) and HOMA-IR (P=0.041) **(Figures 12** and **13)**.

Neck circumference contribution in the prediction of cardiometabolic conditions

Multiple logistic regression analyses were used to estimate the odds ratios (OR) for the development of the cardiometabolic risk factors [central obesity (WC ≥80 cm for women), hypertriglyceridemia (triglycerides ≥1.7 mmol/L or specific treatment for lipid abnormality), low HDLc (<1.29 mmol/L for women or specific treatment for this lipid abnormality), high LDLc (≥4.12 mmol/L or specific treatment for lipid abnormality),

hyperglycemia (fasting plasma glucose ≥5.6 mmol/L or previously diagnosed Type 2 diabetes) and hypertension (systolic BP ≥130 mmHg, diastolic BP ≥85 mmHg or treatment for previously diagnosed hypertension), HOMA-IR >75th (present/absent), metabolic syndrome as per the harmonized criteria (the presence of three or more of the risks), metabolic syndrome as per the IDF criteria (the presence of abdominal obesity and two or more of the risks)] according to the increment increase in neck circumference, and controlling for age, menopausal status, and hormone use **(Table 14, Figure 13)**. Elevated neck circumference was associated with increased ORs of metabolic syndrome and all cardiometabolic risk factors, except for LDLc (all P<0.0001). After the further adjustment of BMI, WC, and body fat percentage, neck circumference remained the independent predictor of all binary cardiometabolic risk factors (all P<0.05).

To determine the dose-response of enlarging neck circumference with cardiometabolic risk, quartiles of neck circumference were derived (cut points for NC were <35 cm, 35 cm–36.5 cm, 36.6 cm–38 cm, >38 cm). The ORs and 95% confidence interval (CI) for metabolic syndrome and its components according to quartiles of neck circumference are presented in **Table 15.** The ORs of metabolic syndrome or its components increased from the 1st to the 4th quartile of neck circumference (*P-trend*, <0.001 for all). Compared with women in the lowest neck quartile, those in the highest quartile had ORs of 8.76 (95% CI: 5.13, 14.96) for hypertension, 15.28 (95% CI: 7.95, 29.36) for elevated fasting plasma glucose, 4.38 (95% CI: 2.67, 7.18) for elevated triglycerides, 3.54 (95% CI: 2.08, 6.02) for reduced HDLc, 3.54 (95% CI: 2.08, 6.03) for elevated LDL cholesterol, 3.10 (95% CI: 1.63, 5.84) for elevated HOMA-IR, 6.34 (95% CI: 3.65, 11.01) for obesity, 27.01 (95% CI: 11.87, 61.46) for central obesity, 17.13 (95%

CI: 8.38, 34.99) for having two or more cardiometabolic risks, and 17.98 (95% CI: 8.79, 36.78) for metabolic syndrome (all $P<0.01$) (Model 1). After adjustment for age, menopausal status, and hormone use (Model 2), similar trends were found in the risk of the components of metabolic syndrome across increasing quartiles of neck circumference, except the Q4 group for high HOMA-IR (all $P< 0.01$). Women in the highest neck circumference quartile were 12 times more likely (95% CI: 5.67, 26.47) to have two or more metabolic risk factors when compared to the lowest neck circumference quartile. Moreover, women with the largest neck were 13 times more likely (95% CI: 6.35, 28.23) to have metabolic syndrome when compared to the lowest neck circumference quartile and after adjustment for the mentioned confounders (all $P<0.01$).

Optimal cut-off points to predict cardiometabolic risks

The receiver operating characteristic (ROC) curves were presented in **Figures 14 –17.** For metabolic syndrome, neck circumference presented the largest area under the curve compared with WC, BMI, and body fat percentage in women, which were 0.796 (0.757–0.836) for neck circumference, and 0.711 (0.667–0.756), 0.659 (0.612–0.706), and 0.587 (0.532–0.642), respectively, for WC, BMI, and body fat percentage (all $P<0.001$, except for body fat percentage, where $P<0.01$).

According to the ROC curve analysis, the optimal neck circumference cutoff values with the highest Youden index (maximum sensitivity and specificity) for predicting the presence of three or more metabolic risk factors was NC=36 cm, Youden index=0.468. However, the shortest distance on the ROC curve from perfect predictor

was for NC=35 cm, distance in ROC curve=0.323. We determined that NC=35.5 cm, with distance in ROC curve=0.327, and Youden index=0.450, should be our neck circumference cut-off point. The accuracy, sensitivity, and specificity of this cutoff were 75%, 78.7%, and 66.3%, respectively (**Table 16**).

To define the optimal WC cutoff values, we located a WC cutoff with the highest Youden index (maximum sensitivity and specificity) for predicting the presence of two or more metabolic risk factors (WC=95.5cm, Youden index=0.319). Since IDF criteria require the presence of central obesity for the diagnosis of metabolic syndrome, we justified choosing a cutoff point that obtains a higher sensitivity. Therefore, we determined that WC=92 cm, with the shortest distance in ROC curve=0.434 and a Youden index=0.318, is our WC cutoff point. This cutoff point has better sensitivity (78.1%) and accuracy (70.7%). The specificity of this cutoff was 53.7% (**Table 17).**

Therefore, the appropriate neck circumference and WC to predict metabolic syndrome in the Saudi female population were 35.5 cm and 92 cm, respectively. Moreover, 27.7 kg/m^2 for women emerged as the optimal cutoff point for BMI with maximum sensitivity and specificity for predicting the presence of three or more metabolic risk factors , Youden index=0.254 and distance in ROC curve=0.504, with a sensitivity and specificity of 84.9% and 40.5%, respectively (**Table 18**).

Prevalence of metabolic syndrome

After applying the modified WC of 92 cm for women, we observed a 23% reduction in the prevalence of central obesity (94.2% to 71.3%). The prevalence of metabolic syndrome as per the harmonized definition in women also decreased from

69.3% to 61.7%. A higher reduction was observed in the prevalence of metabolic syndrome as per the IDF definition (**Table 19**).

When dividing the subjects according to neck circumference dichotomized by 35.5 cm in women, the prevalence of metabolic syndrome, obesity, and central obesity were all significantly higher in the above group (≥35.5 cm) than those in the below groups (<35 cm) (**Table 20**).

We further examined the combined effects between NC (<35.5 cm vs. >35.5 cm, women) and WC (<92 cm vs. >92 cm) or BMI (<25 kg/m^2 vs. >25 kg/m^2) in predicting metabolic syndrome using a stratified analysis (**Figures 18, 19,** and further details available in **Appendix 5**). In the women with high neck circumference values, the ORs (95% CI) of metabolic syndrome for the group with high WC, or BMI, were 8.27 (4.97–13.78), and 11.09 (5.17–23.83), respectively (all P<0.001), which were much greater than those of 1.48–1.91 in the women with low neck circumference values. A high neck circumference value was associated with a significantly greater risk of metabolic syndrome, even in participants with a normal WC or BMI. In addition, the combined effects between NC (<35.5 cm vs. >35.5 cm, women) and WC (<80 cm vs. >80 cm) in predicting metabolic syndrome revealed very high ORs (95% CI) of metabolic syndrome for the group with high neck circumference and high WC, 23.18 (6.57–81.78). It is interesting to find that no women with a small WC had a large neck circumference **(Figure 20)**.

The additive interaction of neck circumference and other anthropometric measures on metabolic syndrome was evaluated. The relative excess risk due to

interaction (RERI) of neck circumference vs. WC or BMI was 2.05(-6.16 - 10.26), and 3.7(-11.6 - 19.01), respectively. The attributable proportions due to interaction (AP) values were 0.25(-0.07 - 0.57) and 0.33(-0.89 - 1.55). The synergy indices (S) were 1.39(0.88 - 1.9), and 1.58(0.202 - 3.677), respectively. These indicated the absence of an additive interaction between neck circumference and other anthropometric measures on metabolic syndrome (**Appendix 5**).

Figure 2. Consort flow diagram for subjects recruited and retained

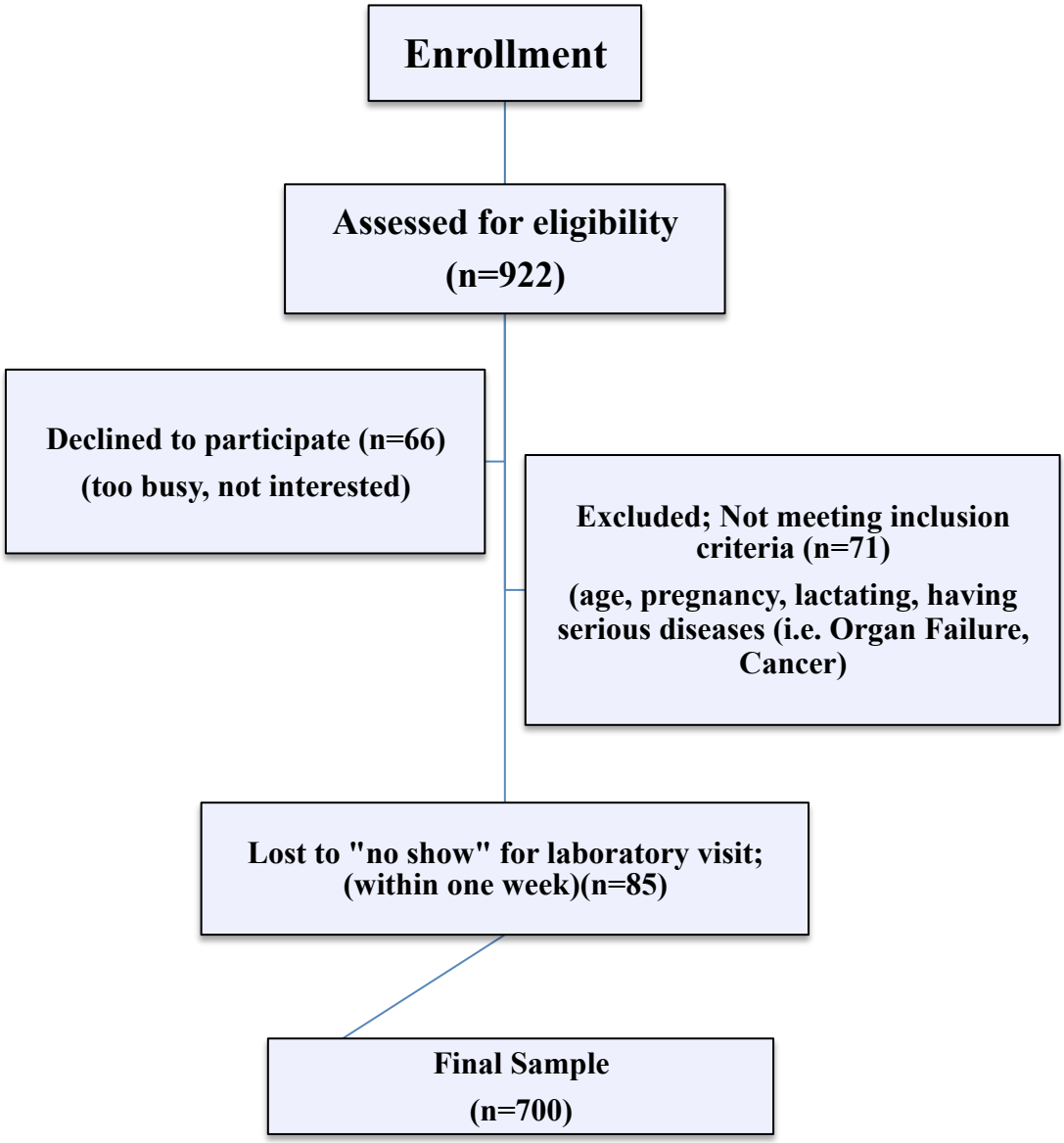


Table 5. Socio – economic and behavioral characteristics of the study subjects

Characteristics	Total	Men N (%) 77 (11%)	Women N (%) 623 (89%)
Age in years			
< 25	21 (3.0)	0 (00.0)	21 (3.4)
25-34	62 (9.0)	1 (1.3)	61 (9.9)
35-44	132 (19.1)	9 (11.9)	123 (20.0)
45-54	299 (43.3)	34 (44.7)	265 (43.0)
>55	177 (25.6)	31 (40.8)	146 (23.7)
Marital Status:			
Unmarried	42 (6.0)	6 (7.9)	37 (5.9)
Married	497 (71.2)	63 (82.9)	434 (69.7)
Separated or divorced	68 (9.8)	2 (2.6)	66 (10.6)
Widowed	91 (13.0)	5 (6.6)	86 (13.8)
Number of parity[¥]:			
None			72 (12.1)
One			12 (2.0)
2-3			76 (12.7)
4-6			190 (31.8)
More than 6			247 (41.4)
Education level:			
Illiterate	166 (23.7)	2 (2.6)	164 (26.3)
Less than high school	287 (41.1)	32 (41.5)	255 (40.9)
Completed high school or diploma	130 (18.5)	35 (45.5)	95 (15.3)
Bachelor degree or higher education	117 (16.7)	8 (10.4)	109 (17.5)
Occupation:			
Unemployed (Housewife)	196 (28.1)	2 (2.6)	194 (31.2)
Student	10 (1.4)	0 (0.0)	10 (1.6)
Teacher	36 (5.2)	4 (5.3)	32 (5.1)
Office work	178 (25.5)	17 (22.4)	161 (25.9)
Business	37 (5.3)	9 (11.8)	28 (4.5)
Medical Doctor	3 (0.4)	0 (0.0)	3 (0.5)
Nurse	5 (0.7)	0 (0.0)	5 (0.8)
Militaries	11 (1.6)	11 (14.5)	0 (0.0)
Retired	112 (16.0)	22 (28.9)	90 (14.5)
Other	110 (15.8)	11 (14.5)	99 (15.9)
Monthly Family Income:			
Less than 10,000	257 (37.0)	6 (8.0)	251 (40.6)
10.000 SR - 19.999 SR	96 (13.8)	4 (5.2)	92 (14.9)
More than 20.000 SR	40 (5.8)	0 (0.0)	40 (6.5)
Un known – No response	301 (43.4)	66 (86.8)	235 (38.0)
Dietary habits and practice:			
Poor	270 (38.6)	46 (59.7)	224 (36.0)
Fair	427 (61.0)	31 (40.3)	396 (63.5)
Good	3 (0.4)	0 (0.0)	3 (0.5)
Physical activity and life style levels:			
Poor	402 (57.4)	56 (72.7)	346 (55.5)
Fair	228 (32.6)	12 (15.6)	216 (34.7)
Good	70 (10.0)	9 (11.7)	61 (9.8)

[¥] Women only

Table 6. Clinical and biochemical characteristics of the study subjects

Parameters Continuous characteristics	All		Men		Women		P-Value	Adjusted for Age
	N	**Mean ± SD**	**N**	**Mean ± SD**	**N**	**Mean ± SD**		
Age in years	691	47.9 ± 10.6	75	52.6 ± 8.7	616	47.3 ± 10.6	0.000	
Height cm	700	155.6 ± 7.4	77	167.4 ± 6.9	623	154.2 ± 6.1	0.000	0.000
Wight kg	700	77.8 ± 15.7	77	82.1 ± 18.0	623	77.3 ± 15.3	0.027	0.059
BMI (kg/m^2)	699	32.1 ± 6.2	76	28.9 ± 4.9	623	32.5 ± 6.2	0.000	0.001
Hip circumference (cm)	695	109.1 ± 12.1	76	102.5 ± 9.4	619	109.9 ± 12.1	0.000	0.000
Waist Hip Ratio (WHR)	690	0.9 ± 0.09	74	1.0 ± 0.05	616	0.90 ± 0.1	0.000	0.000
Waist circumference (cm)	699	99.4 ± 12.9	76	102.9 ± 11.7	623	98.9 ± 13.0	0.011	0.418
Neck circumference (cm)	691	36.7 ± 2.8	77	39.5 ± 2.9	614	36.3 ± 2.6	0.000	0.000
Body Fat%	601	44.5 ± 6.7	74	32.9 ± 4.9	527	46.9 ± 5.1	0.000	0.000
Systolic BP (mm Hg)	692	124.8 ± 17.0	72	128.6 ± 8.3	620	124.3 ± 17.7	0.046	0.357
Diastolic BP (mm Hg)	692	75.3 ± 10.5	74	79.3 ± 5.5	618	74.8 ± 10.8	0.000	0.029
Total cholesterol (mmol/L)	693	5.0 ± 0.9	77	4.7 ± 1.2	616	5.0 ± 0.9	0.004	0.005
Triglycerides¥ (mmol/L)	685	1.51 (1.2- 2.7)	77	1.8 (1.4-2.8)	608	1.5 (1.1-2.0)	0.000	0.058
Fasting glucose# (mmol/L)	683	6.1 (5.1- 8.8)	76	8.3 (6.6-13.6)	607	5.9 (5.1- 8.4)	0.000	0.000
HDL cholesterol (mmol/L)	688	1.2 ± 0.3	75	1.1 ± 0.2	613	1.26 ± 0.3	0.000	0.045
LDL cholesterol (mmol/L)	681	3.4 ± 0.8	75	3.1 ± 0.9	606	3.42 ± 0.8	0.000	0.000
HOMA-IR¥ (mmol/L × µU/mL)★	354	7.7 (4.9-12.2)	23	10.2 (5.1-26.3)	331	7.7 (4.8-11.6)	0.050	0.011
Insulin¥ (µU/mL)★	353	1.9 (1.2- 3.2)	22	2.4 (1.4- 7.6)	331	1.9 (1.2- 3.1)	0.049	0.026

★Excluding diabetes subjects

Data Represent Mean ± SD for Gaussian Variables and Median (25th -75th) percentiles for Non Gaussian variables.

The means of all continuous variables were compared in men and women using independent t test for Gaussian variable and Mann Whitney U test for Non Gaussian variable, and univariate analysis adjusted for age using all non-Gaussian variable transform to normal (log# and SQRT¥).

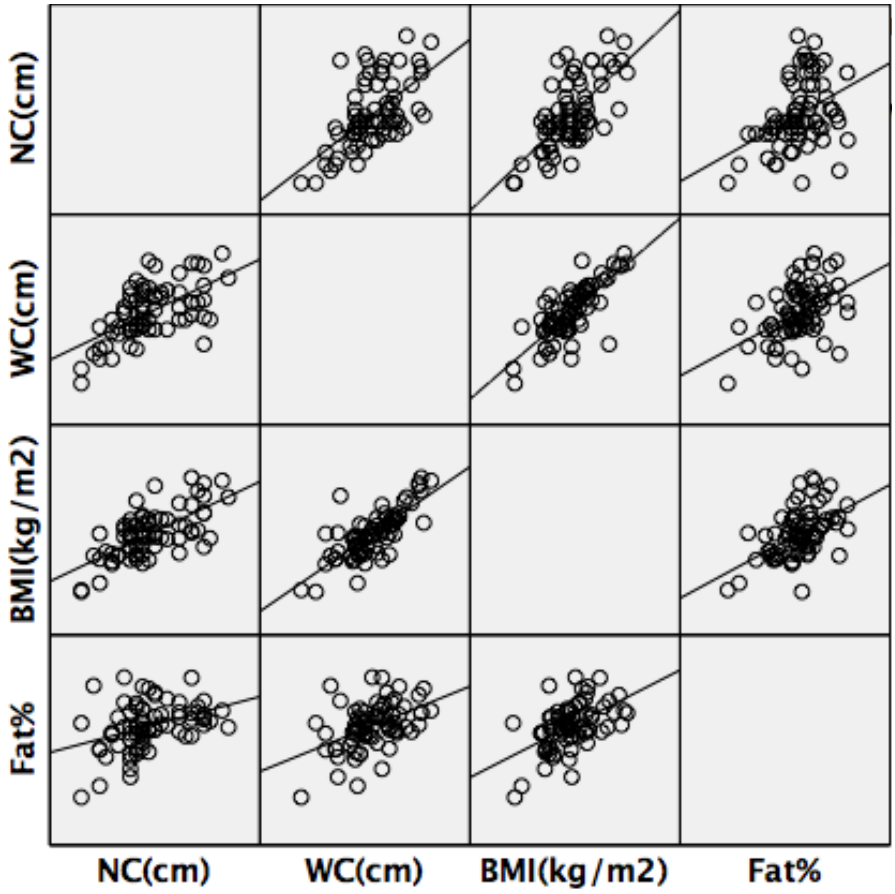
Table 7. Biochemical and medical characteristics of the study subjects

Categorical characteristics **Metabolic risk factors[1]:**	*n*	All *n (%)*	n	Men *n (%)*	n	Women *n (%)*	P-Value
Waist circumference (cm)	699	651 (93.1)	76	64 (83.1)	623	587 (94.2)	0.001
High blood pressure (mmHg**)**	699	313 (44.8)	76	47 (61.0)	623	266 (42.7)	0.002
High fasting glucose (mmol/L) [2]	683	472 (69.1)	77	67 (87.0)	622	406 (65.3)	0.000
High triglycerides (mmol/L) [2]	685	309 (45.1)	77	45 (58.4)	619	264 (42.6)	0.010
Low HDL cholesterol (mmol/L) [2]	688	465 (67.9)	75	38 (49.4)	613	427 (68.9)	0.001
High total cholesterol (mmol/L) [2]	695	270 (38.8)	77	24 (31.2)	618	246 (39.8)	0.172
High LDL cholesterol (mmol/L) [2]	697	257 (36.9)	77	20 (26.0)	620	237 (38.2)	0.044
HOMA-IR ≥75th Percentile[3]	349	103 (29.5)	24	15 (62.5)	325	88 (27.1)	0.001
Medical history:							
Laboratory results							
Pre-diabetes[4] Fasting glucose 6.1-6.9 (mmol/L)	683	82 (19.7)	76	6 (7.9)	607	45 (7.4)	0.000
Diabetes[5] Fasting glucose >7(mmol/L)	683	385 (56.3)	76	60 (78.9)	607	298 (49.1)	0.000
Hypertension	700	313 (44.7)	77	47 (61.0)	623	266 (42.7)	0.002
Reported by subjects							
Pre-diabetes	697	46 (6.6)	77	0 (0.0)	620	46 (7.4)	0.006
Diabetes	697	337 (48.3)	77	50 (64.9)	620	287 (46.2)	0.002
Hypertension	700	100 (14.3)	77	2 (2.6)	623	98 (15.7)	0.001
Treatments: **Diabetes treatment**	700	362 (51.7)	77	50 (64.9)	623	285 (45.7)	0.006
Cholesterol treatment	700	218 (31.1)	77	14 (18.2)	623	204 (32.7)	0.005
Triglycerides treatment	700	76 (10.8)	77	6 (7.8)	623	70 (11.2)	0.584
Metabolic syndrome (harmonized) [6]	699	496 (70.9)	77	65 (84.4)	622	431 (69.3)	0.006
Metabolic syndrome (IDF) [7]	699	489 (69.9)	77	61 (79.2)	622	428 (68.8)	0.060
Current cigarette smoker	700	11 (1.6)	77	6 (7.8)	623	5 (0.8)	0.001
Postmenopausal[¥]				-	623	162 (26.0)	-
Current hormone use[¥]				-	623	33 (5.3)	-
Family history of cardiometabolic diseases:							
Diabetes	692		76	60 (78.9)	616	388 (63.0)	0.006
Hypertension	695		77	33 (42.9)	618	269 (43.5)	0.911
Dyslipidemia	683		77	4 (5.2)	606	71 (11.7)	0.119
Heart diseases	697		77	5 (6.5)	620	56 (9.0)	0.668
Stroke	698		77	0 (0.0)	621	16 (2.6)	0.240

Note: The frequencies of categorical variables were compared in men and women using Chi square and Fisher exact test where appropriate.

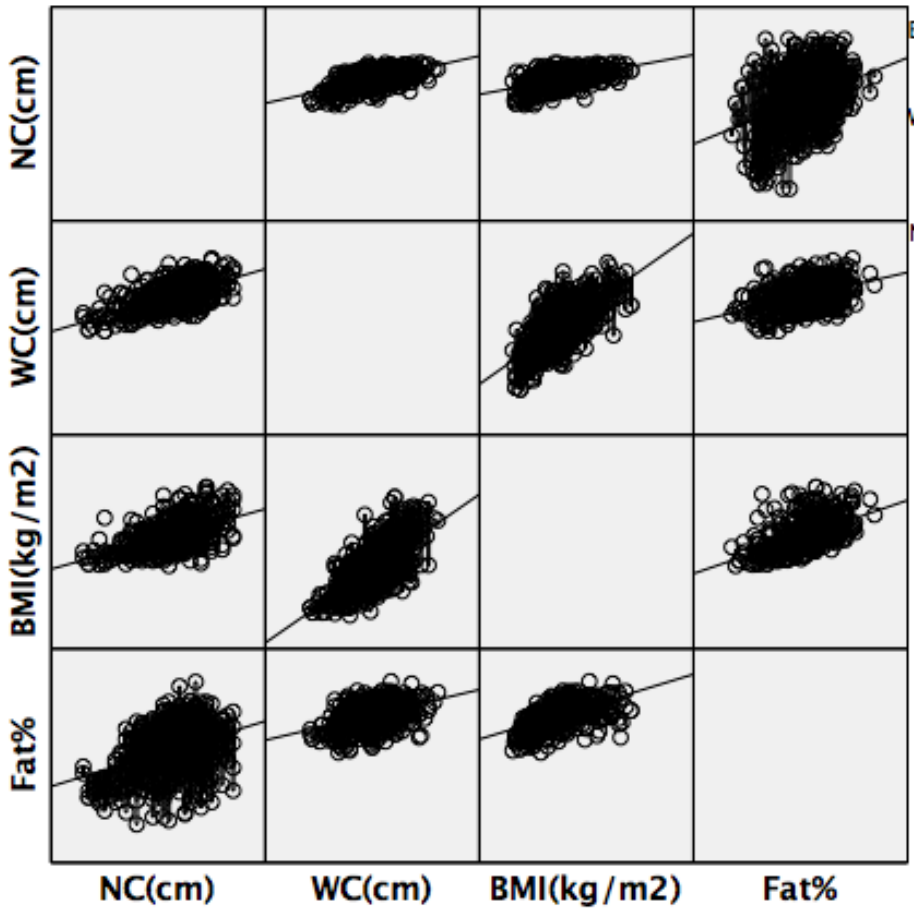
[¥] Women only; 1) Using IDF criteria; 2) high levels or medications use ; 3) Excluding diabetes subjects; 4) Fasting glucose: 6.1-6.9(mmol/L); 5) Fasting glucose: >7(mmol/L) or taking diabetes medications as per ADA ; 6) Metabolic syndrome (harmonized definition) as having 3 or more of the following (WC, TG, HTN, HDLc, GLUC); 7) Metabolic syndrome (IDF criteria) as having abdominal obesity and 2 or more of the following (TG, HTN, HDLc, GLUC)

Figure 3. Scatter plot matrix of the correlation of anthropometric indices in men



BMI= body mass index; **WC=** waist circumference; **NC=** neck circumference; **Fat %=** body fat %.
NC (cm) vs BMI kg/m^2, R_2linear=**0.452;** NC (cm) vs WC (cm), R_2linear=**0.367;** NC (cm) vs body fat%, R_2linear=**0.150**.
WC (cm) vs BMI kg/m^2, R_2linear=**0.593**; WC (cm) vs body fat%, R_2linear=**0.217**.
BMI kg/m^2 vs body fat %, R_2linear=**0.276.**

Figure 4. Scatter plot matrix of the correlation of anthropometric indices in women



BMI: body mass index; **WC:** waist circumference; **NC:** neck circumference; **Fat%:** body fat%.
NC (cm) vs BMI kg/m^2, R_2linear=**0.278;** NC (cm) vs WC (cm), R_2linear=**0.404;** NC (cm) vs body fat%, R_2linear=**0.123**.
WC (cm) vs BMI kg/m^2, R_2linear=**0.489**; WC (cm) vs body fat%, R_2linear=**0.192**.
BMI kg/m^2 vs body fat %, R_2linear=**0.313**.

Table 8. Age adjusted correlation of anthropometric indices

	Over all n=584				Men n=70				Women n=514			
	Body Fat%	**BMI (kg/m^2)**	**WC (cm)**	**NC (cm)**	**Body Fat%**	**BMI (kg/m^2)**	**WC (cm)**	**NC (cm**	**Body Fat%**	**BMI (kg/m^2)**	**WC (cm)**	**NC (cm)**
Body Fat%	1.000	0.528***	0.266***	-0.006	1.000	0.466***	0.364**	0.289*	1.000	0.550***	0.424***	0.326***
BMI (kg/m^2)		1.000	0.676***	0.418***		1.000	0.765***	0.612***		1.000	0.697***	0.516***
WC (cm)			1.000	0.590***			1.000	0.537***			1.000	0.607***
NC (cm)				1.000				1.000				1.000

BMI= body mass index; **WC=** waist circumference; **NC=** neck circumference; **Fat%=** body fat%.
Note: Correlation adjusted for age (years). Data presented as coefficient (R); * denotes significance at 0.05 level; ** denotes significance at 0.01 level; *** denotes significance at 0.001 level.

Table 9. Age adjusted correlation of anthropometric indices by body mass index groups for male subjects

	Over all n=70				Normal weight n=15				Over-weight n=27				Obese n=28			
	Body Fat%	BMI (kg/m^2)	WC (cm)	NC (cm)	Body Fat%	BMI (kg/m^2)	Waist (cm)	Neck (cm)	Body Fat%	BMI (kg/m^2)	Waist (cm)	Neck (cm)	Body Fat%	BMI (kg/m^2)	Waist (cm)	Neck (cm)
Body Fat%	1.000	0.466***	0.364**	0.289*	1.000	0.203	-0.458	-0.294	1.000	0.073	0.587**	0.510**	1.000	-0.012	-0.017	-0.106
BMI (kg/m^2)		1.000	0.765***	0.612***		1.000	0.470	0.592*		1.000	0.317	0.265		1.000	0.553**	0.581**
WC (cm)			1.000	0.537***			1.000	0.715**			1.000	0.408*			1.000	0.214
NC (cm)				1.000				1.000				1.000				1.000

BMI= body mass index; **WC=** waist circumference; **NC=** neck circumference; **Fat%=** body fat%.
Note: Correlation adjusted for age (years). Data presented as coefficient (R); * denotes significance at 0.05 level; ** denotes significance at 0.01 level; *** denotes significance at 0.001 level.

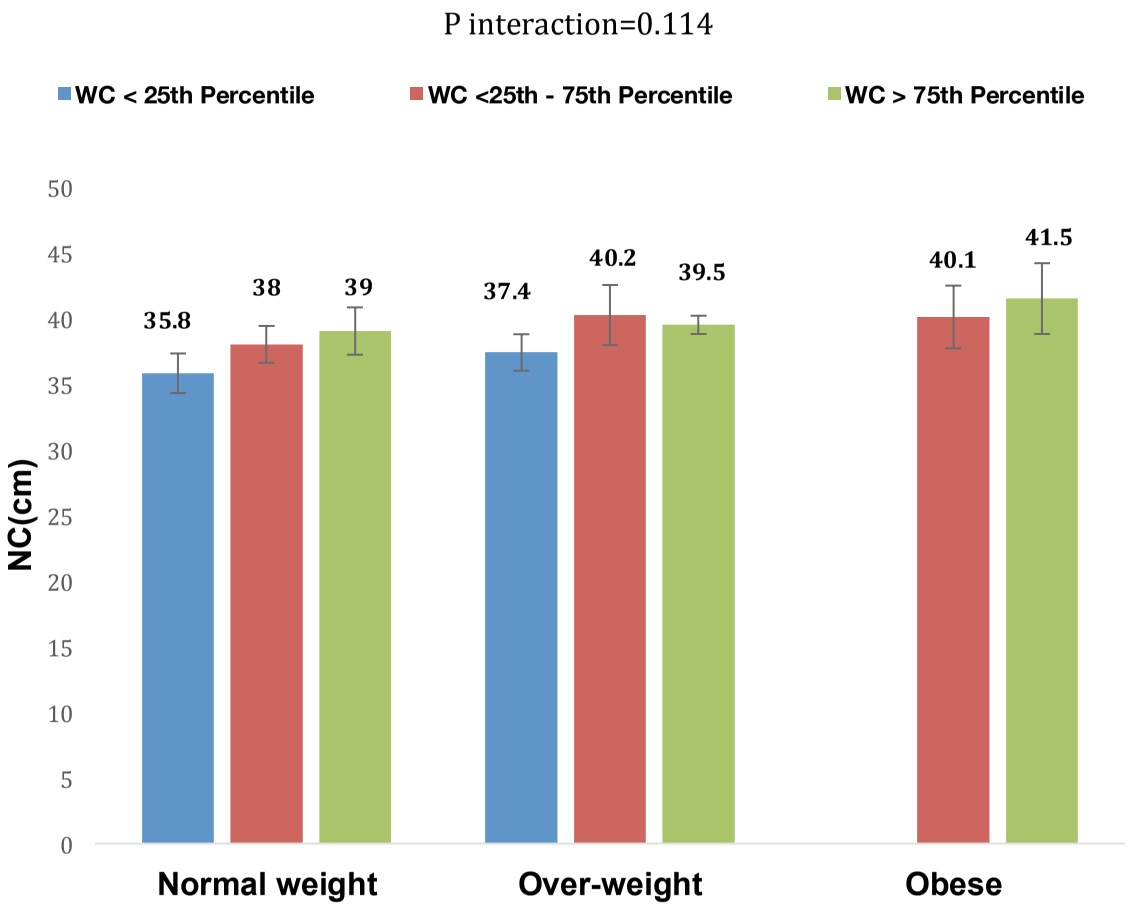
Table 10. Adjusted correlation of anthropometric indices by body mass index groups for female subjects

	Overall n=514				Normal weight n=41				Over-weight n=131				Obese n=342			
	Body Fat%	BMI (kg/m^2)	Waist (cm)	Neck (cm)	Body Fat%	BMI (kg/m^2)	Waist (cm)	Neck (cm)	Body Fat%	BMI (kg/m^2)	Waist (cm)	Neck (cm)	Body Fat%	BMI (kg/m^2)	Waist (cm)	Neck (cm)
Body Fat%	1.000	0.551***	0.424***	0.333***	1.000	0.464**	0.324*	0.261	1.000	0.272**	0.099	0.214*	1.000	0.109*	0.062	0.019
BMI (kg/m^2)		1.000	0.698***	0.523***		1.000	0.390*	0.206		1.000	0.184*	0.431***		1.000	0.559***	0.395***
WC (cm)			1.000	0.605***			1.000	0.511**			1.000	0.410***			1.000	0.514***
NC (cm)				1.000				1.000				1.000				1.000

BMI= body mass index; **WC=** waist circumference; **NC=** neck circumference; **Fat%=** body fat%.

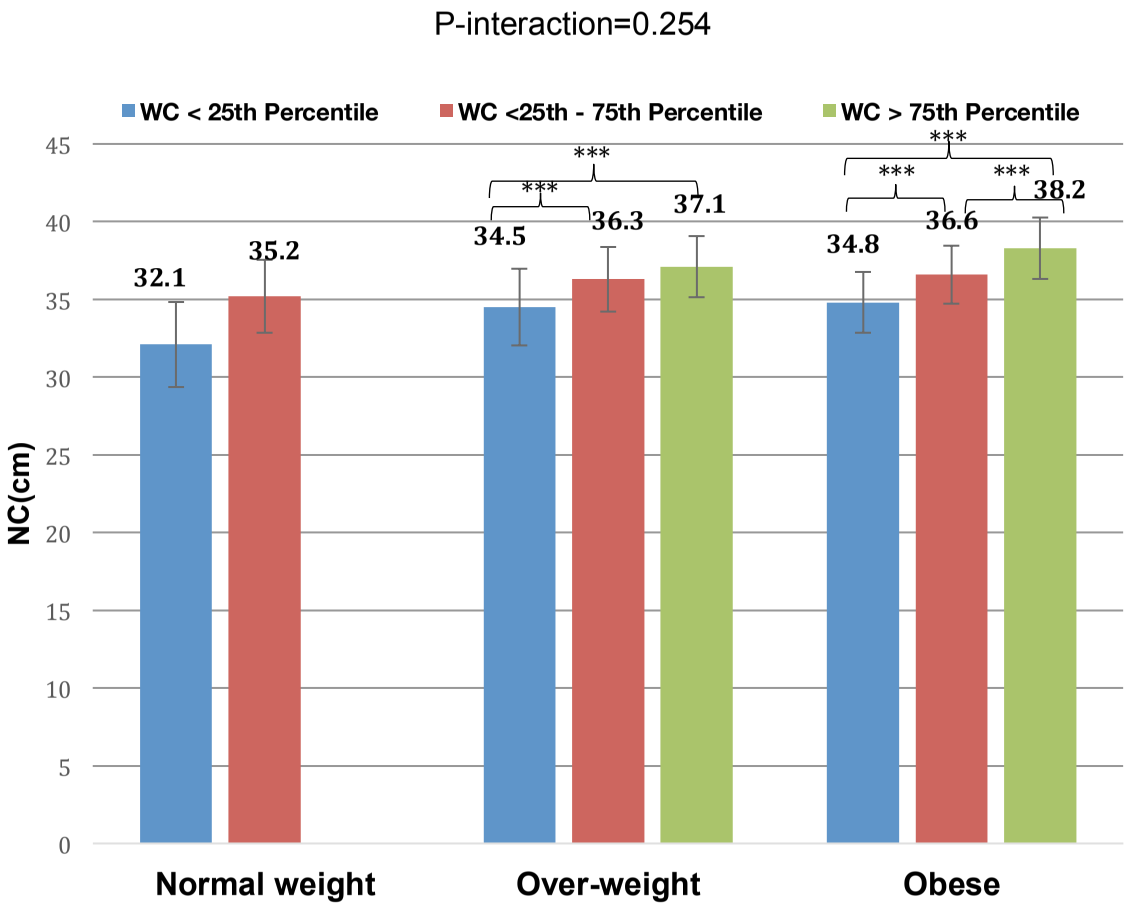
Note: Correlation adjusted for age (years), postmenopausal, and hormones use. Data presented as coefficient (R); * denotes significance at 0.05 level; ** denotes significance at 0.01 level; *** denotes significance at 0.001 level.

Figure 5. Neck circumference levels by waist circumference and body mass index tertiles for men



* No obese men has WC < 25th percentile.
BMI= body mass index= **WC:** waist circumference; **NC=** neck circumference.

Figure 6. Neck circumference levels by waist circumference and body mass index tertiles for women



- No normal weight women has WC > 75th percentile.
BMI= body mass index; **WC=** waist circumference; **NC=** neck circumference.
*** Denotes significance post hoc analysis at 0.001 level

Table 11. Adjusted correlation coefficients between anthropometric indices and cardiometabolic risk factors by body mass index in female subjects

	Overall n=470				Normal n=36				Overweight n=118				Obese n=316			
	Body Fat%	BMI (kg/m^2)	WC (cm)	NC (cm)	Body Fat%	BMI (kg/m^2)	WC (cm)	NC (cm)	Body Fat%	BMI (kg/m^2)	WC (cm)	NC (cm)	Body Fat%	BMI (kg/m^2)	WC (cm)	NC (cm)
SBP	0.080	0.205***	0.242***	0.298***	-0.033	0.055	-0.133	-0.112	-0.040	0.064	0.266**	0.379***	0.027	0.210***	0.235***	0.302***
DBP	0.065	0.156**	0.169***	0.287***	0.302	0.415*	0.005	0.064	-0.046	0.008	0.130	0.319***	-0.001	0.152**	0.157**	0.263***
TC	0.089	-0.005	-0.007	0.070	0.274	0.192	0.442	0.324	0.231	0.069	-0.100	0.098	0.052	-0.038	-0.023	0.021
HDLc	0.058	-0.100*	-0.138**	-0.159***	0.343	0.163	0.095	0.123	0.097	-0.095	-0.164	-0.142	0.149**	-0.050	-0.101	-0.170**
LDLc	0.079	-0.016	-0.043	0.020	0.236	0.126	0.383*	0.243	0.229	0.048	-0.149	0.033	0.071	-0.014	-0.038	-0.002
TG^{v}	0.024	0.138**	0.247***	0.344***	-0.225	0.101	0.354*	0.327	-0.015	0.170	0.305**	0.376***	-0.155*	-0.027	0.130*	0.255***
FG$^{\#}$	-0.101*	0.087	0.142**	0.347***	-0.297	-0.139	-0.003	0.207	-0.235*	-0.010	0.039	0.349***	-0.156**	0.079	0.157**	0.355***
	n= 244				n= 29				n= 60				n= 155			
HOMA-IR*	0.215**	0.194**	0.252***	0.420***	0.152	-0.337	-0.004	0.043	0.186	0.088	0.175	0.376**	-0.007	-0.024	0.116	0.378***
Insulin*	0.232***	0.222**	0.280***	0.385***	0.164	-0.378	-0.008	-0.011	0.172	0.072	0.216	0.322*	0.011	0.012	0.139	0.347***

BMI: body mass index= WC= waist circumference; NC= neck circumference; SBP= Systolic BP (mm Hg), DBP= Diastolic BP (mm Hg), TC= Total Cholesterol (mmol/L), TG: Triglycerides (mmol/L), FG= Fasting glucose (mmol/L), HDLc= high density lipoprotein Cholesterol (mmol/L), LDLc= low density lipoprotein Cholesterol (mmol/L), HOMA-IR= homeostasis model assessment of insulin resistance (mmol/L × μU/mL).

Note: Correlation adjusted for age (years), postmenopausal, hormones use. Data presented as coefficient (R); * denotes significance at 0.05 level; ** denotes significance at 0.01 level; *** denotes significance at 0.001 level; $^{\#}$ log and ^{v} SQRT transformed values; * Excludes individuals with diabetes.

Table 12. The associations of neck circumference with metabolic and cardiovascular disease risk factors, using multiple linear regression analysis

Dependent Variables	Independent Variables	β (SE)	P-Value	Adjusted R^2	R Square Change
SBP [a]	Model 1	4.87(0.705)	<0.001	0.200**	0.063**
	Model 2	4.33(0.824)	<0.001	0.201**	0.037**
	Model 3	3.98(0.869)	<0.001	0.203**	0.028**
	Model 4	3.91(0.888)	<0.001	0.202**	0.026**
	Model 5	4.18(0.952)	<0.001	0.217**	0.030**
DBP [a]	Model 1	3.38(0.462)	<0.001	0.103**	0.080**
	Model 2	3.25(0.541)	<0.001	0.101**	0.054**
	Model 3	3.47(0.570)	<0.001	0.101**	0.055**
	Model 4	3.38(0.583)	<0.001	0.100**	0.050**
	Model 5	3.50(0.641)	<0.001	0.110**	0.052**
Glucose[# b]	Model 1	0.035(0.006)	<0.001	0.340**	0.035**
	Model 2	0.044(0.007)	<0.001	0.345**	0.041**
	Model 3	0.045(0.008)	<0.001	0.344**	0.039**
	Model 4	0.047(0.008)	<0.001	0.345**	0.041**
	Model 5	0.051(0.008)	<0.001	0.354**	0.048**
Triglycerides[v c]	Model 1	0.040(0.005)	<0.001	0.140**	0.094**
	Model 2	0.047(0.006)	<0.001	0.146**	0.094**
	Model 3	0.037(0.006)	<0.001	0.140**	0.052**
	Model 4	0.042(0.006)	<0.001	0.154**	0.062**
	Model 5	0.041(0.007)	<0.001	0.162**	0.066**
Cholesterol [d]	Model 1	0.121(0.041)	0.002	0.026**	0.014*
	Model 2	0.154(0.048)	0.001	0.027**	0.016*
	Model 3	0.157(0.051)	0.002	0.027**	0.015*
	Model 4	0.165(0.052)	0.002	0.026**	0.016*
	Model 5	0.155(0.058)	0.002	0.034**	0.014*
HDL cholesterol [d]	Model 1	-0.037(0.016)	0.003	0.038**	0.014*
	Model 2	-0.036(0.016)	0.022	0.036**	0.009*
	Model 3	-0.037(0.016)	0.023	0.036**	0.008*
	Model 4	-0.036(0.017)	0.033	0.034**	0.007*
	Model 5	-0.031(0.018)	0.082	0.048**	0.006
LDL cholesterol [d]	Model 1	0.049(0.038)	0.198	0.040**	0.003
	Model 2	0.066(0.045)	0.139	0.040**	0.004
	Model 3	0.070(0.047)	0.135	0.040**	0.004
	Model 4	0.073(0.048)	0.124	0.038**	0.004
	Model 5	0.061(0.052)	0.241	0.036**	0.003
HOMA-IR [v e]	Model 1	0.266(0.033)	<0.001	0.186**	0.170**
	Model 2	0.265(0.039)	<0.001	0.183**	0.122**
	Model 3	0.252(0.040)	<0.001	0.184**	0.105**
	Model 4	0.256(0.041)	<0.001	0.182**	0.101**
	Model 5	0.243(0.047)	<0.001	0.154**	0.094**
Insulin [v e]	Model 1	0.466(0.058)	<0.001	0.170**	0.168**
	Model 2	0.441(0.069)	<0.001	0.169**	0.109**
	Model 3	0.417(0.070)	<0.001	0.171**	0.093**
	Model 4	0.417(0.073)	<0.001	0.169**	0.087**
	Model 5	0.387(0.084)	<0.001	0.139**	0.074**

BMI= body mass index; WC= waist circumference; NC= neck circumference; SBP= Systolic BP (mm Hg); DBP= Diastolic BP (mm Hg); TC= Total Cholesterol (mmol/L); TG= Triglycerides (mmol/L); FG= Fasting glucose (mmol/L); HDLc= high density lipoprotein cholesterol (mmol/L) LDLc= low density lipoprotein cholesterol (mmol/L; HOMA-IR= homeostasis model assessment of insulin resistance (mmol/L × μU/mL). **Model 1:** one dependent (cardiometabolic risk factor), one independent (NC) (in the second block), controlling for confounders (age, dietary habit & practices, activity level & life style, postmenopausal status, and hormone use) (in the first block). **Model 2:** one dependent, one independent (NC) (in the second block), controlling for confounders (age, dietary habit & practices, activity level & life style, postmenopausal status, hormone use, and BMI) (in the first block). **Model 3:** one dependent one independent (NC) (in the second block), controlling for confounders (age, dietary habit & practices, activity level & life style, postmenopausal status, hormone use, and WC) (in the first block). **Model 4:** one dependent, one independent (NC) (in the second block), controlling for confounders (age, dietary habit & practices, activity level & life style, postmenopausal status, hormone use, BMI, and WC) (in the first block). **Model 5:** one dependent, one independent (NC) (in the second block), controlling for confounders (age, dietary habit & practices, activity level & life style, postmenopausal status, hormone use, BMI, WC and Fats (in the first

block). Additionally adjusted for (a) Hypertension treatment (b) diabetes treatment, (c) hyperlipidemia treatment (d) Hyper cholesterol. (e) Excludes individuals with diabetes. **#** Log and **V** SQRT transformed values.

R square change is the amount of the increase in predictive power after entering the NC to the model (second block). * denotes significance at 0.05 level; ** denotes significance at 0.01 level; *** denotes significance at 0.001 level.

Table 13. The associations of anthropometrics indices with metabolic and cardiovascular disease risk factors, using multiple linear regression analysis

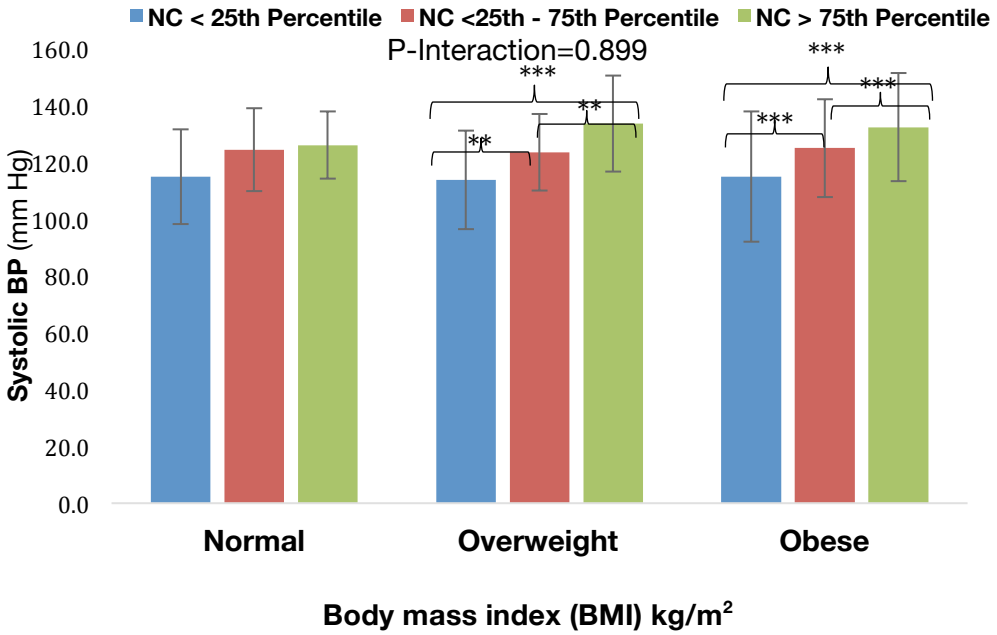
Dependent Variables	Independent Variable	β (SE)	P-Value	Adjusted R^2	R Square Change
SBP [a]					
	NC	4.189(0.952)	0.000	0.217	0.082**
	Waist	1.638(1.165)	0.160		
	BMI	1.117(1.116)	0.317		
	Fats%	-1.201(0.883)	0.174		
DBP [a]					
	NC	3.502(0.641)	0.000	0.110	0.089**
	Waist	-0.323(0.775)	0.677		
	BMI	0.919(0.745)	0.218		
	Fat%	-0.611(0.588)	0.300		
Glucose [# b]					
	NC	0.051(0.008)	0.000	0.354	0.058**
	Waist	-0.013(0.010)	0.176		
	BMI	0.001(0.009)	0.900		
	Fat%	-0.023(0.007)	0.002		
Triglycerides [v c]					
	NC	0.041(0.007)	0.000	0.162	0.127**
	Waist	0.020(0.008)	0.012		
	BMI	-0.013(0.008)	0.098		
	Fat%	-0.010(0.006)	0.090		
Cholesterol [d]					
	NC	0.155(0.058)	0.007	0.034	0.022*
	Waist	-0.061(0.071)	0.389		
	BMI	-0.068(0.067)	0.307		
	Fat%	0.093(0.054)	0.083		
HDL Cholesterol [d]					
	NC	-0.031(0.018)	0.082	0.049	0.024*
	Waist	-0.017(0.022)	0.453		
	BMI	-0.018(0.021)	0.394		
	Fat%	0.043(0.017)	0.009		
LDL Cholesterol [d]					
	NC	0.066(0.049)	0.178	0.036	0.007
	Waist	-0.065(0.061)	0.291		
	BMI	-0.027(0.064)	0.676		
	Fat%	0.061(0.052)	0.241		
HOMA-IR[v e]					
	NC	0.243(0.047)	0.000	0.154	0.167**
	Waist	0.021(0.055)	0.707		
	BMI	-0.025(0.055)	0.646		
	Fat%	0.023(0.048)	0.636		
Insulin[v e]					
	NC	0.387(0.084)	0.000	0.139	0.154**
	Waist	0.078(0.099)	0.432		
	BMI	-0.022(0.100)	0.822		
	Fat%	0.034(0.088)	0.702		

BMI= body mass index; WC= waist circumference; NC= neck circumference; SBP= Systolic BP (mm Hg), DBP= Diastolic BP (mm Hg), TC= Total Cholesterol (mmol/L), TG= Triglycerides (mmol/L), FG= Fasting glucose (mmol/L), HDLc= high density lipoprotein cholesterol (mmol/L), LDLc= low density lipoprotein cholesterol (mmol/L), HOMA-IR= homeostasis model assessment of insulin resistance (mmol/L × μU/mL).

Models are: one dependent (cardiometabolic risk factor) and four independents (BMI, WC, NC, Fat %) (in the second block), controlling for confounders (age, dietary habit & practices, activity level & life style, postmenopausal status, and hormone use) (in the first block). Additionally adjusted for (a) Hypertension treatment (b) diabetes treatment, (c) hyperlipidemia treatment (d) Hyper cholesterol. (e) Excludes individuals with diabetes. **#** Log and **V** SQRT transformed values.

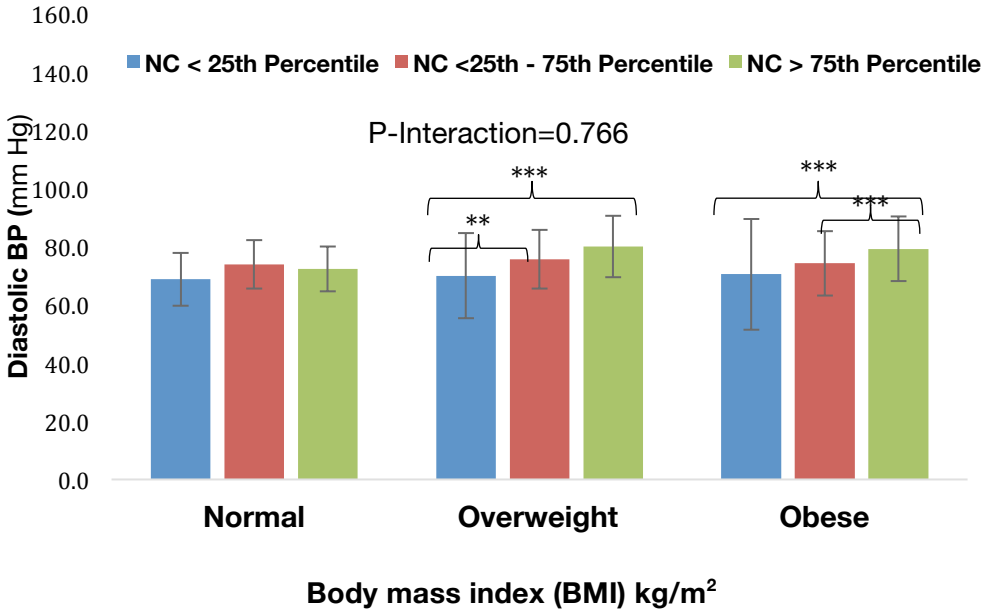
R square change is the amount of the increase in predictive power after entering the NC to the model (second block). * denotes significance at 0.05 level; ** denotes significance at 0.01 level; *** denotes significance at 0.001 level.

Figure 7. Systolic blood pressure levels by neck circumference and body mass index subgroups for women



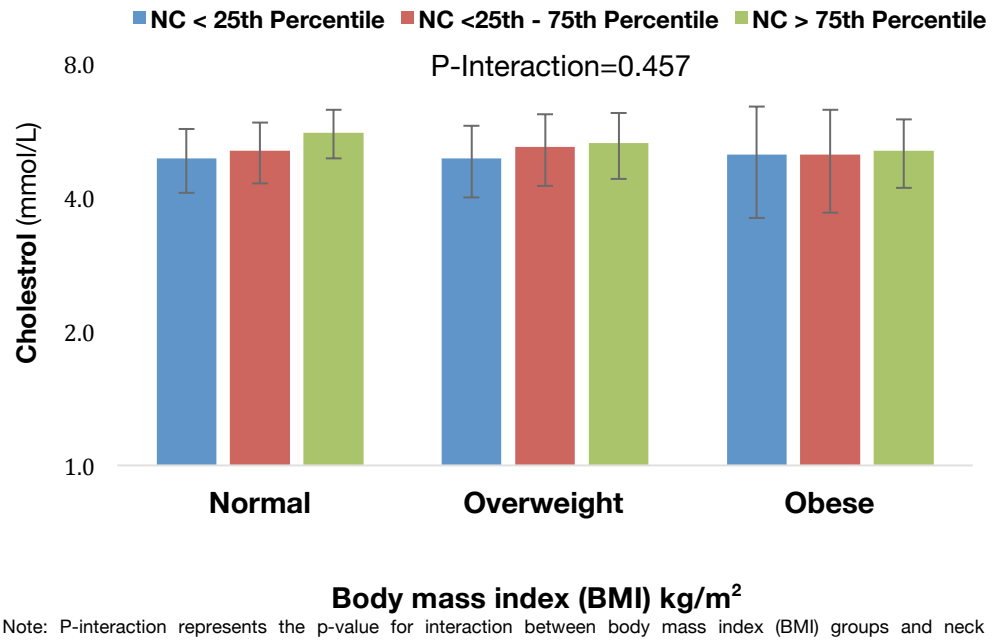
Note: P-interaction represents the p-value for interaction between body mass index (BMI) groups and neck circumference levels (tertiles); all means are adjusted for age (years), postmenopausal, hormones use; ** Denotes significance post hoc analysis at 0.01 level; *** denotes significance at 0.001 level.
NC= neck circumference

Figure 8. Diastolic blood pressure levels by neck circumference and body mass index subgroups for women



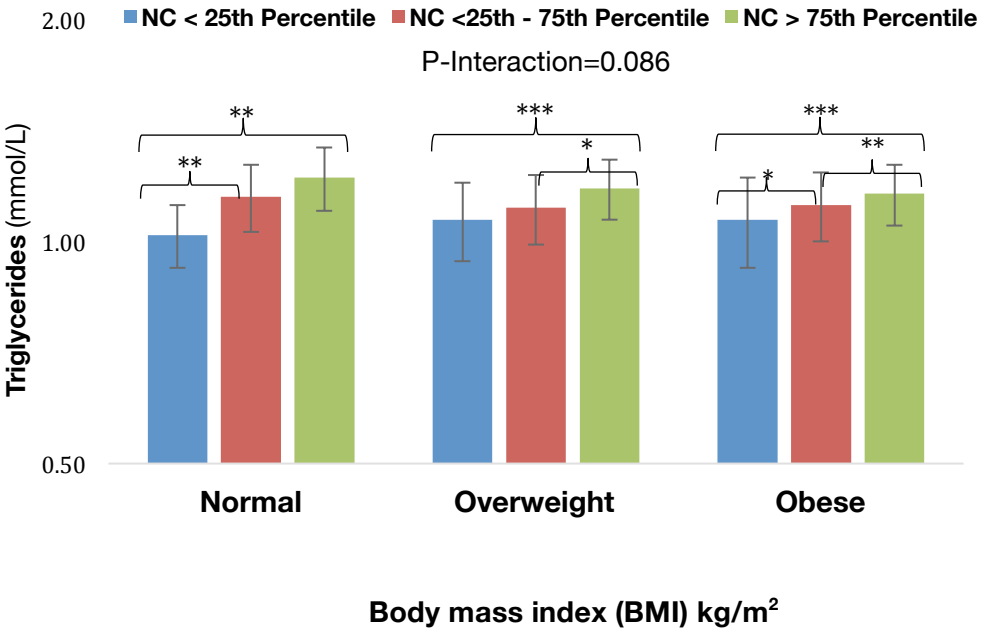
Note: P-interaction represents the p-value for interaction between body mass index (BMI) groups and neck circumference levels (tertiles); all means are adjusted for age (years), postmenopausal, hormones use; ** Denotes significance post hoc analysis at 0.01 level; *** Denotes significance at 0.001 level.
NC= neck circumference

Figure 9. Total Cholesterol levels by neck circumference and body mass index subgroups for women



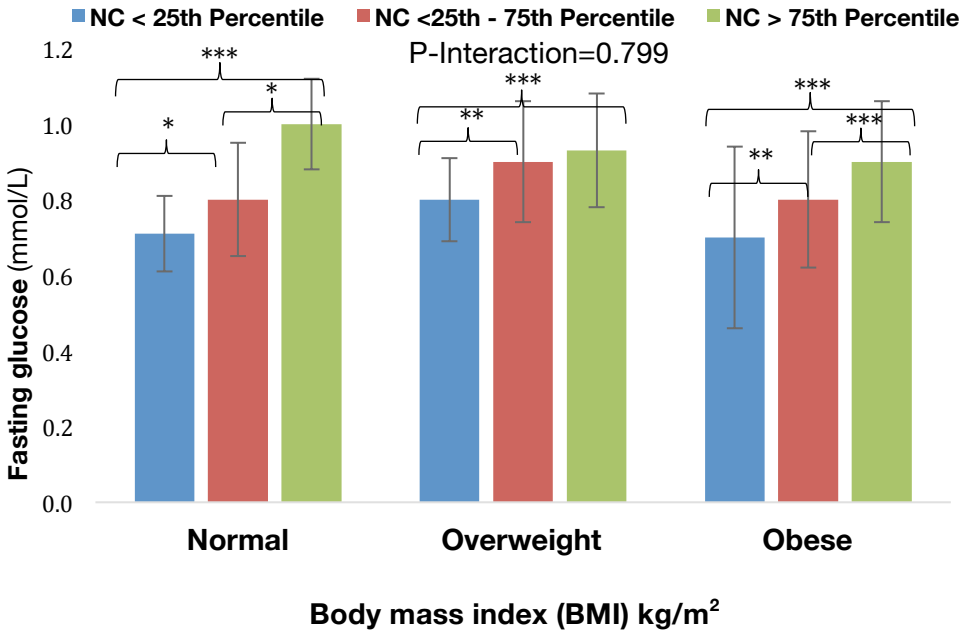
Note: P-interaction represents the p-value for interaction between body mass index (BMI) groups and neck circumference levels (tertiles); all means are adjusted for age (years), postmenopausal, hormones use.
NC= neck circumference

Figure 10. SQRT triglycerides levels by neck circumference and body mass index subgroups for women



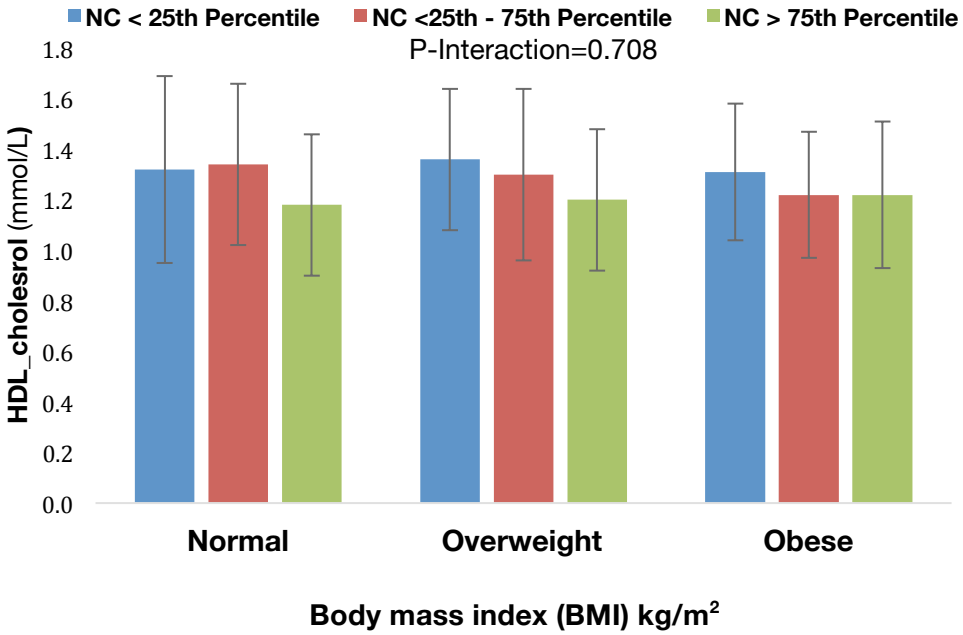
Note: P-interaction represents the p-value for interaction between body mass index (BMI) groups and neck circumference levels (tertiles); all means are adjusted for age (years), postmenopausal, hormones use; * denotes significance post hoc analysis at 0.05 level; ** denotes significance at 0.01 level; *** denotes significance at 0.001 level.
NC= neck circumference

Figure 11. Log fasting glucose levels by neck circumference and body mass index subgroups for women



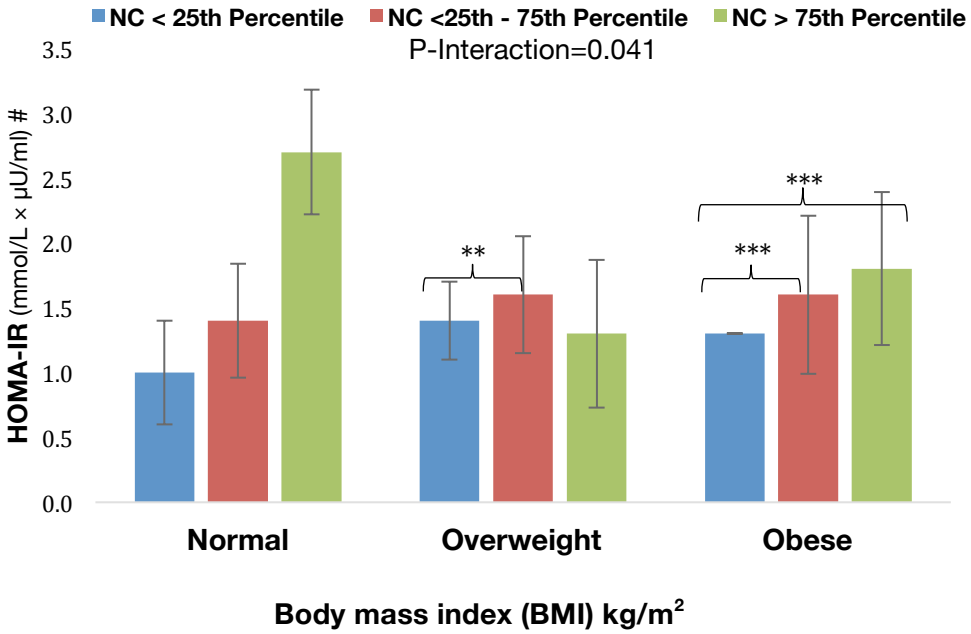
Note: P-interaction represents the p-value for interaction between body mass index (BMI) groups and neck circumference levels (tertiles); all means are adjusted for age (years), postmenopausal, hormones use; * denotes significance post hoc analysis at 0.05 level; ** denotes significance at 0.01 level; *** denotes significance at 0.001 level.
NC= neck circumference

Figure 12. HDL cholesterol levels by neck circumference and body mass index subgroups for women



Note: P-interaction represents the p-value for interaction between body mass index (BMI) groups and neck circumference levels (tertiles); all means are adjusted for age (years), postmenopausal, hormones use.
NC= neck circumference

Figure 13. SQRT HOMA-IR levels by neck circumference and body mass index subgroups for women



Note: P-interaction represents the p-value for interaction between body mass index (BMI) groups and neck circumference levels (tertiles); all means are adjusted for age (years), postmenopausal, hormones use; ** denotes significance post hoc analysis at 0.01 level; *** denotes significance at 0.001 level.

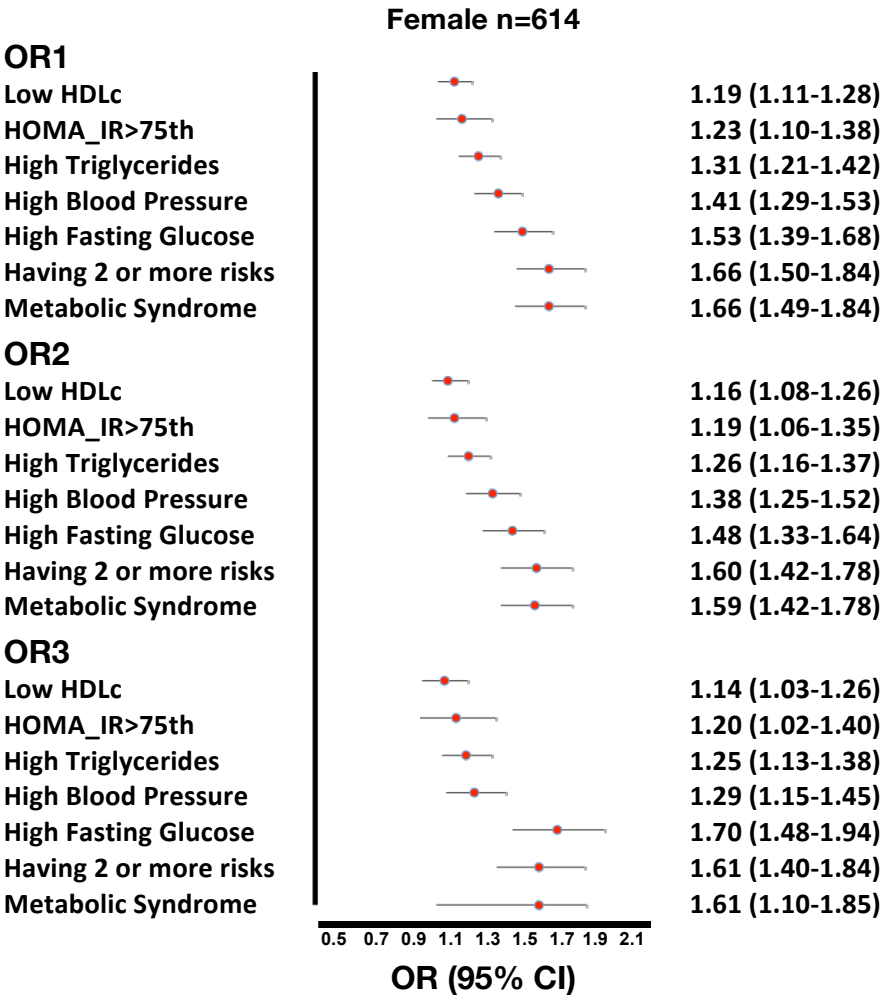
Exclude individual with diabetes; **NC=** neck circumference.

Table 14. Multiple binary logistic regression analysis, using each cardiovascular disease risk as the dependent variable on neck circumference

Dependent Variables		OR(95%CI)	P-Value
Hypertension			
	Model 1	1.38(1.25-1.52)	0.000
	Model 2	1.32(1.18-1.46)	0.000
	Model 3	1.29(1.15-1.45)	0.000
	Model 4	1.29(1.15-1.45)	0.000
Elevated Triglycerides			
	Model 1	1.26(1.16-1.37)	0.000
	Model 2	1.27(1.16-1.40)	0.000
	Model 3	1.25(1.12-1.38)	0.000
	Model 4	1.25(1.13-1.38)	0.000
Elevated fasting glucose			
	Model 1	1.48(1.33-1.64)	0.000
	Model 2	1.62(1.43-1.84)	0.000
	Model 3	1.67(1.46-2.91)	0.000
	Model 4	1.70(1.48-2.94)	0.000
HOMA_IR-Normal>75th			
	Model 1	1.19(1.06-1.35)	0.004
	Model 2	1.21(1.04-1.39)	0.009
	Model 3	1.21(1.03-1.41)	0.017
	Model 4	1.20(1.02-1.40)	0.027
Reduced HDL cholesterol			
	Model 1	1.27 (1.08-1.27)	0.000
	Model 2	1.15(1.05-1.26)	0.002
	Model 3	1.13(1.02-1.24)	0.017
	Model 4	1.14(1.03-1.26)	0.012
Elevated LDL cholesterol			
	Model 1	1.11(1.02-1.19)	0.014
	Model 2	1.08(0.99-1.18)	0.101
	Model 3	1.06(0.96-1.16)	0.270
	Model 4	1.06(0.96-1.16)	0.268
Central obesity			
	Model 1	1.47(1.34-1.62)	0.000
	Model 1+(BMI, Fat%)	1.48(1.29-1.71)	0.000
Having two or more risks			
	Model 1	1.59(1.42-1.78)	0.000
	Model 2	1.59(1.40-1.81)	0.000
	Model 3	1.58(1.34-1.82)	0.000
	Model 4	1.61(1.40-1.85)	0.000
Metabolic Syndrome (harmonize)			
	Model 1	1.59(1.42-1.78)	0.000
	Model 2	1.59(1.40-1.81)	0.000
	Model 3	1.58(1.38-1.82)	0.000
	Model 4	1.61(1.40-1.85)	0.000
Metabolic Syndrome (IDF)			
	Model 1	1.61(1.44-1.81)	0.000
	Model 2	1.61(1.42-1.83)	0.000
	Model 3	1.59(1.39-1.83)	0.000
	Model 4	1.62(1.41-1.86)	0.000

Note:
Model 1: one dependent, one independent (NC) controlling for confounders (age, postmenopausal status, hormone use dietary habit & practices, activity level & life style).
Model 2: one dependent, one independent (NC) controlling for confounders (age, postmenopausal status, hormone use, dietary habit & practices, activity level & life style, and BMI)
Model 3: one dependent, one independent (NC) controlling for confounders (age, postmenopausal status, hormone use, dietary habit & practices, activity level & life style, BMI, WC)
Model 4: one dependent, one independent (NC) controlling for confounders (age, postmenopausal status, and hormone use, dietary habit & practices, activity level & life style, BMI, WC and Fats)

Figure 14. Multiple binary logistic regression analysis of cardiovascular disease risk factors for neck circumference



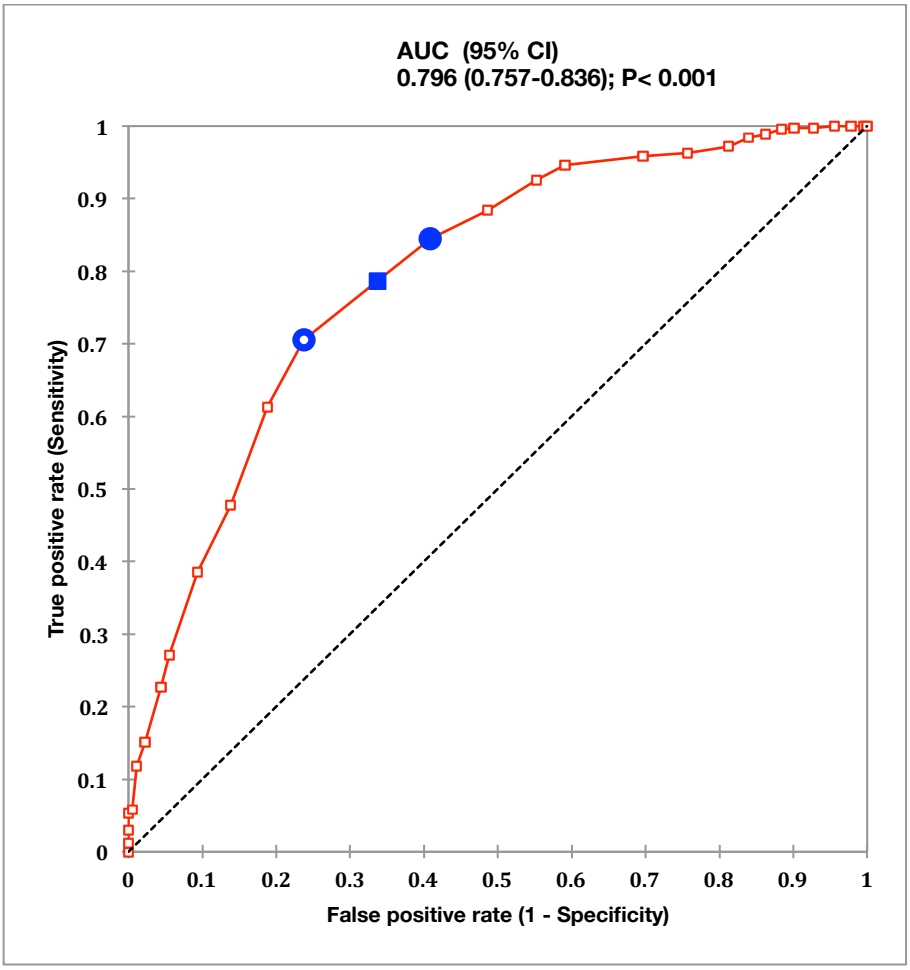
Note: **OR1:** unadjusted, **OR2:** adjusted for age, menopausal status, and hormonal use, eating index, activity index. **OR3:** adjusted for age, menopausal status, hormonal use, BMI, fat%, and WC.

Table 15. Logistic regression analysis of risk for metabolic syndrome and its components by quartile of neck circumference level

		OR(95%CI)		
NC cm Women N (614)	Q1 <35cm 144	Q2 35.0 - 36.5cm 172	Q3 36.6 - 38cm 171	Q4 >38cm 127
	All P-trend<0.0001			
Hypertension				
Model 1	1	3.04(1.82-5.09)**	5.55(3.39- 9.08)**	8.76(5.13-14.96)**
Model 2	1	2.39(1.38-4.12)**	4.77(2.82- 8.07)**	6.76(3.78-12.08)**
High glucose				
Model 1	1	3.14(1.97-4.99)**	7.81(4.74-12.87)**	15.28(7.95-29.36)**
Model 2	1	2.47(1.51-4.05)**	6.85(4.05-11.57)**	11.51(5.81-22.77)**
High Triglycerides				
Model 1	1	1.79(1.11-2.89)*	2.63(1.67- 4.14)**	4.38(2.67- 7.18)**
Model 2	1	1.57(0.96-2.56)	2.30(1.44- 3.66)**	3.37(2.02- 5.65)**
Low HDL cholesterol				
Model 1	1	2.17(1.35-3.49)**	2.60(1.64- 4.13)**	3.54(2.08- 6.02)**
Model 2	1	2.09(1.28-3.42)**	2.36(1.46- 3.81)**	3.28(1.87- 5.75)**
High LDL cholesterol				
Model 1	1	2.17(1.35-3.49)**	2.60(1.64- 4.13)**	3.54(2.08- 6.03)**
Model 2	1	2.09(1.28-3.42)**	2.36(1.46- 3.81)**	3.28(1.87- 5.75)**
HOMA-IR >75th				
Model 1	1	2.98(1.62-5.50)**	3.29(1.83- 5.93)**	3.10(1.63- 5.84)**
Model 2	1	2.67(1.44-4.98)**	2.95(1.62- 5.38)**	2.59(1.34- 5.03)**
Obesity: BMI≥ 30				
Model 1	1	2.58(1.62-4.09)**	4.78(2.97- 7.67)**	6.34(3.65-11.01)**
Model 2	1	2.68(1.67-4.31)**	4.83(2.97- 7.88)**	6.57(3.69-11.70)**
Central-obesity: WC ≥ 92				
Model 1	1	5.37(3.25-8.85)**	10.07(5.89-17.23)**	27.01(11.87-61.46)**
Model 2	1	4.86(2.92-8.12)**	9.07(5.25-15.67)**	23.12(10.00-53.46)**
Having two risks or more				
Model 1	1	3.66(2.27-5.90)**	9.35(5.48-15.98)	17.13(8.38-34.99)**
Model 2	1	2.89(1.74-4.79)**	7.65(4.38-13.38)**	12.57(5.67-26.47)**
Metabolic Syndrome (harmonized)				
Model 1	1	3.84(2.38-6.20)**	9.82(5.74-16.80)**	17.98(8.79-36.78)**
Model 2	1	3.06(1.84-5.08)**	8.13(4.64-14.22)**	13.39(6.35-28.23)**
Metabolic Syndrome (IDF)				
Model 1	1	4.14(2.56-6.69)**	10.58(6.18-18.13)**	19.38(9.47-39.67)**
Model 2	1	3.30(1.98-5.49)**	8.83(5.04-15.49)**	14.55(6.89-30.72)**

Model 1: Unadjusted. **Model 1:** Adjusted for age, postmenopausal status, hormone use dietary habit & practices, activity level & life style. ** represented significant at 0.001 level.

Figure 15. ROC curve for neck circumference to predict the presence of three or more metabolic syndrome risk factors based on IDF definition in women

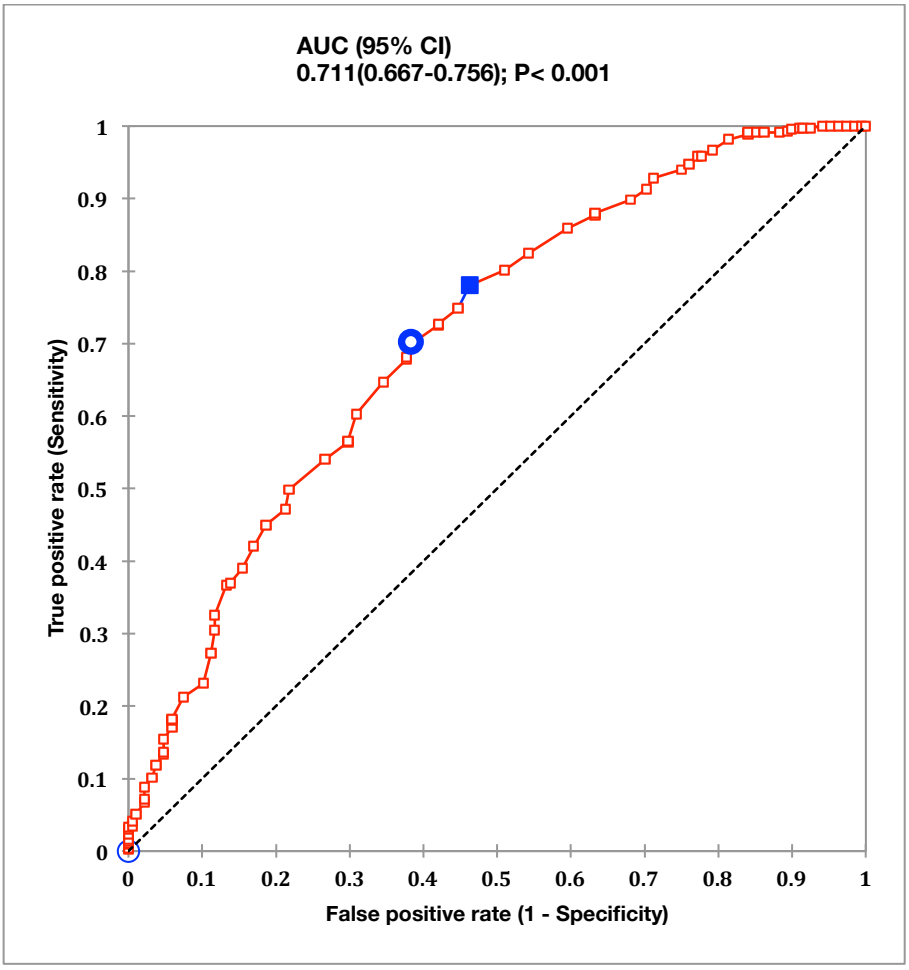


■ Neck circumference cutoff (NC= 35.5cm), with distance in ROC curve=0.327; Youden Index= 0.450, sensitivity= 78.7%; specificity= 66.3%; and accuracy= 75% in predicting the presence of risk factors.

○ Neck circumference cutoff (NC= 35cm), with shortest distance on the ROC curve from perfect predictor (0.323).

● Neck circumference cutoff (NC= 36cm), with highest Youden Index, maximum sensitivity and specificity, (0.468).

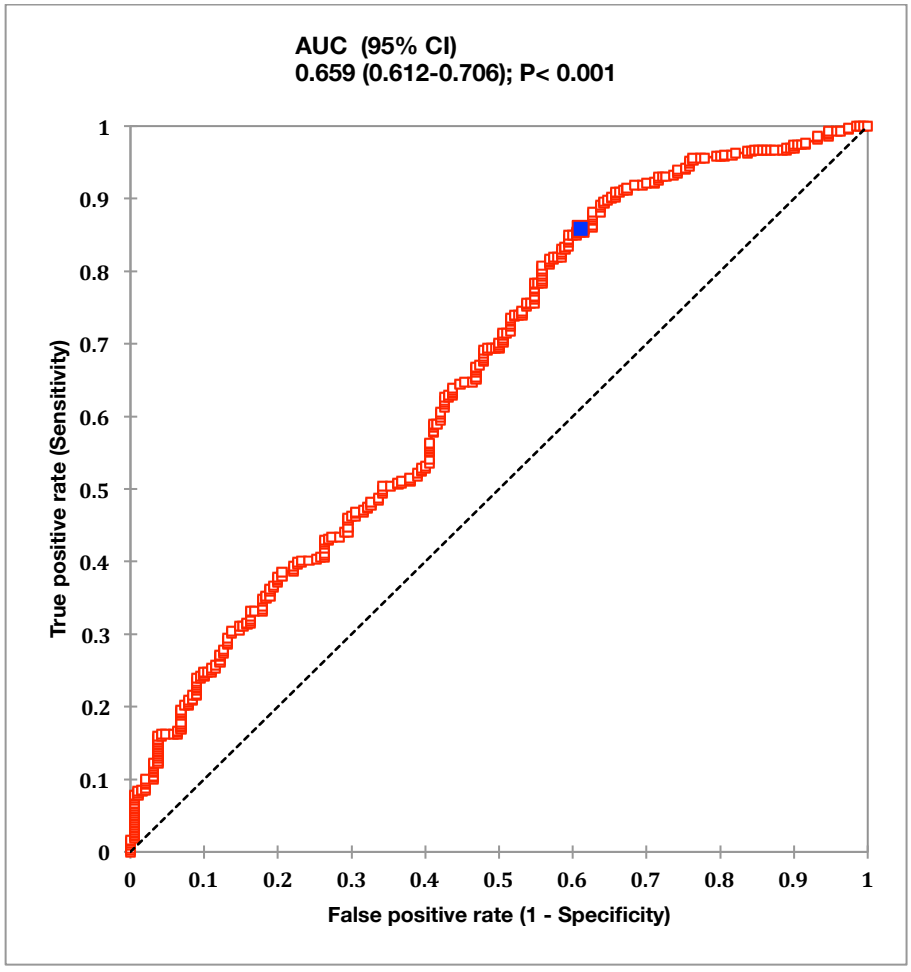
Figure 16. ROC curve for waist circumference to predict the presence of two or more metabolic syndrome risk factors based on IDF definition in women



■ Waist circumference cutoff (WC=92cm) with shortest distance on the ROC curve=0.434; Youden Index= 0.318, sensitivity= 78.1%; specificity= 53.7%; and accuracy= 70.7% in predicting the presence of risk factors. This cutoff has higher sensitivity.

◯ Waist circumference cutoff (WC=95cm) with highest Youden Index, maximum sensitivity and specificity, (0.319).

Figure 17. ROC curve for body mass index to predict the presence of three or more metabolic syndrome risk factors based on IDF definition in women



■ Body mass index cutoff (BMI=27.7kg/m^2) with shortest distance on the ROC curve and 84.9% sensitivity in predicting the presence of risk factors.

Figure 18. ROC curve for body fat percentage to predict the presence of three or more metabolic syndrome risk factors based on IDF definition in women

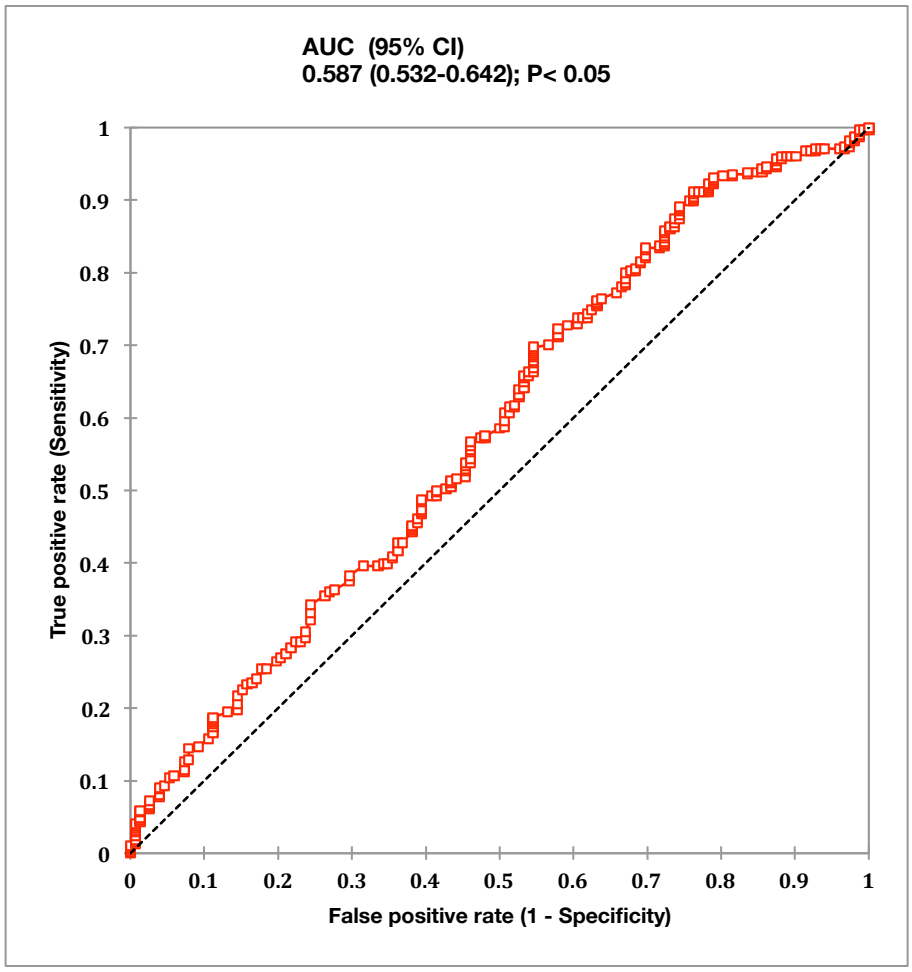


Table 16. Sensitivity, specificity, Youden Index, and distance in receiving operating characteristic (ROC) curve for neck circumference cutoff values in Saudi women*

	3 or more metabolic risk factors																
NC cutoff(cm)	Sensitivity	Lower bound (95%)	Upper bound (95%)	Specificity	Lower bound (95%)	Upper bound (95%)	PPV	NPV	LR+	LR-	TP	TN	FP	FN	Accuracy	Youden Index	Distance in ROC curve
28.000	1.000	0.989	1.000	0.006	0.000	0.034	0.705	1.000	1.006	0.000	431	1	180	0	0.706	0.006	0.989
28.500	1.000	0.989	1.000	0.022	0.007	0.058	0.709	1.000	1.023	0.000	431	4	177	0	0.711	0.022	0.956
29.000	1.000	0.989	1.000	0.044	0.021	0.087	0.714	1.000	1.046	0.000	431	8	173	0	0.717	0.044	0.914
29.500	0.998	0.985	1.000	0.072	0.042	0.120	0.719	0.929	1.075	0.032	430	13	168	1	0.724	0.070	0.864
30.000	0.998	0.985	1.000	0.099	0.063	0.153	0.725	0.947	1.108	0.023	430	18	163	1	0.732	0.097	0.813
30.500	0.995	0.982	1.000	0.116	0.077	0.172	0.728	0.913	1.126	0.040	429	21	160	2	0.735	0.111	0.786
31.000	0.988	0.972	0.996	0.138	0.095	0.197	0.732	0.833	1.147	0.084	426	25	156	5	0.737	0.127	0.754
31.500	0.984	0.966	0.993	0.160	0.114	0.221	0.736	0.806	1.171	0.101	424	29	152	7	0.740	0.144	0.722
32.000	0.972	0.951	0.984	0.188	0.138	0.252	0.740	0.739	1.197	0.148	419	34	147	12	0.740	0.160	0.687
32.500	0.963	0.940	0.977	0.243	0.186	0.311	0.752	0.733	1.272	0.153	415	44	137	16	0.750	0.206	0.610
33.000	0.958	0.934	0.974	0.304	0.242	0.375	0.766	0.753	1.377	0.137	413	55	126	18	0.765	0.262	0.526
33.500	0.947	0.921	0.964	0.409	0.340	0.482	0.792	0.763	1.601	0.131	408	74	107	23	0.788	0.355	0.403
34.000	0.926	0.897	0.947	0.448	0.377	0.520	0.800	0.717	1.676	0.166	399	81	100	32	0.784	0.373	0.379
34.500	0.884	0.850	0.911	0.514	0.441	0.586	0.812	0.650	1.818	0.226	381	93	88	50	0.775	0.398	0.352
35.000	**0.845**	**0.807**	**0.876**	**0.591**	**0.518**	**0.660**	**0.831**	**0.615**	**2.066**	**0.263**	**364**	**107**	**74**	**67**	**0.770**	**0.436**	**0.323**
35.500	0.787	0.745	0.823	0.663	0.591	0.728	0.848	0.566	2.334	0.322	339	120	61	92	0.750	0.450	0.327
36.000	**0.705**	**0.661**	**0.746**	**0.762**	**0.695**	**0.819**	**0.876**	**0.521**	**2.969**	**0.386**	**304**	**138**	**43**	**127**	**0.722**	**0.468**	**0.351**
36.500	0.613	0.566	0.657	0.812	0.748	0.862	0.886	0.468	3.261	0.477	264	147	34	167	0.672	0.425	0.423
37.000	0.478	0.431	0.525	0.862	0.803	0.905	0.892	0.409	3.460	0.606	206	156	25	225	0.592	0.340	0.541
37.500	0.385	0.340	0.432	0.906	0.854	0.941	0.907	0.382	4.101	0.679	166	164	17	265	0.539	0.291	0.624
38.000	0.271	0.232	0.315	0.945	0.900	0.971	0.921	0.353	4.913	0.771	117	171	10	314	0.471	0.216	0.732
38.500	0.227	0.190	0.269	0.956	0.913	0.979	0.925	0.342	5.144	0.808	98	173	8	333	0.443	0.183	0.775
39.000	0.151	0.120	0.188	0.978	0.942	0.993	0.942	0.326	6.824	0.868	65	177	4	366	0.395	0.129	0.849
39.500	0.118	0.091	0.153	0.989	0.957	0.999	0.962	0.320	10.709	0.892	51	179	2	380	0.376	0.107	0.881
40.000	0.058	0.039	0.085	0.994	0.966	1.000	0.962	0.307	10.499	0.947	25	180	1	406	0.335	0.052	0.942
40.500	0.053	0.036	0.079	1.000	0.974	1.000	1.000	0.307	+Inf	0.947	23	181	0	408	0.333	0.053	0.947
41.000	0.030	0.017	0.052	1.000	0.974	1.000	1.000	0.302	+Inf	0.970	13	181	0	418	0.317	0.030	0.969
41.500	0.012	0.004	0.028	1.000	0.974	1.000	1.000	0.298	+Inf	0.988	5	181	0	426	0.304	0.012	0.988
42.000	0.000	0.000	0.011	1.000	0.974	1.000		0.296		1.000	0	181	0	431	0.296	0.000	1.00

* Metabolic risk factors were defined according to IDF definition (21): elevated triglycerides, ≥ 150 mg/dL or specific treatment for hypertriglyceridemia; reduced HDL cholesterol, < 40 mg/dL for men and <50 mg/dL for women or specific treatment for this lipid abnormality; elevated blood pressure, systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥85 mmHg or treatment for previously diagnosed hypertension; elevated fasting plasma glucose ≥ 100 mg/dL or previously diagnosed type 2 diabetes. Youden Index= TPF-FPF= Sensitivity+ Specificity -1. Distance in ROC curve = square root of $(1\text{-TPF})^2+ \text{FPF}^2=(1\text{-sensetivity})^2+ (1\text{-specificty})^2$

Table 17. Sensitivity, specificity, Youden Index, and distance in receiving operating characteristic (ROC) curve for waist circumference cutoff values in Saudi women*

	2 or more metabolic risk factors																
WC cutoff(cm)	Sensitivity	Lower bound (95%)	Upper bound (95%)	Specificity	Lower bound (95%)	Upper bound (95%)	PPV	NPV	LR+	LR-	TP	TN	FP	FN	Accuracy	Youden Index	Distance in ROC curve
79.0	0.988	0.972	0.996	0.160	0.114	0.219	0.730	0.857	1.176	0.072	428	30	158	5	0.738	0.148	0.718
80.0	0.982	0.963	0.991	0.186	0.137	0.248	0.735	0.814	1.206	0.099	425	35	153	8	0.741	0.168	0.681
81.0	0.968	0.946	0.981	0.207	0.156	0.272	0.738	0.736	1.221	0.156	419	39	149	14	0.738	0.175	0.660
82.0	0.958	0.935	0.974	0.223	0.170	0.289	0.740	0.700	1.234	0.186	415	42	146	18	0.736	0.182	0.645
82.5	0.958	0.935	0.974	0.229	0.174	0.294	0.741	0.705	1.243	0.182	415	43	145	18	0.738	0.187	0.636
83.0	0.947	0.921	0.965	0.239	0.184	0.306	0.741	0.662	1.245	0.222	410	45	143	23	0.733	0.186	0.632
84.0	0.940	0.913	0.959	0.250	0.194	0.317	0.743	0.644	1.253	0.240	407	47	141	26	0.731	0.190	0.623
85.0	0.928	0.900	0.949	0.287	0.227	0.356	0.750	0.635	1.303	0.249	402	54	134	31	0.734	0.216	0.579
86.0	0.912	0.881	0.936	0.298	0.237	0.367	0.750	0.596	1.299	0.295	395	56	132	38	0.726	0.210	0.581
87.0	0.898	0.866	0.924	0.319	0.257	0.389	0.752	0.577	1.320	0.318	389	60	128	44	0.723	0.218	0.565
88.0	0.880	0.846	0.907	0.367	0.302	0.438	0.762	0.570	1.390	0.327	381	69	119	52	0.725	0.247	0.521
88.5	0.878	0.843	0.905	0.367	0.302	0.438	0.762	0.566	1.386	0.334	380	69	119	53	0.723	0.245	0.523
89.0	0.859	0.823	0.889	0.404	0.337	0.476	0.769	0.555	1.442	0.348	372	76	112	61	0.721	0.263	0.496
90.0	0.824	0.786	0.857	0.457	0.388	0.529	0.778	0.531	1.520	0.384	357	86	102	76	0.713	0.282	0.469
91.0	0.801	0.761	0.836	0.489	0.419	0.560	0.783	0.517	1.569	0.406	347	92	96	86	0.707	0.291	0.459
92.0	**0.781**	**0.739**	**0.817**	**0.537**	**0.466**	**0.607**	**0.795**	**0.515**	**1.687**	**0.408**	**338**	**101**	**87**	**95**	**0.707**	**0.318**	**0.434**
93.0	0.748	0.705	0.787	0.553	0.482	0.622	0.794	0.488	1.675	0.455	324	104	84	109	0.689	0.301	0.451
94.0	0.727	0.684	0.767	0.580	0.508	0.648	0.799	0.480	1.731	0.470	315	109	79	118	0.683	0.307	0.449
94.5	0.725	0.681	0.765	0.580	0.508	0.648	0.799	0.478	1.726	0.474	314	109	79	119	0.681	0.305	0.451
95.0	0.702	0.657	0.743	0.612	0.540	0.678	0.806	0.471	1.808	0.487	304	115	73	129	0.675	0.314	0.448
95.5	**0.702**	**0.657**	**0.743**	**0.617**	**0.546**	**0.683**	**0.809**	**0.473**	**1.833**	**0.483**	**304**	**116**	**72**	**129**	**0.676**	**0.319**	**0.445**
96.0	0.681	0.636	0.723	0.622	0.551	0.688	0.806	0.459	1.804	0.512	295	117	71	138	0.663	0.304	0.461
96.5	0.679	0.634	0.721	0.622	0.551	0.688	0.805	0.457	1.798	0.516	294	117	71	139	0.662	0.301	0.464
97.0	0.647	0.600	0.690	0.654	0.584	0.718	0.812	0.446	1.870	0.540	280	123	65	153	0.649	0.301	0.473
98.0	0.603	0.556	0.648	0.691	0.622	0.753	0.818	0.430	1.954	0.574	261	130	58	172	0.630	0.294	0.492

* Metabolic risk factors were defined according to IDF definition (21): elevated triglycerides, ≥ 150 mg/dL or specific treatment for hypertriglyceridemia; reduced HDL cholesterol, < 40 mg/dL for men and <50 mg/dL for women or specific treatment for this lipid abnormality; elevated blood pressure, systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥85 mmHg or treatment for previously diagnosed hypertension; elevated fasting plasma glucose ≥ 100 mg/dL or previously diagnosed type 2 diabetes. Youden Index= TPF-FPF= Sensitivity+ Specificity -1. Distance in ROC curve = square root of $(1\text{-TPF})^2 + FPF^2 = (1\text{-sensetivity})^2 + (1\text{-specificty})^2$

Table 18. Sensitivity, specificity, Youden Index, and distance in receiving operating characteristic (ROC) curve for body mass index cutoff values in Saudi women*

	2 or more metabolic risk factors																
BMI cutoff (kg/m^2)	Sensitivity	Lower bound (95%)	Upper bound (95%)	Specificity	Lower bound (95%)	Upper bound (95%)	PPV	NPV	LR+	LR-	TP	TN	FP	FN	Accuracy	Youden Index	Distance in ROC curve
25.10	0.951	0.926	0.968	0.242	0.187	0.308	0.740	0.687	1.255	0.201	410	46	144	21	0.734	0.193	0.623
25.11	0.949	0.923	0.966	0.242	0.187	0.308	0.740	0.676	1.252	0.211	409	46	144	22	0.733	0.191	0.625
25.30	0.944	0.918	0.963	0.242	0.187	0.308	0.739	0.657	1.246	0.230	407	46	144	24	0.729	0.186	0.630
25.39	0.942	0.915	0.961	0.247	0.191	0.314	0.740	0.653	1.252	0.234	406	47	143	25	0.729	0.189	0.624
25.53	0.940	0.913	0.959	0.247	0.191	0.314	0.739	0.644	1.249	0.244	405	47	143	26	0.728	0.187	0.627
25.56	0.940	0.913	0.959	0.258	0.201	0.325	0.742	0.653	1.266	0.234	405	49	141	26	0.731	0.198	0.611
25.64	0.937	0.910	0.957	0.258	0.201	0.325	0.741	0.645	1.263	0.243	404	49	141	27	0.729	0.195	0.613
25.67	0.935	0.907	0.955	0.258	0.201	0.325	0.741	0.636	1.260	0.252	403	49	141	28	0.728	0.193	0.616
25.78	0.933	0.905	0.953	0.263	0.206	0.330	0.742	0.633	1.266	0.256	402	50	140	29	0.728	0.196	0.610
25.91	0.930	0.902	0.951	0.274	0.215	0.341	0.744	0.634	1.281	0.254	401	52	138	30	0.729	0.204	0.597
25.92	0.930	0.902	0.951	0.279	0.220	0.347	0.745	0.639	1.290	0.250	401	53	137	30	0.731	0.209	0.589
25.96	0.930	0.902	0.951	0.284	0.225	0.352	0.747	0.643	1.300	0.245	401	54	136	30	0.733	0.215	0.582
26.02	0.928	0.899	0.949	0.284	0.225	0.352	0.746	0.635	1.297	0.253	400	54	136	31	0.731	0.212	0.584
26.04	0.926	0.897	0.947	0.284	0.225	0.352	0.746	0.628	1.293	0.261	399	54	136	32	0.729	0.210	0.587
26.08	0.923	0.894	0.945	0.289	0.230	0.358	0.747	0.625	1.300	0.265	398	55	135	33	0.729	0.213	0.581
26.13	0.921	0.891	0.943	0.289	0.230	0.358	0.746	0.618	1.296	0.273	397	55	135	34	0.728	0.211	0.584
26.14	0.921	0.891	0.943	0.300	0.239	0.369	0.749	0.626	1.316	0.263	397	57	133	34	0.731	0.221	0.569
26.17	0.919	0.889	0.941	0.305	0.244	0.374	0.750	0.624	1.323	0.266	396	58	132	35	0.731	0.224	0.563
26.22	0.919	0.889	0.941	0.316	0.254	0.385	0.753	0.632	1.343	0.257	396	60	130	35	0.734	0.235	0.549
26.30	0.914	0.883	0.937	0.326	0.264	0.396	0.755	0.626	1.357	0.263	394	62	128	37	0.734	0.240	0.539
26.31	0.912	0.881	0.935	0.326	0.264	0.396	0.754	0.620	1.354	0.270	393	62	128	38	0.733	0.238	0.542
26.35	0.912	0.881	0.935	0.332	0.269	0.401	0.756	0.624	1.364	0.266	393	63	127	38	0.734	0.243	0.535
26.56	0.910	0.878	0.933	0.337	0.274	0.407	0.757	0.621	1.371	0.269	392	64	126	39	0.734	0.246	0.530
26.57	0.910	0.878	0.933	0.342	0.278	0.412	0.758	0.625	1.382	0.265	392	65	125	39	0.736	0.252	0.523
26.62	0.907	0.876	0.931	0.342	0.278	0.412	0.758	0.619	1.379	0.271	391	65	125	40	0.734	0.249	0.526
26.64	0.905	0.873	0.929	0.342	0.278	0.412	0.757	0.613	1.375	0.278	390	65	125	41	0.733	0.247	0.528
26.67	0.903	0.871	0.927	0.342	0.278	0.412	0.757	0.607	1.372	0.285	389	65	125	42	0.731	0.245	0.530
26.75	0.903	0.871	0.927	0.347	0.283	0.418	0.758	0.611	1.383	0.281	389	66	124	42	0.733	0.250	0.523
26.76	0.900	0.868	0.925	0.347	0.283	0.418	0.758	0.606	1.379	0.287	388	66	124	43	0.731	0.248	0.525
26.78	0.898	0.865	0.923	0.353	0.288	0.423	0.759	0.604	1.387	0.290	387	67	123	44	0.731	0.251	0.521
26.84	0.896	0.863	0.921	0.358	0.293	0.428	0.760	0.602	1.395	0.292	386	68	122	45	0.731	0.253	0.517
26.89	0.893	0.860	0.919	0.358	0.293	0.428	0.759	0.596	1.391	0.298	385	68	122	46	0.729	0.251	0.519
26.90	0.891	0.858	0.917	0.363	0.298	0.434	0.760	0.595	1.399	0.300	384	69	121	47	0.729	0.254	0.514
26.91	0.889	0.855	0.915	0.363	0.298	0.434	0.760	0.590	1.395	0.307	383	69	121	48	0.728	0.252	0.517
26.99	0.882	0.847	0.909	0.363	0.298	0.434	0.758	0.575	1.384	0.326	380	69	121	51	0.723	0.245	0.524

27.06	**0.882**	**0.847**	**0.909**	**0.374**	**0.308**	**0.444**	**0.762**	**0.582**	**1.408**	**0.317**	**380**	**71**	**119**	**51**	**0.726**	**0.255**	**0.511**
27.11	0.877	0.842	0.905	0.374	0.308	0.444	0.761	0.573	1.400	0.329	378	71	119	53	0.723	0.251	0.515
27.18	0.875	0.840	0.903	0.374	0.308	0.444	0.760	0.568	1.397	0.335	377	71	119	54	0.721	0.248	0.518
27.19	0.872	0.837	0.901	0.374	0.308	0.444	0.760	0.563	1.393	0.341	376	71	119	55	0.720	0.246	0.519
27.24	0.870	0.835	0.899	0.374	0.308	0.444	0.759	0.559	1.389	0.348	375	71	119	56	0.718	0.244	0.522
27.27	0.863	0.827	0.892	0.374	0.308	0.444	0.758	0.546	1.378	0.366	372	71	119	59	0.713	0.237	0.529
27.30	0.861	0.825	0.890	0.374	0.308	0.444	0.757	0.542	1.374	0.373	371	71	119	60	0.712	0.234	0.531
27.34	0.861	0.825	0.890	0.384	0.318	0.455	0.760	0.549	1.398	0.362	371	73	117	60	0.715	0.245	0.518
27.39	0.858	0.822	0.888	0.384	0.318	0.455	0.760	0.545	1.394	0.368	370	73	117	61	0.713	0.243	0.521
27.41	0.858	0.822	0.888	0.389	0.323	0.460	0.761	0.548	1.406	0.363	370	74	116	61	0.715	0.248	0.514
27.45	0.856	0.820	0.886	0.389	0.323	0.460	0.761	0.544	1.402	0.369	369	74	116	62	0.713	0.246	0.516
27.53	0.854	0.817	0.884	0.389	0.323	0.460	0.760	0.540	1.399	0.375	368	74	116	63	0.712	0.243	0.518
27.56	0.854	0.817	0.884	0.395	0.328	0.466	0.762	0.543	1.411	0.370	368	75	115	63	0.713	0.249	0.512
27.59	0.852	0.815	0.882	0.395	0.328	0.466	0.761	0.540	1.407	0.376	367	75	115	64	0.712	0.246	0.514
27.70	0.849	0.812	0.880	0.395	0.328	0.466	0.761	0.536	1.403	0.382	366	75	115	65	0.710	0.244	0.517
27.76	0.849	0.812	0.880	0.400	0.333	0.471	0.763	0.539	1.415	0.377	366	76	114	65	0.712	0.249	0.511
27.77	**0.849**	**0.812**	**0.880**	**0.405**	**0.338**	**0.476**	**0.764**	**0.542**	**1.428**	**0.372**	**366**	**77**	**113**	**65**	**0.713**	**0.254**	**0.504**
27.78	0.845	0.807	0.876	0.405	0.338	0.476	0.763	0.535	1.420	0.384	364	77	113	67	0.710	0.250	0.509
27.83	0.842	0.805	0.874	0.405	0.338	0.476	0.763	0.531	1.416	0.389	363	77	113	68	0.709	0.247	0.511
27.85	0.840	0.802	0.872	0.405	0.338	0.476	0.762	0.527	1.412	0.395	362	77	113	69	0.707	0.245	0.514
27.89	0.835	0.797	0.867	0.405	0.338	0.476	0.761	0.520	1.404	0.406	360	77	113	71	0.704	0.241	0.518
27.93	0.833	0.795	0.865	0.411	0.343	0.482	0.762	0.520	1.413	0.407	359	78	112	72	0.704	0.243	0.514
27.94	0.831	0.792	0.863	0.411	0.343	0.482	0.762	0.517	1.409	0.413	358	78	112	73	0.702	0.241	0.516
28.00	0.831	0.792	0.863	0.416	0.348	0.487	0.763	0.520	1.422	0.407	358	79	111	73	0.704	0.246	0.511
28.20	0.826	0.787	0.859	0.416	0.348	0.487	0.762	0.513	1.414	0.419	356	79	111	75	0.700	0.242	0.515
28.31	0.824	0.785	0.857	0.416	0.348	0.487	0.762	0.510	1.410	0.424	355	79	111	76	0.699	0.239	0.517
28.38	0.819	0.780	0.852	0.416	0.348	0.487	0.761	0.503	1.402	0.435	353	79	111	78	0.696	0.235	0.522

* Metabolic risk factors were defined according to IDF definition (21): elevated triglycerides, ≥ 150 mg/dL or specific treatment for hypertriglyceridemia; reduced HDL cholesterol, < 40 mg/dL for men and <50 mg/dL for women or specific treatment for this lipid abnormality; elevated blood pressure, systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥85 mmHg or treatment for previously diagnosed hypertension; elevated fasting plasma glucose ≥ 100 mg/dL or previously diagnosed type 2 diabetes. Youden Index= TPF-FPF= Sensitivity+ Specificity -1. Distance in ROC curve = square root of $(1\text{-TPF})^2 + FPF^2 = (1\text{-sensetivity})^2 + (1\text{-specificty})^2$

Table 19. The prevalence of the metabolic syndrome and central obesity among adult's Saudi women aged 18-70 years

	Metabolic syndrome (Harmonized)v	Metabolic syndrome (IDF)¤	Central obesity
	n(%) n=622	n(%) n=622	n(%) n=623
IDF waist circumference[v]	431(69.3)	428(68.8)	587(94.2)
Modified waist circumference[#]	384(61.7)	347(55.8)	444(71.3)

v Metabolic syndrome defined as per (IDF, NHLBI, AHA, IAS, IASO) harmonized definition guidelines (73); the presence of any three or more of the risk factors. ¤Metabolic syndrome defined as per IDF definition guidelines (38); the presence of abdominal obesity and two or more of the risk factors. Metabolic risks defined according to IDF criteria (38): central obesity, waist circumference ≥ 80 cm for women; raised triglycerides (≥1·7 mmol/L); reduced HDL cholesterol (<1·03 mmol/L for men and 1·29 mmol/L for women or specific treatment for this lipid abnormality); raised fasting plasma glucose (≥5·6 mmol/L or previously diagnosed type 2 diabetes); raised blood pressure (systolic BP ≥ 130 mmHg, diastolic BP≥ 85) or treatment for previously diagnosed hypertension. IDF Waist circumference ≥ 80 cm for women, [#] Modified waist circumference ≥ 92 for women.

Table 20. Comparison of the prevalence of metabolic syndrome and obesity by cut-off point of neck circumference for women

	NC < 35.5	NC ≥ 35.5
n	175	439
Neck circumference (means ± SD)	33.1(32.8-33.3)	37.6(37.5 - 37.8)***
Waist circumference (means ± SD)	88.9(87.3-90.6)	103.6(102.6-104.5)***
Metabolic syndrome (%)	67(38.3)	364(82.9)***
Metabolic syndrome-IDF (%)	64(36.6)	364(82.9)***
Having 2 or more risks (%)	69(39.4)	364(82.9)***
Obesity (%)	73(41.7)	332(75.6)***
Central obesity (%)	148(84.6)	439(100)***

NC: neck circumference. Categorical data were described as n (%), and continuous data were described as means ± standard deviation. ***p-values = 0.000 between the groups of the above and below cut-off points of NC in women.

Figure 19. Age adjusted ORs of metabolic syndrome according to joint classification of neck circumference and the modified waist circumference cutoff point.

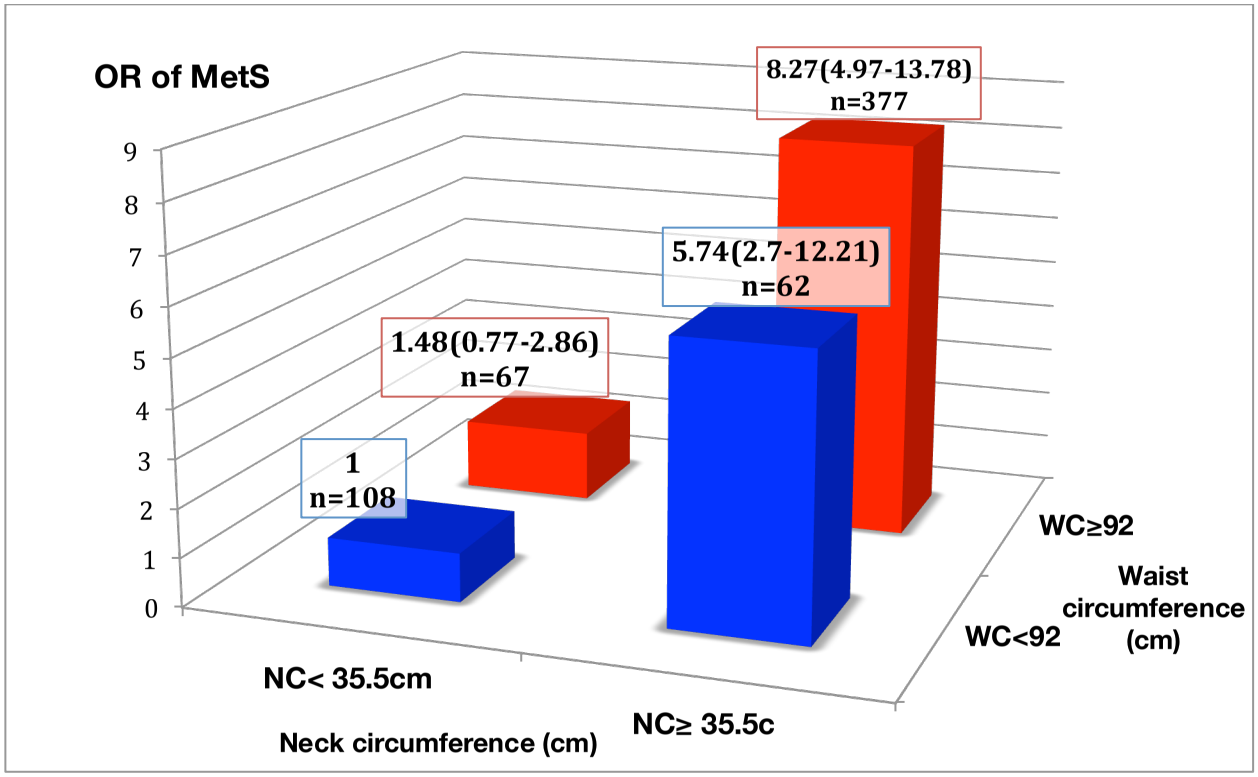


Figure 20. Age adjusted ORs of metabolic syndrome according to joint classification of neck circumference and the WHO overweight cutoff point.

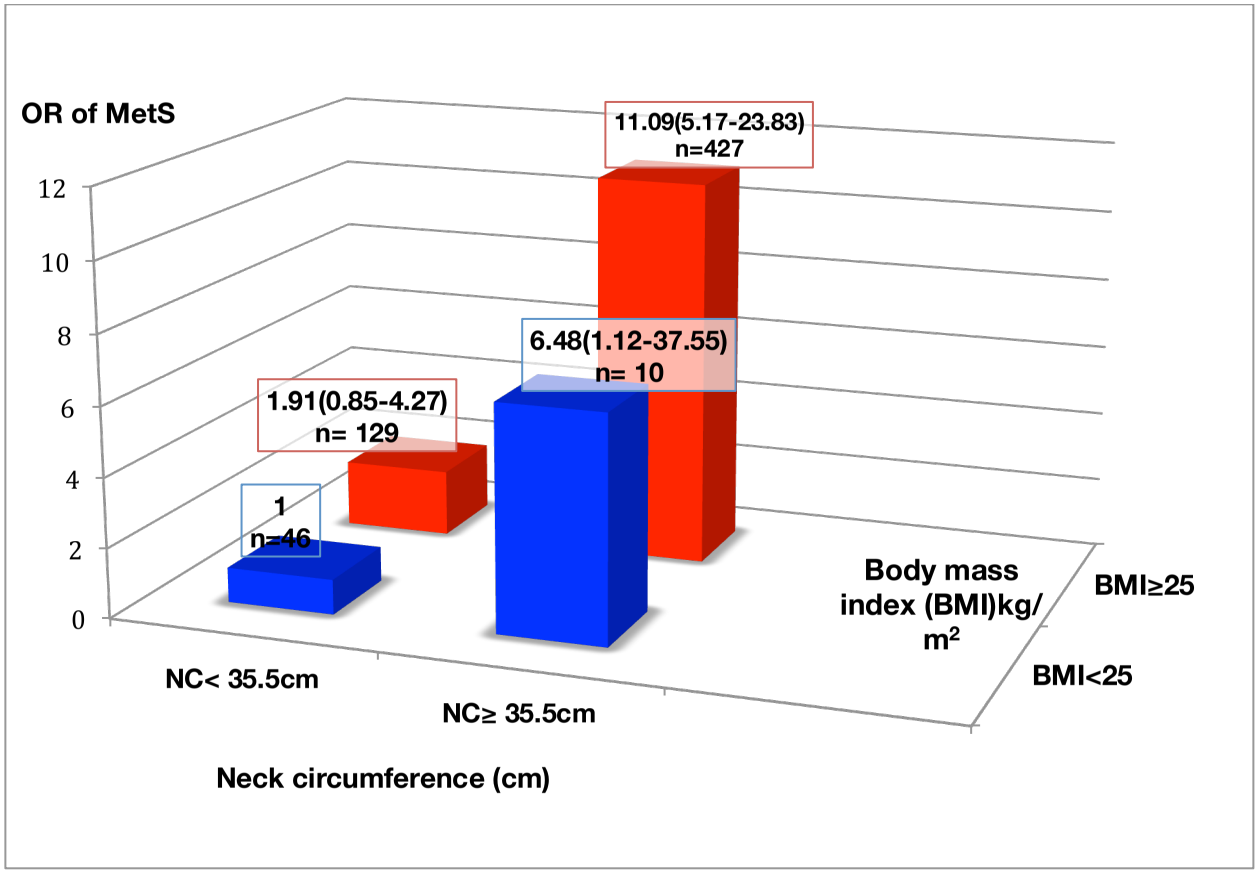
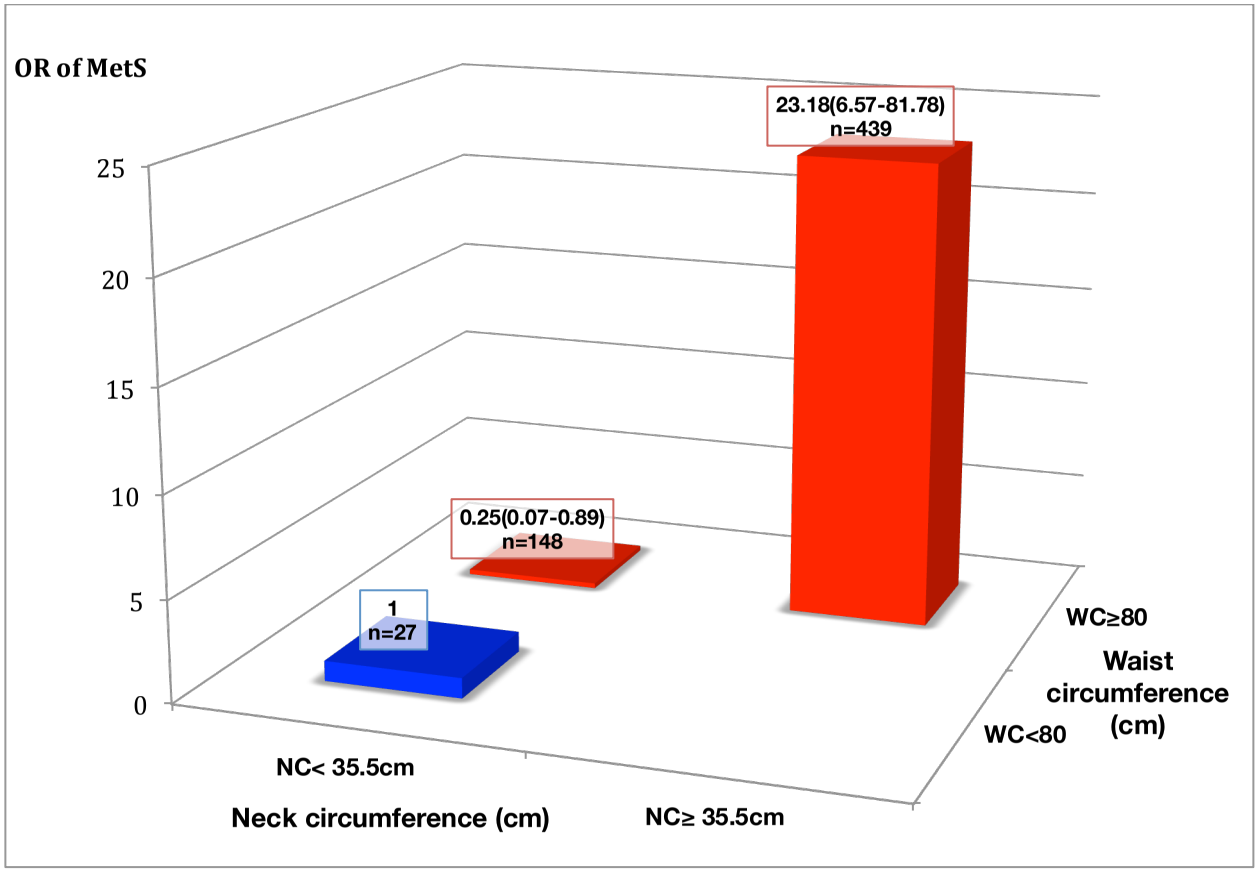


Figure 21. Age adjusted ORs of metabolic syndrome according to joint classification of neck circumference and the IDF waist circumference cutoff point



Chapter 4: Discussion

Obesity is steadily increasing in the Middle East, especially in Saudi Arabia, and is currently one of the most serious health problems in the region. Because of the comorbidity associated with obesity, early diagnosis is crucial for more effective intervention. The most widely used index of excess body fat is the body mass index (BMI). However, several studies have shown that regional (upper body) adiposity is a more serious clinical entity than total body fatness. BMI is a poor indicator of central adiposity (18). Therefore, other anthropometric measures of upper body adiposity have been pronounced. To our knowledge, this is the first study designed to address the association between neck circumference and cardiometabolic risk factors in Saudi adults.

In this cross-sectional analysis of 700 adults aged 18-70 years, the association between body composition indices: body fat percentage, body mass index (BMI), neck circumference, and waist circumference (WC), as well as, cardiometabolic risk factors were examined. First, neck circumference is associated with waist circumference in men and women. Second, in women, neck circumference is associated with cardiometabolic risk factors beyond the other anthropometric indices. Third, neck circumference independently contributes to the prediction of cardiometabolic risk. Fourth, for women the body mass index, waist circumference, and neck circumference of ≥ 27.7 Kg/m^2, 92 cm, and ≥ 35.5 cm, respectively, were the best cutoff points to determine subjects with metabolic syndrome. Finally, no synergistic effect between NC and BMI or WC on metabolic syndrome was observed.

Neck circumference and the other indices: The age-adjusted neck circumference measurements were significantly associated with BMI (total adiposity index) as well as WC, which is frequently used as a surrogate marker of abdominal or upper-body (subcutaneous and visceral) fat mass (50, 51). The results show a strong positive correlation of neck circumference with BMI and WC in both men and women subjects. This was in line with several studies that have examined the association of conventional anthropometric measures of adiposity with neck circumference (20, 153, 154). Onat et al. and Hingorjo et al. reported strong correlations of neck circumference with BMI and WC ($r > 0.6$) (21, 150). Stabe et al. found that neck circumference is associated with the intra-abdominal (visceral) fat (27). However, BMI and WC are age and sex dependent when they are used as indicators of body fatness (108).). Most importantly, our study was controlled for age and all analyses were sex specific. Furthermore, as in Yang et al.'s study (147), our results showed a positive association between neck circumference and increase of WC in all BMI levels in women, but not in men. Klein et al. stated that the cutoff points of WC > 40 in (102 cm) in men and > 35 in (88 cm) in women are derived from a regression curve that identified the WC values associated with obesity (BMI > 30) (17). This explains our finding that WC has higher correlations with BMI and body fat percentage compared to neck circumference, which is in line with finding from a recent study in overweight and obese adults by Joshipura et al (197). The finding from this study implied that the incremental added value of using neck circumference would be higher as neck circumference would be more independent of BMI compared to waist circumference (197). This may also be applied to the body fat percentage in our study. We used a DEXA scan as a gold standard for the assessment of body fat percentage,

however, the DEXA dose not quantify the vascular and subcutaneous fat, especially in morbid obese (198). Computed tomography (CT) and magnetic resonance imaging (MRI) are considered the gold standard for detailed assessment of upper body fat sections (199, 200).

Anthropometric measurements are the most basic assessment tools with a well-established relationship with body fat distribution and metabolic complications that overcome the expense and availability limitations of the gold-standard methods (e.g., CT, MRI) in clinical practice (199, 200). Neck circumference measurement requires less effort for both the examiner and the subject than other anthropometric methods. It requires a single measurement site with less bias of anatomical and observer variations (27). In addition, the measurement of neck circumference may be more socially acceptable, convenient, and tolerable, especially for overweight and obese women (153, 154, 201). Neck circumference is measured directly at the body surface, which is more stable than the surface used for the measurement of WC or HC because light clothing may make the measurement challenging. Thus, the use of WC or HC may increase the chance of getting false results due to researcher or subjects' effect (201). Neck circumference provides good inter- and intra-observer reliability (202). On the other hand, the risk prediction of WC is influenced by the anatomic location of measurement, especially in women. Comparison of WC values is complicated by the absence of generally accepted anatomic landmarks for measuring the WC in different clinical studies: the midpoint between the last intercostal arch and iliac crest; the upper border of the iliac crest; the narrowest circumference abdomen; and distance above the umbilicus. Whereas, each specific site used to measure the WC influences the obtained WC value,

which can limit the evaluation of body fat distribution and their corresponding metabolic risks, especially in women (17, 25, 26, 27). The cutoff values of WC for overweight and obesity vary widely throughout the world. WC may also be biased by the absence of specific, standardized cutoff points for some populations, including those of the Arabian Gulf region.

Measuring neck circumference is a straight-forward process with minimal cost and time requirements (154, 196). As a result, neck circumference measurement provides a better and potentially more accurate clinical screening tool for predicting obesity and metabolic syndrome.

Neck circumference and the cardiometabolic risk factors: General obesity (designated by BMI) and regional adiposity (designated by WC or NC) have been related to elevated risk for metabolic and cardiovascular diseases (16, 50, 108). Few studies have examined the relationship between neck circumference and cardiometabolic risk factors in adults and, at the same time, examined the association of other anthropometric indices (BMI, WC, WHR, or body fat percentage). Zhou et al. study (152), in southern China, has implemented a similar analysis performed in this study (Table **11)**. Their study showed that neck circumference is associated with elevated SBP, DBP, triglycerides, fasting glucose, insulin, IR, and reduced HDL. Our findings are consistent with associations detected in that study. However, they found that the associations were higher between BMI and WC with the cardiometabolic risks than with neck circumference. In contrast, we found that neck circumference has the highest association with the cardiometabolic risks. The correlation in their study was not gender specific, which may imply that the observed disagreement is due to gender differences. Moreover, that study was among

Chinese adults with normal weight (mean BMI= 22.67±3.1) and with no previously prescribed medication for hypertension, diabetes, or dyslipidemia. Thus, that study is different from our study, in which they included only healthy adults with no obesity-induced health problems (152). The data from San Juan Overweight Adults Longitudinal Study (SOALS), which recruited overweight or obese adults who were free of previously diagnosed diabetes, has shown consistent results to our study (197). Neck circumference revealed higher positive associations with prediabetes and lipid abnormality than BMI, WC, and body fat percentage.

Nevertheless, the association of neck circumference with cardiometabolic risk factors has been conducted in several studies. The results of the present study demonstrated a clear and consistent positive association of neck circumference measurement with elevated SBP, DBP, triglycerides, fasting glucose, insulin, and IR in women. These associations were present on both univariate and multivariate analyses and remained highly significant after the adjustment for various demographic, lifestyle, and medical characteristics. These findings are in line with numerous studies (18, 22, 155). Brazilian women's neck circumferences showed an association with hypertension, insulin insensitivity, hypertriglyceridemia, lower HDLc, and higher fasting glucose level. In addition, neck circumference and WC measurements shared significant and independent predictions of IR and metabolic syndrome risks and neck circumference was a better risk indicator for women than for men (27). This deferential effect of neck circumference by sex has also been reported in other studies (18, 22). On the contrary, the contribution of neck circumference in predicting metabolic syndrome was stronger in men compared to women in the Turkish population (21). Although gender differences exist in these studies,

neck circumference was significantly associated with cardiometabolic risks. And after further control for the other anthropometric indices, neck circumference was positively associated with each component of metabolic syndrome except for low HDLc (18). Our findings are in agreement with these studies in which the neck circumference was related to cardiovascular risk factors independent of body fat percentage, WC, and BMI (27, 155, 156). In a longitudinal cohort study of 364 subjects, Ben-Noun and Laor reported that changes in the neck circumference did not affect HDLc levels after the adjustment for WC (148). Another previous study reported that neck circumference is correlated with triglycerides and reduced HDLc beyond BMI and waist circumference (203). The Framingham Heart Study demonstrated that the neck circumference is associated with IR, hypertension, and dyslipidemia, independent of vascular adiposity (18). Neck circumference was also an associated factor for Type 2 diabetes after the control for BMI and waist circumference (170). Likewise, neck circumference has been associated with hypertension after adjustment for BMI (204).

A recent study observed a significant association of neck circumference with indicators of chronic kidney disease [the Cockcroft-Gault formula (eGFRCG), 24-hour urine creatinine clearance rate (24 hr CCR), uric acid, and urine microalbuminuria] and with the traditional cardiovascular risk factors [High-sensitivity C-reactive protein (hsCRP), triglycerides, LDLc, and HDLc] (204). Neck circumference also correlated significantly with intima-media thickness of common or internal carotid arteries, which is a direct measure of subclinical atherosclerosis, independent of BMI and WC (205). In a Brazilian study that included 43 obese adults, neck circumference demonstrated a strong

relationship with Plasminogen Activator Inhibitor (PAI-1), which is an adipokines related to hyperthrombotic state, inflammatory state, and cardiovascular diseases (206).

Our data and results from other studies suggest that neck circumference contributes to the cardiometabolic adverse consequence as an upper body fat marker (18, 21, 27, 155, 156). Upper body subcutaneous fat, as measured by neck circumference, may confer risk beyond vascular adiposity (18, 152). The precise mechanism of neck circumference in the prediction of metabolic problems is not well understood. However, changes in regional fat distribution, including subcutaneous fat of the neck, are associated with adipose tissue dysfunction and abnormal adipokine secretion leading to metabolic diseases (21, 22). Upper body fat is more lipolytically active than lower body adipose tissue, which may be another mechanism to explain the association of neck circumference with cardiometabolic risk. Upper body subcutaneous fat is responsible for a much larger proportion of systemic free fatty acid release than visceral fat, specifically in obese individuals (19, 85). This lipolytic activity of upper body fat and high levels of plasma free fatty acids could result in insulin resistance (85), increased VLDL-triglyceride production (158), oxidative stress (167), and the development of hypertension. Therefore, neck circumference, as representative of upper body fat, should be able to predict the metabolic and cardiovascular risk (18, 27, 156, 157, 197, 207, 208)

***Prediction of cardiometabolic risks*:** In our study, adjustment for various metabolic risk factors, such as age, sex, menopausal status, hormonal use, lifestyle, BMI, and WC, did not change the associations between neck circumference and cardiometabolic risks, suggesting that the effects of larger neck circumference for women are less likely to be mediated by these factors. The regression procedure indicated that the

enlargement of neck circumference increases the risk of developing IR, hypertriglyceridemia, hypertension, central obesity, metabolic syndrome, and hyperglycemia by 1.2; 1.2; 1.3; 1.5; 1.6; and 1.7 times, respectively. Several studies have demonstrated similar results, in which, even after they control for BMI and WC, neck circumference presented significant prediction of metabolic syndrome components by 1.3 to 1.9 times (18, 150). In our study, women in the fourth quintile (NC >38) are associated with an increased OR of all metabolic syndrome components. We observed an extremely elevated risk, as much as 23-fold, 13-fold, and 11-fold, in central obesity, metabolic syndrome, and hyperglycemia, respectively. In addition, Laakso et al. reported that women with neck circumference in the highest quintile were associated with about a fivefold increased risk of elevated fasting glucose and a threefold increased OR of hypertension after adjustment for BMI (100). Other studies established that neck circumference in the highest quartile added sevenfold, eightfold, or 17 fold risks to the IR, metabolic syndrome, and obesity compared with that in the lowest quartile (197).

Importantly, a significant synergistic effect between neck circumference and visceral adipose tissue on cardiometabolic risk factors was established in the Framingham Heart Study (18). The present study is the first to examine the synergistic effect between neck circumference and BMI or WC on metabolic syndrome. Our study reported the absence of synergistic effect between neck circumference and other obesity indices on metabolic syndrome. The findings of our study and the Framingham Heart Study (18) suggest that neck circumference, as a proxy of upper-body section fat, would be helpful to better predict metabolic syndrome than the other indices.

Neck circumference cutoff points: The overall performance of neck circumference, area under curve AUC (0.796), in predicting metabolic syndrome using the IDF criteria was better than other anthropometric indices: WC (0.667); BMI (0.659); and body fat percentage (0.587). Few studies have compared the prediction power of neck circumference with other anthropometric indices. Yan et al. found that neck circumference and WC shared the same predictive power AUC (NC=0.73, WC=0.74) in women (156). However, in Zhou et al.'s study, neck circumference had a significantly large AUC (0.703), but was relatively lower than those of WHR (0.766); WC (0.764); and BMI (0.723) (152).

For women, the optimal cutoff point to predict metabolic syndrome was 35.5 cm. The optimal cutoff point was within the range of 33-36 cm reported in the literature of neck studies (21, 27, 147, 151, 152, 155, 156, 157). Some studies considered NC =35 cm as the optimal cutoff value for the prediction of the development of metabolic syndrome (21, 145, 156)

We suggest that the WC value of 92 cm would be more appropriate for defining central obesity and predicting the presence of two or more metabolic risk factors in Saudi women. This value differs from the recommended thresholds for American (88 cm) and European (80 cm) women by 4 and 12 cm, respectively (38). However, our finding concurs with the results from previous studies in the Arabian Gulf region on determining the optimal waist circumference cutoff for metabolic syndrome in Qatari and Iranian women (127, 129). Other studies showed that optimal WC cutoff points are 84.5 cm for Omani women, and 99 cm for Iraqi women (126, 128).

Differences in the definitions of metabolic syndrome and in body sizes could explain the discrepancies in the optimal cutoffs of neck circumference and WC among different populations. As a result, ethnic specific cutoff values of neck circumference and WC are required for the prediction of cardiometabolic abnormalities (152,157, 210).

Neck circumference is an excellent independent cardiometabolic predictor that exceeds other anthropometric indices in this study of Saudi women. However, WC, BMI, and body fat percentage denoted lower prediction power. WC could underestimate the real cardiovascular risk in subjects with small stature, which may be important in many populations, such as our Saudi sample (211, 212). Another reason might be from the different settings of studied populations, as our study included subjects in their late middle ages to older adults since our inclusion criteria was for subjects who were 18-70 years old (156, 157). For individuals with a BMI $\geq$ 35, waist circumference adds little to the predictive power of the disease risk classification of BMI (130). Aging women tend to gain weight and have less estrogen protecting them against cardiovascular diseases (213). Fat distribution changes with aging and women develop a more central distribution (android shape) that has been related to cardiometabolic abnormalities (214).

These findings imply that associations between WC and cardiometabolic risks might be mediated by obesity (BMI, body fat percentage) in our sample. Consequently, ethnic-specific cutoff points of neck circumference should be required for the prediction of metabolic syndrome (147, 152, 156), particularly for Saudi women.

Lastly, although neck circumference shows a strong association with both central obesity and metabolic syndrome, the consideration of neck circumference as a screening test is a reasonable approach. Women with NC < 35.5 cm do not require additional

evaluation. Women with a neck circumference above this level require a more comprehensive evaluation of their metabolic and cardiovascular risk.

Strength and limitations of the study: To our knowledge, this is the first study to determine cutoff values of neck circumference for Saudi women that identify overweight and obesity and its associated cardiometabolic risk factors. These data add to the current literature by showing that neck circumference is an independent predictor of obesity and metabolic syndrome after adjusting for other anthropometric indices. In this study, the effects of all possible confounders were assessed. In this study, DEXA scan was used to quantify total body fat percentages. However, other methods, such as CT scan, could quantify upper body fat much better. In addition, the cross-sectional nature of this study prevents firm causal conclusions. This study was conducted in one city, limiting the generalization of our findings to all Saudi women. However, given the significant and consistent associations detected in our study and the similar findings from different populations in other studies, neck circumference shows promise as an alternative marker for the metabolic and cardiovascular risks associated with central or visceral adiposity. In addition to medical-center-based, community-based, prospective research is needed to evaluate whether neck circumference is an important risk factor for the development of cardiometabolic conditions.

Summary

The current study shows that neck circumference is associated with other anthropometric measurements in men and women. In Saudi women, neck circumference is an independent predictor for metabolic and cardiovascular risks above and beyond the body mass index and waist circumference. Our results indicated that the appropriate neck circumference to predict three or more metabolic risk factors in Saudi women is 35.5 cm. In addition, the appropriate waist circumference to predict two or more metabolic risk factors is 92 cm. The prevalence of central obesity and metabolic syndrome was reduced among women according to this waist circumference cutoff. Metabolic syndrome, obesity, and central obesity are more prevalent in women with a neck circumference ≥35.5 cm.

The current study will contribute not only to the understanding of the importance of the appropriate assessment of upper body obesity in screening metabolic syndrome but also to the providing of practical guidance in identifying individuals with metabolic syndrome. This work is aimed to contribute to the establishment of proper procedures for the prevention or delay in the development of diabetes and/or cardiovascular disease.

To our knowledge, this is the first study to investigate the appropriate neck circumference cutoff for the diagnosis of upper body obesity and metabolic syndrome in the entire Arabian Gulf region. However, our results are not applicable to all Arab women. The findings of the present study are derived from a sample of adult Saudi women in Riyadh city and are applicable to this population.

Appendix 1A

السلام عليكم، أنا <.....> باحثة. حالياً أنا أقوم بجمع معلومات حول أفضل الطرق لتقيم زيادة الوزن والسمنة عند السعوديون كمتطلب لرسالة الدكتوراه. أود دعوتك إلى المشاركة في مشروع بحثي هذا و سوف تسهم هذه المشاركة في تحديد معايير التقييم اللازمة لتحديد نسبة انتشار السمنة بدقة، تحسين برامج العلاج، ومحاربة السمنة في السعودية. بمشاركتك لنا ، سوف تقدم هذه الدراسة معلومات مفيدة من شائنها أن تقلل انتشار السمنة وأعراضها الجانبية ليس في السعودية فحسب بل في دول الخليج العربي أجمع.

وأود أن أؤكد أننا سوف نبذل قصارى جهدنا للحفاظ على سرية المعلومات التي سوف نحصل عليها منك أو من خلال الملف الخاص بك ,كما أننا سوف نحتفظ بهذه المعلومات في ملف سري خاص . كما أؤكد لك أيضا أنه لن يكتب اسمك أو أي معلومات شخصية متعلقة بك في الاستبيان ولن يطلع عليها أحد سوى أنا ومشرفي الدراسي في الولايات المتحدة الأمريكية.

كل ما سوف أقوم به هو أن أطرح عليك بعض الأسئلة حول تاريخ حالتك الصحية، سلوكياتك الغذائية، ممارستك للرياضة , نمط حياتك المعيشي ، وكذلك خلال التحضيرات السابقة لدخولك للطبيب, ممرضة العيادة سوف تأخذ قياساتك الجسمية (الطول، الوزن، محيط الرقبة، و محيط الخصر) وحرصنا أن تكون من نفس جنس المشارك لتفادي حدوث أي حرج. وسوف يستغرق ٥ الي ١٠ دقائق. إذا أذنت لي بذلك ، سوف نستخدم جهاز DEXA لقياس الدهون في الجسم وكمية الكتلة العضلية. بعد الانتهاء من زيارة الطبيب ، سوف يطلب منك زيارة قسم النتائج المخبرية، سوف نقوم بجدولة زيارة أخرى إلى المختبر في نفس العيادة في غضون أسبوع و احد. حيث يلزمك الأشعة في نفس المركز .فني الأشعة المتمكن سيشرح لك الإجراء ت اللازمة، وبعد ذلك سوف يطلب منك الاستلقاء على السرير، وسيتم عرض الأشعة السينية من الجهاز(DEXA) على جسمك. وسيستغرق مسح الجهاز لجسمك حوالي ١٠-٥ دقائق. أحتاج أيضا إلى تسجيل بعض النتائج المخبرية الحديثة(أسبوعين) من الملف الطبي الخاص بك في حال عدم توفر الحضور صائم لمدة ١٠-١٢ساعه وبعد ذلك؛ فني المختبر سوف يشرح لك الإجراءات اللازمة، و بعدها سيطلب منك الجلوس و سيتم سحب الدم من الوريد في ذراعك باستخدام إبرة .كمية الدم المطلوب هي ٦مل (حوالي نصف ملعقة). إذا كان هناك صعوبة في إيجاد الوريد سيتم استبعادك لتجنب أي ألم لا لزوم له .

مشاركتكم في هذا البحث هو عمل تطوعي بحت كما أن لك كامل الحق في عدم المشاركة و إذا قررت عدم المشاركة في هذا البحث، يمكنك التوقف في أي وقت دون أي عقوبة ولن يؤثر ذلك على حقوقك وعلى الخدمات التي توفرها(تقدمها) العيادة لك.

إذا كان لديك أي سؤال حول حقوقك كمشارك في بحث علمي أو تريد الإبلاغ عن إصابات ناجمة عن هذا البحث، الرجاء الاتصال:

هاتف٣٠١-٤٠٥-٠٦٧٨ :

البريد الإلكتروني irb@umd.edu :

أو يمكنكم المراسلة على العنوان التالي:

University of Maryland College Park
Institutional Review Board Office
١٢٠٤ Marie Mount Hall
College Park, Maryland, ٢٠٧٤٢

Appendix 1A

وأخيرا' تمت مراجعة و تقييم هذا البحث وفقا لمجلس المراجعة المؤسسي (IRB) بجامعة ميريلاند، كولج بارك، الجنة المختصة بأبحاث الإنسان. قبولك اللفظي يشير إلى أنك لا تقل عن ١٨ سنة، سمعت طلب المشاركة اللفظي (قرأت لك)، تم الإجابة على كل أسئلتك بشكل مرضى و وافي, وأنك توافق طوعا على المشاركة في هذه الدراسة البحثية.

إذا كانت الإجابة لا: شكرا لوقتكم الكريم.

إذا كانت الإجابة نعم: أكمل الحوار

قبل المشاركة، أود أن اطرح عليك بعض الأسئلة والتي ستستغرق بضع دقائق، هل لديك الوقت الآن؟

إذا كانت الإجابة لا: حدد وقت آخر لإجراء المقابلة.

إذا كانت الإجابة نعم: أكمل الحوار

Screening Questionnaire

Interviewer _____ Date _____/_____/_____

Participant ID Number _____

١) هل عمرك بين ١٨ -٧٠ عام؟

A. نعم

B. لا

٢) هل أنت سعودي الجنسية؟

A. نعم

B. لا

٣) هل تعاني من فشل في الأعضاء، أو تمت لك زراعة لعضوء، أو تشكو من السرطان؟

A. لا

B. نعم

٤) هل سبق و شخصك الطبيب بتضخم الغدة الدرقية؟

A. لا

B. نعم

- للنساء فقط:

٥) هل أنتي حامل ؟

A. لا

B. نعم

٦) هل ترضعين رضاعة طبيعية في الفترة الحالية؟

A. لا

B. نعم

❖ يتوجب أن تكون إجابة السؤالين الأول والثاني نعم، وبقية الأسئلة(٣-٦) لا.

❖ في حال كان خيار أي إجابة من الأسئلة B أو رفض المشارك الإجابة عن سؤال أو أكثر: يعتبر غير مؤهل أو مستحق للمشاركة في الدراسة.

Appendix 1A

- غير مؤهل أو مستحق للمشاركة."اشكر مبادرتك للمشاركة، ولكن للأسف شروط المشاركة غير مستوفية في حالتك."
- كل الآجابات A : "أنت مؤهل للمشاركة معنا. وأود أن اشرح لك بعض تفاصيل المشاركة."

كما سبق وذكرت، المشاركة في هذه الدراسة يستوجب لقاء واحد في نفس هذا المركز_____(اسم المركز الصحي)-

عندما نبداء بالمقابلة سوف نخبرك بما لك من حقوق مرة أخرى. ونجري معك حوار لمدة ١٥ دقيقة، أطرح عليك بعض الأسئلة حول تاريخ حالتك الصحية، سلوكياتك الغذائية، ممارستك للرياضة , نمط حياتك المعيشي، وكذلك خلال التحضيرات السابقة لدخولك للطبيب, ممرضة العيادة سوف تأخذ قياساتك الجسمية (الطول، الوزن، محيط الرقبة، و محيط الخصر) وحرصنا أن تكون من نفس جنس المشارك لتفادي حدوث أي حرج. ويستغرق ذلك ٥ إلي ١٠ دقائق, ويجب أن ترتدي ملابس خفيفة وان تكون عاري الرأس و حافي القدمين. وفي نهاية الزيارة ستحصل علي ملخص قياساتك الجسمية.

"هل يمكننا إجراء المقابلة الآن ولمدة ٥-١٠ دقيقة, قد جهزنا غرفة معزولة هنا في نفس المركز وذلك لمزيد من الخصوصية

إذا كانت الإجابة نعم: اشكر تعاونكم, هيا بنا لنبدأ الحوار"

إذا كانت الإجابة لا: حدد وقت آخر لإجراء المقابلة.

لنحدد تاريخ موعد قدومك للعيادة. (الرجاء إدخال الموعد في الجدول ادناة)

Mon	Tue	Wed	Thu	Fri

أبلغ المشارك:

- هل لديك أي سؤال أو استفسار؟
- أتطلع لرؤيتك في [مكان الموعد] [تاريخ الموعد] وشكراً. [نهاية]

Visit #A Appointment (١٥mn)

Day: Mon Tue Wed Thu Fri Sat

Date: _____/_____/_____

Time: _____ to _____

Appendix 1B

"Hello, my name is < Reem Al-bassam >. I am, a PhD student at the University of Maryland in the United States of America. I'm collecting data about the best way of assessing overweight and obesity in Saudi people as a Doctor's dissertation requirement. I am inviting you to participate in this project since your valued participant will aid us to find standardized assessment tools to determine accurate prevalence, treatment protocols, and achieve control of obesity among Saudi population. By participation, findings of this study will contribute to the prevention of the epidemic of obesity and its complications in Saudi Arabia and the entire Arabian Gulf.

In our study, we guarantee the confidentiality of the collected information that we will get from you or through your file, and we will keep this information in a confidential file. Also I assure you that we will not write your names or any other information that can directly be linked to you. Only the file number will be obtained and linked to serial number to be used in the event if there is any missing data. Only my advisor in United States (Dr. David K. Y. Lei) and I (Reem AlBassam) will have access to the data through password protection.

All I need is to ask some question related to your socio-demographic data, medical history, dietary habit and practices, as well as your physical activity and lifestyle. Also, if you authorized me to do so, I will obtain some recent laboratory results of your medical record. If your medical record does not have required biochemical parameters, we will schedule you for another visit to the laboratory in the same clinic within one week. Prior to seeing your doctor and during the routine preparation session, some extra measurements other than height (cm), weight (kg) will be taken for you, with estimated time of 5-10 minutes in order to be completed. These include: neck circumference (cm), waist circumference (cm). Finally, after completing the doctor visit, you will be asked to visit the radiology department within the same center and do a DEXA X-ray, with estimated time of 15-20 minutes in order to be completed.

Your participation in this research is completely voluntary. You may choose not to take part at all. If you decide to participate in this research, you may stop participating at any time. If you decide not to participate in this study or if you stop participating at any time, you will not be penalized or lose any benefits to which you otherwise qualify.

File number should not be on survey with serial number; when is serial # assigned? Participant serial #

_____

If you have questions about your rights as a research participant or wish to report a research-related injury, please contact:

University of Maryland College Park
Institutional Review Board Office
1204 Marie Mount Hall
College Park, Maryland, 20742
E-mail: irb@umd.edu
Telephone: 301-405-0678

Finally' this research has been reviewed according to the University of Maryland, College Park IRB procedures for research involving human subjects. Your written acceptance (signature) indicates that you are at least 18 years of age; you have read this consent (have had it read to you); your questions have been answered to your satisfaction and you voluntarily agree to participate in this research study.

If NO: "Ok… not a problem thank you for your time."

If OK, complete below.

"In order to participate, I need to ask you a few questions that will take just a minute or so to answer. Do you have a couple of minutes that I can ask these questions now?"

If NO, schedule a better time to screened.

If YES, complete information below.

File number should not be on survey with serial number; when is serial # assigned? Participant serial #

_____

Screening Questionnaire

Interviewer _____ **Date** _____/_____/_____

Participant ID Number _____

1) Are you between 18 to 70 years of age?

A. Yes
B. No.

2) Are you Saudi?

A. Yes
B. No.

3) Have you had Organ Failure, Transplant, or Cancer?

A. No
B. Yes

4) Have you been diagnosed with a thyroid nodule?

A. No
B. Yes

For females only

5) Are you pregnant or do you think you may be pregnant before the clinic visit?

A. No
B. Yes

6) Are you nursing or lactating?

A. No
B. Yes

First and second questions must be YES; the followed (3-6) must be NO.
If ANY question has the choice "B" or the individual declines to complete one or more questions: Check box for ineligible.

- ○ Ineligible. "Thank you for your interest in the study, but unfortunately you do not qualify for this study."
- ○ **If NO FLAGS for exclusion:** "You seem to be a good candidate for this study. Let me tell you more about it."

"As I mentioned, participants in the study will be measured 1-2 times here at the same Primary heath center name: _____].

File number should not be on survey with serial number; when is serial # assigned? Participant serial # _____

Appendix 1B

"The time we start our meeting, we will go over the written consent. We will ask some question related to your socio-demographic data, medical history, dietary habit and practices, as well as your physical activity and lifestyle. Also, if you authorized me to do so, I will obtain some recent laboratory results of your medical record. If your medical record does not have required biochemical parameters, we will schedule you for another visit to the laboratory in the same clinic within one week. Prior to seeing your doctor and during the routine preparation session, some extra measurements other than height (cm), weight (kg) will be taken for you, with estimated time of 5-10 minutes in order to be completed. These include: neck circumference (cm), waist circumference (cm). Finally, after completing the doctor visit, you will be asked to visit the radiology department within the same center and do a DEXA X-ray, with estimated time of 15-20 minutes in order to be completed."

"You will receive a full report of your measurements at the completion of this visit." Supporting document # 5

"Do you have 15 minutes that we can start our interview session now?"

If Yes, "thank you for your time. We have arranged an empty room within this center for the interview for more privacy, lets go there and start our session."

If No, schedule a better time to meet.

Let's schedule a 30min block for the measurements and the interview during another Visit. (Enter visit information in the box below.)

Mon	Tue	Wed	Thu	Fri

Inform the candidate

- Do you have any questions?
- I look forward to seeing you at < the interview *Visit appointment time and date*>. End

Visit #1 Appointment (30min)

Day: Mon Tue Wed Thu Fri Sat

Date: _____/_____/_____

Time: _____ to _____

File number should not be on survey with serial number; when is serial # assigned? Participant serial # _____

Appendix 2A

إقرار بالموافقة على المشاركة بالدراسة البحثية

إقرار بالموافقة على المشاركة بالدراسة:

٢/١

عنوان البحث إيجاد معيار قياسي جسمي لتقييم زيادة الوزن والبدانة وأضرارها الصحية عند سكان مدينة الرياض السعوديين البالغين.

الغرض من الدراسة

الغرض من دراستي هو اختبار قدرة محيط الرقبة على تشخيص زيادة الوزن والسمنة، ارتفاع الدهون والأعراض المصاحبة له. وكذلك نود تحديد قياسات معيارية للجنسين من السعوديون المقيمين في مدينة الرياض.

ومشاركتكم سوف تسهم في تحديد معايير التقييم اللازمة لتحديد نسبة انتشار السمنة بدقة، تحسين برامج العلاج، ومحاربة السمنة في السعودية. بمشاركتك لنا ، سوف تقدم هذه الدراسة معلومات مفيدة من شأنها أن تقلل انتشار السمنة وأعراضها الجانبية ليس في السعودية فحسب بل في دول الخليج العربي اجمع.

الإجراءات المتبعة

الخطوات المتبعة: بعد أن قرأت ووقعت هذه الموافقة ووافقت على المشاركة ، ستتم المقابلة في غرفة فارغة داخل هذه العيادة لنوفر لك الراحة.

الاستبانة: خلال هذه الزيارة سيطلب منك استكمال هذا الاستبيان التي تشمل بعض الأسئلة حول التاريخ الطبي الخاص بك وبعائلتك ، مستوى نشاطك البدني ، وبعض العادات و الممارسات الغذائية.

القياسات الجسمية: وكذلك خلال التحضيرات السابقة لدخولك للطبيب, ممرضة العيادة سوف تأخذ قياساتك الجسمية (الطول، الوزن، محيط الرقبة، و محيط الخصر) وحرصنا أن تكون من نفس جنس المشارك لتفادي حدوث أي حرج. يجب أن ترتدي ملابس خفيفة و تكون حافي القدمين. وسوف يستغرق أخذ القياسات الى ٥ إلى ١٠ دقائق.

إذا أذنت لي بذلك ، سوف نستخدم جهاز DEXA لقياس الدهون في الجسم وكمية الكتلة العضلية. بعد الانتهاء من زيارة الطبيب ، سوف يطلب منك زيارة قسم الأشعة في نفس المركز. فني الأشعة المتمكن سيشرح لك الإجراء ت اللازمة، وبعد ذلك سوف يطلب منك الاستلقاء على السرير. وسيتم عرض الأشعة السينية من الجهاز(DEXA) على جسمك. وسيستغرق مسح الجهاز لجسمك حوالي ٥-١٠ دقائق.

التحاليل المخبرية: أحتاج أيضا إلى تسجيل بعض النتائج المخبرية الحديثة(أسبوعين) من الملف الطبي الخاص بك. في حال عدم توفر النتائج المخبرية، سوف نقوم بجدولة زيارة أخرى إلى المختبر في نفس العيادة في غضون أسبوع و احد .

الزيارة الثانية إذا لزم الأمر (خلال أسبوع واحد) :

يلزمك الحضور صائم لمدة ١٠-١٢ساعه. وبعد ذلك؛ فني المختبر سوف يشرح لك الإجراءات اللازمة، و بعدها سيطلب منك الجلوس و سيتم سحب الدم من الوريد في ذراعك باستخدام إبرة . كمية الدم المطلوب هي ٦مل (حوالي نصف ملعقة). إذا كان هناك صعوبة في إيجاد الوريد سيتم استبعادك لتجنب أي ألم لا لزوم له .

المخاطر المحتملة والمضايقات

- مشاركتك بهذا البحث تشمل الحد الأدنى من المخاطر . قد تشعر بقليل من الانزعاج أثناء إجراء القياسات الجسمية ولك حرية القرار حينها بالتوقف عن المشاركة بهذا البحث. خلال التحضيرات السابقة لدخولك للطبيب, ممرضة العيادة سوف تأخذ قياساتك الجسمية وحرصنا أن تكون من نفس جنس المشارك لتفادي حدوث أي حرج.
- ويرتبط جهاز(DEXA) بالحد الأدنى من احتمالية زيادة المخاطر. سوف تكون عرضة لكمية ضئيلة من الإشعاع الضوئي ما يعادل ٠,٠١-٠,٠٤ $_{mrem}$، وتقارب الكمية التي تتعرض لها عندما تكون تحت أشعة الشمس لمدة خمس ساعات. وهو اقل من ما يتعرضه الجسم خلال أشعة الصدر مثلا ($_{mrem}$٤٠)، ولكن يمكن أن يكون هناك بعض الانزعاج الطفيف من الاستلقاء على نفس الوضعية. وسوف نختصر وقت القياسات قدر الإمكان، و كذلك سوف نسمح لك بوقت فاصل إذا لزم الأمر.

سحب الدم يحتمل بعض المضاعفات و تشمل الإغماء والدوخة. ومع ذلك ، إذا فقدت الوعي أو شعرت بالدوار أثناء الإجراء، سنتوقف على الفور، و سوف يطلب منك أن تضع رأسك بين ركبتيك . ثم سوف يطلب منك الاستلقاء على الأرض. إلى جانب ذلك، إذا كان هناك صعوبة في إيجاد الوريد سيتم استبعادك لتجنب أي ألم لا لزوم له . وكذلك يمكن أن تتعرض لبعض الألم أثناء سحب عينية الدم وفي بعض الحالات تحصل بعض الكدمات بعد اخذ العينة، ولكن هذا يختفي عادة خلال يوم أو يومين. في حالات نادرة قد يلتهب موضع الإبرة، مما يسبب بعض الألم

Appendix 2A

والاحمرار بالذراع، ولكن في مثل هذه الحالة سوف يطلب منك أن تأتي إلى العيادة للعلاج بالمضادات الحيوية على الفور.

الفوائد المحتملة رغم عدم وجود فوائد مباشرة، سوف يسهم هذا البحث في تحديد معايير التقييم اللازمة لتحديد نسبة انتشار السمنة بدقة، تحسين برامج العلاج، ومحاربة السمنة في السعودية. بمشاركتك لنا ، سوف تقدم هذه الدراسة معلومات مفيدة من شانها أن تقلل انتشار السمنة وأعراضها الجانبية ليس في السعودية فحسب بل في دول الخليج العربي اجمع.

الخصوصية

أننا سوف نبذل قصارى جهدنا للحفاظ على سرية المعلومات التي سوف نحصل عليها منك أو من خلال الملف الخاص بك ,كما أننا سوف نحتفظ بهذه المعلومات في ملف سري خاص . كما أؤكد لك أيضا أنه لن يكتب اسمك أو أي معلومات شخصية متعلقة بك في الاستبيان ولن يطلع عليها أحد سوى أنا ومشرفي الدراسي في الولايات المتحدة الأمريكية.

الحق في التوقف وعدم المشاركة : مشاركتكم في هذا البحث هو عمل تطوعي بحت كما أن لك كامل الحق في التوقف و عدم المشاركة و إذا قررت عدم المشاركة في هذا البحث، يمكنك التوقف في أي وقت دون أي عقوبة ولن يؤثر ذلك على حقوقك وعلى الخدمات التي توفرها(تقدمها) العيادة لك.

٢/٢

حق المشاركة

إذا كان لديك أي سؤال حول حقوقك كمشارك في بحث علمي أو تريد الإبلاغ عن إصابات ناجمة عن هذا البحث، الرجاء الاتصال :

هاتف: ٠٦٧٨-٤٠٥-٣٠١

البريد الإلكتروني irb@edu.umd

أو يمكنكم المراسلة على العنوان التالي:

University of Maryland College Park
Institutional Review Board Office
١٢٠٤Marie Mount Hall
College Park, Maryland, ٢٠٧٤٢

بيان الموافقة

وأخيرا تمت مراجعة و تقييم هذا البحث وفقا لمجلس المراجعة المؤسسي (IRB) بجامعة ميريلاند، كولج بارك، الجنة المختصة بأبحاث الإنسان. توقيعك يشير إلى أنك لا تقل عن ١٨ سنة، قرأت طلب المشاركة (قرأ لك)، تم الإجابة على كل أسئلتك بشكل مرضى و وافي, وأنك توافق طوعا على المشاركة في هذه الدراسة البحثية.

إذا كنت توافق على المشاركة، يرجى تسجيل اسمك أدناه.

الباحث _____ **التاريخ** _____/_____/_____

أسم المشارك _____

التوقيع _____

Appendix 2B

Project title:	The development of a new anthropometric tool for assessing overweight and obesity in Saudi adult population.
Purpose of the Study	The purpose of this study is to examine whether neck circumference (NC) can be used to identify overweight, obesity, high lipid profile and their associated risk factors, as well as to establish NC gender-specific cut-off point values for Saudi population in the city of Riyadh. Your participation in this project will aid us to find standardized assessment tools to determine accurate prevalence, treatment protocols, and achieve control of obesity among Saudi population.
Procedures	**Baseline:** After you have read and signed this consent and agreed to participate, you will be interviewed in an empty room within the same clinic to provide you comfort. ***Questionnaires*:** During this visit you will also be asked to complete a questionnaires that will ask you about yourself, your medical history and immediate family medical history, your level of physical activity, as well as a variety of dietary habit and practices. ***Physical Measures:*** prior to seeing your doctor and during the routine preparation session, well- trained clinic in charge nurse, of the same sex as you, will take some extra measurements other than height (cm), weight (kg), with estimated time of 5-10 minutes in order to be completed. These include: neck circumference (cm), waist circumference (cm), and body fat (%). You should be wearing light clothes, bare head and feet. We will use DEXA to measure your whole body fat and your lean body mass (muscle). After completing the doctor visit, you will be asked to visit the radiology department within the same center. A well-trained technician will explain the procedure to you, and then you will lie flat on the DEXA table. X-rays from the machine will be introduced into your body. We will ask you to lie still for about 5-10 minutes while the DEXA machine scans over your body. This procedure is not painful, but there could be some minor discomfort from lying in the same position. This discomfort will be minimized by keeping the time involved in making the measurements as short as possible, and by allowing you a break if necessary. During the DEXA scanning, you will be exposed to a tiny amount of radioactivity. The amount of radioactivity is equivalent to the amount you are exposed to when you are

outside for five hours. The level of exposure is associated with a minimally increased risk.

The physician will inform you about the study measures, e.g., weight, height, BMI along with a chart of weight categories, blood pressure, waist circumference along with risk cut-offs, body fat percentage along with a chart of typical ranges

Blood test results: I will obtain some recent laboratory results (within 1week) of your medical record; plasma glucose, insulin, HDL cholesterol, triglycerides, and blood pressure. If your medical record does not have required biochemical parameters, we will schedule you for another visit to the laboratory in the same clinic within one week.

Second visit if needed: within one week to Baseline:

You have to attend fasting for 10-12hrs. A well-trained technician will explain the procedure to you, and then you will be seated and blood will be drawn from a vein in your arm using a needle. Total blood volume required is 6mL (approximately half tablespoon). If you have poor quality vein you will be excluded to avoid any unnecessary pain.

Potential Risks and Discomforts

There are minimal risks involved with assessment of body composition. you may feel uncomfortable having your body measured and you can elect not to participate in this portion of the assessment if you experience discomfort. The anthropometric measurements will be taken prior to visiting the doctor and during the routine preparation session by clinic in charge nurse, of the same sex as each participant, to minimize risk of discomfort or embarrassment.

The DEXA level of exposure is associated with a minimally increased risk. The total radiation dose is extremely low, 0.01 to 0.04 mrem per scan, which is within the range of background radiation and considerably less than conventional X-rays. A chest X-ray, for example, delivers a radiation dose of 40 mrem. This procedure is not painful, but there could be some minor discomfort from lying in the same position. This discomfort will be minimized by keeping the time involved in making the measurements as short as possible, and by allowing you a break if necessary.

The risks associated with blood drawing include fainting, dizziness or becoming light-headed. However, If you loose consciousness or feel dizzy during the procedure, it will be

	discontinued. And you will be asked to place your head between your knees. You will then be asked to lie down (in a supine position). Besides, if you with poor quality vein you will be excluded to avoid any unnecessary pain. You may also experience slight pain during the drawing of blood samples, and in some cases the possibility of bruising after the sample has been taken, but this generally disappears in about one to two days. In rare cases, the site of the blood draw can be infected, causing arm pain and redness; however, in such case you will be advised to come to the clinic for immediate antibiotic treatment.
Potential benefits	Although there are no direct benefits; this research will contribute to the establishment of an accurate prevalence of obesity and cardio-metabolic risk factors and better treatment protocols. Moreover, it will be a part of future novel research in the development of standardized assessment tools for Saudi Arabia.
Confidentiality	Any potential loss of confidentiality will be minimized by storing data in a locked cabinet in a locked office and in a password-protected computer. If we write a report or article about this research project, your identity will be protected to the maximum extent possible. Your information may be shared with representatives of the University of Maryland, College Park or governmental authorities if you or someone else is in danger or if we are required to do so by law.
Right to Withdraw and Questions	Your participation in this research is completely voluntary. You may choose not to take part at all. If you decide not to participate in this study or if you stop participating at any time, you will not be penalized or lose any benefits to which you otherwise qualify. If you decide to stop taking part in the study, if you have questions, concerns, or complaints, or if you need to report an injury related to the research, please contact the investigator, David Lei, PhD at: 0121 Skinner Bldg. University of Maryland, College Park, MD 20742, 301-405-2143 dlei@mail.umd.edu, or Co-Investigator Reem Albassam. 9524 Lagersfield Cir Vienna, VA 22181, 571-239-9940, reem.albassam@gmail.com

Participant Rights	*If you have questions about your rights as a research participant or wish to report a research- related injury, please contact:* **University of Maryland College Park** **Institutional Review Board Office** **1204 Marie Mount** **College Park, Maryland, 20742** **E-mail: irb@umd.edu** **Telephone: 301-405-0678** *This research has been reviewed according to the University of Maryland, College Park IRB procedures for research involving human subjects.*
Statement of Consent	*Your signature indicates that you are at least 18 years of age; you have read this consent form or have had it read to you; your questions have been answered to your satisfaction and you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.* *If you agree to participate, please sign your name below.*
Signature and Date	**PARTICIPANT NAME** **PARTICIPANT SIGNATURE** **DATE**

Appendix 3A

تاريخ المقابلة / / هـ ١٤٣٦
تاريخ المقابلة / / م ٢٠١٥

Serial No:	Date: / /		Lab Code:

١- هل سبق وشاركت في دراسة بحثية: . . . . . (١) نعم (٢) لا (٣) لا أعرف

البيانات الاجتماعية والديمغرافية:

٢- الجنس: . . . . . (١) ذكر (٢) أنثى

٣- العمر: . . . . . ----------

٤- مستوى التعليم؟: . . . . . (١) أمي (٢) أجيد القراءة والكتابة (٣) الابتدائية (٤) المتوسط (٥) الثانوية (٦) جامعي (٧) دراسات عليا

٥- الحالة الاجتماعية؟: . . . . . (١) أعزب (٢) متزوج (٣) منفصل (٤) مطلق (٥) أرمل

٦- عدد الأطفال: . . . . . (١) لا يوجد (٢) واحد (٣) ٢ - ٣ (٤) ٤ - ٦ (٥) أكثر من ٦ أطفال

٧- الوظيفة : . . . . . (١) عاطلين عن العمل (ربة منزل) (٢) طالب (٣) معلم (٤) أعمال مكتبية (٥) رجل أعمال/تجارة (٦) طبيب (٧) ممرض (٨) أخرى: . . . . . .(حدد/ي)

٨- معدل دخل الأسرة الشهري: . . . . . (١) أقل من ٢،٠٠٠ رس (٢) ٢،٠٠٠ رس - ٤،٩٩٩ رس (٣) ٥،٠٠٠ رس - ٧،٩٩٩ رس (٤) ٨،٠٠٠ رس - ١٠،٩٩٩ رس (٥) ١١،٠٠٠ رس - ١٣،٩٩٩ رس (٦) ١٤،٠٠٠ رس - ١٦،٩٩٩ رس (٧) ١٧،٠٠٠ رس - ١٩،٩٩٩ رس (٨) أكثر من ٢٠،٠٠٠ رس (٩) لا أعرف

٩- هل تدخن: . . . . . (١) لا ابداً (<١٠٠سيجارة) (٢) مدخن سابق(>١٠٠سيجارة) (٣) أدخن بعض الأحيان(<١٠٠سيجارة) (٤) أدخن بشكل يومي (>١٠٠سيجارة)

البيانات الصحية/ تاريخ العائلة الصحي:

١٠- هل يعاني احد أفراد العائلة من السمنة: . . . . . (١) لا يوجد (٢) الأم فقط (٣) الأب فقط (٤) الأم والأب (٥) أخ أو أخت (٦) غير ذلك: . . . . . .(حدد/ي)

١١- هل يعاني احد أفراد العائلة من إحدى الأمراض التالية: . . . . . (١) لا يوجد (٢) السكري (٣) أمراض القلب (٤) الجلطة (٥) ارتفاع الكولسترول (٦) ارتفاع ضغط الدم (٧) السرطان (٨) هشاشة العظام (٩) غير ذلك: . . . . . .(حدد/ي)

Appendix 3A

البيانات الصحية/ تاريخ المشترك الصحي:

١٢- هل سبق وشخصك الطبيب بإحدى الأمراض التالية: . . . . . [ ]

(١) لا (٢) السمنة (٣) ارتفاع ضغط الدم
(٤) معرض للسكري(ارتفاع السكر) (٥) السكري
(٦) الربو (٧) فقر الدم (٨) أمراض القلب
(٩) أخرى: . . . . . .(حدد/ي)

١٣- هل تتناول علاج محدد لارتفاع الدهون الثلاثية: . . . . . [ ]

(١) نعم (٢) لا (٣) لا أعرف

١٤- هل تتناول علاج محدد لارتفاع الكولسترول: . . . . . [ ]

(١) نعم (٢) لا (٣) لا أعرف

١٥- هل تتناول علاج لارتفاع الضغط سبق و وصفه لك الطبيب: . . . . . [ ]

(١) نعم (٢) لا (٣) لا أعرف

١٦- هل تتناول علاج لارتفاع السكر سبق و وصفه لك الطبيب: . . . . . [ ]

(١) نعم (٢) لا (٣) لا أعرف
إذا كانت الإجابة نعم :
(١/أ) اسم الدواء: . . . . . (١/ب) التكرار (كم مرة تتناوله): . . . . . .
(١/ج) الجرعة (الكمية في كل مرة): . . . . . (١/د) المدة (منذ متى وأنت تستخدمه): . . . . . .

١٧- هل تتناول فيتامينات أو مكملات غذائية : . . . . . [ ]

(١) نعم (٢) لا (٣) لا أعرف

١٨- هل تتبع حمية غذائية لغرض طبي (سبق و وصفة لك الطبيب): . . . . . [ ]

(١) نعم (٢) لا (٣) لا أعرف
إذا كانت الإجابة نعم :
(١/أ) الغرض (لماذا تتناوله): . . . . . (١/ب) المدة(منذ متى وأنت تتبعها): . . . . . .

١٩- هل تعاني من أي مشكلة صحية مرتبطة بالعظام / العضلات / المفاصل (أو ألم في الصدر، والدوخة، وضيق في التنفس) يمكن أن تتعارض مع ممارسة الرياضة؟ . . . . . [ ]

(١) لا (٢) نعم . . . . . .(حدد/ي)

<u>للنساء فقط :</u>

٢٠- كم كان عمرك عند البلوغ: . . . . . [ ]

حددي: . . . . . .

٢١- متى كانت أخر دورة شهرية لك (الحيض): . . . . . [ ]

(١) الشهر الماضي(دورة منتظمة) (٢) خلال الـ١٢ شهر الماضي (دورة غير منتظمة)
(٣) متوقفة لمدة ١٢ شهر متواصل

٢٢- هل سبق و تناولتي علاج هرموني مثل الأستروجين أو البروجسترون (سواء كان على هيئة حبوب, كريم, لصاقات الجلد, أو إبر): . . . . . [ ]

(١) نعم (٢) لا (٣) لا أعرف
إذا كانت الإجابة نعم :
(١/أ) الغرض (لماذا تتناوله): . . . . . (١/ب) المدة (منذ متى وأنت تستخدمه): . . . . . .

Appendix 3A

مصدر المعلومات الغذائية:

٢٣- ما هو مصدر معلوماتك الغذائية: . . . . . .

(١) الأصدقاء (٢) العائلة (٣) الجرائد و المجلات (٤) الراديو و التلفزيون (٥) الانترنت و وسائل التواصل الاجتماعي
(٦) المنشورات (٧) أخصائية التغذية (٨) أخرى: . . . . . .(حدد/ي)

العادات والممارسات الغذائية:

٢٤- كم عدد الوجبات المنتظمة التي تتناولها يوميا: . . . . . .

(١) واحدة (٢) اثنتين (٣) ثلاثة (٤) غير منتظم

١١/ أ- إذا لم تكن ثلاث وجبات, ما هي الوجبة التي تهملها (تتركها) عادةً: . . . . . .

(١) الإفطار (٢) الغداء (٣) العشاء

٢٥- عادةً طعامك اليومي يعتمد علي: . . (خيار واحد فقط- النوعية الأكثر استخداماً). . . . . .

(١) أطعمة غنية بالبروتين (اللحوم، الدجاج، الأسماك، البيض، البقوليات، والجبن).
(٢) أطعمة عالية الكربوهيدرات (الخبز، المعكرونة، الأرز، البطاطا).
(٣) أطعمة عالية الدهون (السجق والبطاطس المقلية والكعك وكريم، والزبد).
(٤) أطعمة مختلفة كل يوم.

٢٦- كم حبة من الفاكهة تتناول يومياً: . . . . . .

(١) لا أكل الفاكهة (٢) ليست يومياً (٣) كل يوم

٢٧- هل تحرص أن تشتمل وجباتك اليومية علي الخضار (طازج أو مطبوخ) . . . . . .

(١) لا ابداً (٢) أحيانا (٣) دائماً

٢٨- كم وجبة خفيفة تتناول/باليوم: . . . . . .

(١) خمس مرات أو أكثر (٢) أربع مرات (٣) ثلاث مرات (٤) مرتين (٥) مرة واحدة (٦) لا أتناول

٢٩- وجبتك الخفيفة عادةً تتكون من: . . . . . .

(١) شكولاتة (٢) كيك (٣) رقائق البطاطا(شبس) (٤) مكسرات (٥) مشروبات غازية (٦) فاكهة
(٧) أخرى: . . . . . .(حدد/ي)

٣٠- ما المحليات التي تستخدمها عادة: . . . (خيار واحد فقط- الطريقة الأكثر استخداماً). . . . . .

(١) السكر الأبيض (٢) العسل (٣) سكر الفواكهة
(٤) المحليات الصناعية(سويت ان لو, سبلندا, وغيرة) (٥) أخرى: . . . . . .(حدد/ي)

٣١- طريقة طبخك اليومي عادةً هي:. (خيار واحد فقط- الطريقة الأكثر استخداماً) . . . . . .

(١) الشوي أو السلق (٢) بالفرن وبدون إضافة دهون (٣) التشويح بكمية زيت قليلة
(٤) التشويح بالزيت (٥) لا اعرف (٦) أخرى: . . . . . .(حدد/ي)

٣٢- نوع الدهون المستخدمة بالطبخ عادةً هي: . . (خيار واحد فقط- الدهون الأكثر استخداماً). . . . . .

(١) زيت الذرة او تباع الشمس (٢) زيوت النخيل (٣) سمن نباتي
(٤) سمن حيواني أو زبده (٥) لا اعرف (٦) أخرى: . . . . . .(حدد/ي)

٣٣- من منتجات الألبان, ماذا تتناول عادةً: . . . . . (خيار واحد فقط- المنتج الأكثر استخداماً). . . . . .

(١) كامل الدسم (٢) قليل الدسم (٣) خالي الدسم

٣٤- هل تتناول الوجبات السريعة: . . . . . .

(١) نعم (٢) أحيانا (٣) لا

٣٥- إذا لم تكن الإجابة لا, كم مرة تناولتها خلال الأسبوعين الماضيين: . . . . . .

عدد المرات(. . . . . .)

Appendix 3A

٣٦- ما حجم الوجبة التي تتناولها عادةً (شاورمر, برجركنج, ماك, علاء الدين): . . . . . .

(١) صغير (٢) وسط (٣) كبير (٤) سوبر (٥) أخرى:. . . . . ..(حدد/ي)

طريقة المعيشة و النشاط البدني:

الأنشطة البدنية هي أي نشاط يزيد ضربات القلب عن المعدل الطبيعي، سواء كان هذا الجهد ناتج عن العمل، الحركة, التنقل, أو للمتعة. الفقرة التالية أسئلة عن كمية و حدة(شدة) النشاط البدني الذي تقوم به عادةً. وترتبط حدة (شدة) النشاط بكمية الطاقة التي تستخدمها للقيام بتلك الأنشطة.

٣٧- هل تمارس الرياضة عادةً: . . . . . .

(١) لا (٢) أحيانا (٣) في بعض المواسم (٤) نعم علي مدى العام (طوال السنة)

إذا كانت **الإجابة لا** انتقل إلى سؤال **٣٩**

A٣٧- ما نوع الرياضة التي تمارسها: . . . . . .

(١) المشي (٢) الجري (٣) السباحة (٤) ايروبك

(٥) أخرى: . . . . . .(حدد/ي)

B٣٧- كم مرة بالأسبوع تقوم بممارسة الرياضة: . . . . . .

(١) ليس كل أسبوع (٢) مرة (٣) مرتين (٤) ثلاث (٥) اربع (٦) خمس (٧) ست (٨) كل يوم

(٩) أخرى: . . . . . .(حدد/ي)

C٣٧- كم مدة التمرين في كل مرة: . . . . . .

(١) المدة (. . . . .) (٢) حتى التعرق أو ارتفاع نبضات القلب

٣٨- نمط حياتك المعيشي يعتبر: . (خيار واحد فقط). . . . . .

(١) عديم الحركة (مشاهدة التلفزيون, القراءة, أو الطباعة) (٢) قليل الحركة (أعمال منزلية, تسوق)

(٣) متوسط الحركة (أعمال الحديقة, مشي) (٤) نشيط (سباحة, ركوب الدراجة)

Appendix 3A

هذا الجزء للاستخدام الرسمي فقط
تقوم الباحثة بتعبئة

Anthropometrical data:

HEIGHT (Ht) = ---------- Cm

WEIGHT (Wt)= ---------- Kg

Neck circumference = --------- Cm

Waist circumference = --------- Cm

Body Mass Index (BMI) = ---------Kg/M²

Body fat % = ---------%

Laboratory Results:

Systolic BP	----------		Cholesterol	----------	
Diastolic BP	----------		Triglycerides (TG)	----------	
Fasting glucose	----------		High-density lipoprotein (HDL)	----------	
Fasting Insulin	----------		Low-density lipoprotein (LDL)	----------	

Appendix 3B

Date of the interview [ ][ ] / [ ][ ] / 1 4 3 [ ]

Date of the interview [ ][ ] / [ ][ ] / 2 0 1 [ ]

Center: _____

Serial number: _____

Lab code: _____

1- Have you participated in any research studies before?: . . . . . .

(1) Yes (2) No (3) I don't know

Socio-demographic Data:

2- Age: [ ] _____

3- Gender: [ ] (1) Male (2) Female

4- Education level: . . . . . [ ]

(1) Illiterate (2) read and write (3) Elementary
(4) Intermediate (5) Secondary (6) Graduate (7) Post- graduate[code=8]

5- Marital Status:. . . . . [ ]

(1) Unmarried (2) Married (3) separated
(4) Divorced (5) Widowed

6- Number of children: . . . . . [ ]

(1) None (2) One (3) 2-3
(4) 4-6 (5) More than 6

7- Occupation: . . . . . [ ]

(1) Unemployed (Housewife) (2) Student (3) Teacher
(4) Office work (5) Business (6) Medical Doctor (7) Nurse
(8) Retired (9) Millenarian (10) Other_____ (specify)

8- Average Monthly Family Income:. . . . . [ ]

(1) Less than 1,999 (2) 2,000 SR - 4,999 SR (3) 5,000 SR - 7.999 SR
(4) 8.000 SR -10.999 SR (5) 11,000 SR - 13.999 SR (6) 14.000 SR -16.999 SR
(7) 17,000 SR - 19.999 SR (8) More than 20.000 SR (9) Un known

9- Your smoking status (cigar, pipe, shisha [water pipe or flavored tobacco]) is: . . . . . [ ]

(1) Never smoke (2) Current some day smoker
(3) Former smoker (4) Current every day smoker

Family Medical History / Health History Data:

10-Family history of obesity:. . . . . [ ]

(1) None (2) Mother only (3) Father only]
(4) Mother and Father (5) Sister or Brother (6) Other_____ (specify)

11-Any family history of the following . . . . . [ ]

(1) None (2) Diabetes (3) Heart diseases
(4) Stroke (5) High cholesterol (6) High blood pressure/ Hypertension
(7) Cancer (8) Osteoporosis (9)Other_____
(specify)

Appendix 3B

Subject's Medical History Data:

12-Have you ever been diagnosed with any of the following?. . . . . .

(1) None (2) Obesity (3) High blood pressure (Hypertension)
(4) Pre-diabetes (elevated blood sugar) (5) Diabetes (6) Asthma
(7) Anemia (8) Heart diseases (9) Other_____ (specify)

13-Are you taking specific treatment for hypertriglyceridemia? . . . . . .

(1) Yes (2) No (3) Don't know

14-Are you taking treatment for previously diagnosed hypercholesterolemia?. . . . . .

(1) Yes (2) No (3) Don't know

15-Are you taking treatment for previously diagnosed hypertension?. . . ..

(1) Yes (2) No (3) Don't know

16-Are you taking treatment for previously diagnosed diabetes?. . . ..

(1) Yes (2) No (3) Don't know
If yes:
(2/A) Name: _____ (2/B) Frequency (how often take): _____
(2/C) Dose (how much take): _____ (2/D) Duration (how long been taking): _____

17-Are you taking any vitamins or dietary supplements? . . ..

(1) Yes (2) No (3) Don't know

18-Are you following any special diet for medical purposes?.. . . . .

(1) Yes (2) No (3) Don't know

19-Any orthopedic/muscular/joint/medical conditions (eg. chest pain, dizziness, shortness of breath that would interfere with exercise training?.. . . . .

(1) No (2) Yes: _____ (specify)

For females only,
20-What is the age of the first menstrual cycle?. . . ..

_____ (specify)

21-When was your last menstrual cycle? . . ..

(1) Last month (regular mensuration)
(2) Within the past 12 months (irregular mensuration)
(3) Stopped for at least 12 consecutive months

22-Have you ever used female hormones such as estrogen and progesterone? Please include any forms, such as pills, cream, patch, and injections.. . .. .

(1) No (2) Yes (3) Don't know
If yes:
(2/A) Purpose (why take): _____ (2/B) Duration (how long been following):_____

Appendix 3B

Nutrition knowledge:

23-What is the source of your nutritional information? . .. .

(1) Friends (2) Family (3) Newspaper &Magazine (4) Radio & TV
(5) Internet & social media (6) Booklets
(7) Dietitian (8) Other_____ (specify)

Dietary habit and practices:

24-How many regular main meals do you eat daily? . .. .

(1) One (2) Two (3) Three
(4) Irregular

IF not three, which meal do you skip? . .. .

(1) Breakfast (2) Lunch (3) Dinner

25-Your diet is based mainly on: . .. .

(1) High protein content food (meat, chicken, fish, egg, legumes, and cheese).
(2) High carbohydrate content food (bread, pasta, rice, potato).
(3) High fat content food (sausage, fried potato, cakes, cream, butter).
(4) Different food every day.

26-Do you concern to eat fruit daily? . . . .

(1) Don't eat (2) Not every day (3) Every day

Daily fruit consumption: .. . .
I eat (_____) pieces

27-Do you concern to eat two serving of vegetables daily (Do you ensure that your meals contain vegetables daily)? . .. .

(1) Never (2) Sometimes (3) Always

28-How many snack do you eat /day? . . . .

(1) 5 times or more (2) 4 times (3) 3 times (4) Twice (5) once
(6) never

29-Your snacks are based mainly on: . .. .

(1) Chocolate (2) Cake (3) Chips (4) Nuts
(5) Regular soft drink (6) Canned juices
(7) Other _____ (specify)

30-What sweeteners do you use usually? . .. .

(1) Don't use (2) Regular sugar (3) Honey (4) Fruit sugar (5) Artificial sweeteners
(6) Other _____ (specify)

31-The way that you usually cook with: . .. .

(1) Grilled, boiled (2) Cooks in the oven with out fat (3) Cooks in a pan with little fat
(4) Cooks in a pan with fat (5) Frying (6) Don't know

32-Cooking fat that you use usually? . .. .

(1) Don't use (2) Corn oil, sunflower (3) Palm oil (4) Margarine
(5) Butter (6) Don't know (7) Olive oil

Appendix 3B

33-From dairy products, what do you consume usually?.. . . . .

(1) Don't use (2) Regular (3) Low fat (4) Skimmed

34-Do you eat fast foods? . . ..

(1) Yes (2) Sometimes (3) NO

35-If yes, how many times during the last 2 weeks: . . ..

(_____) times

36-What is your meal size usually? (Aladdin, Burger king, Shawarmer, Mc Donald's). . . . . .

(1) Small (2) Medium (3) Large (4) Super size
(5) Other _____(specify)

Physical activity and life style:

Physical Activities are any activities that increase your heart rate above its resting rate, whether you do them for work, transportation, or pleasure. The following questions ask about the amount and intensity of physical activity you usually do. The intensity of the activity is related to the amount of energy you use to do these activities.

37-Do you usually practice a physical activity? . . ..

(1) Never (2) Some times (3) In some seasons
(4) Always during the entire year

37-A- What type of physical activity you do practice?.. . . . .

(1) Walking (2) Running (3) Swimming
(3) Aerobics (5) Other _____ (specify)

37-B- How many times do you exercise/week?.. . . ..

(1)1 or less (2) (3) (4) (5) (6) (Daily)

37-C- For how long do you exercise each time? . .. .

(1) (_____)minute Or (2) Till sweating or heart beat raises

38-Your lifestyles is: . . . .

(1) Very Sedentary (typing, reading, and watching TV) (2) Sedentary (cleaning, shopping)
(3) Moderate active (hard job) (4) Very active (swimming, cycling)

Appendix 3B

Anthropometrical data:

HEIGHT (Ht) = ---------- Cm

WEIGHT (Wt)= ---------- Kg

Body Mass Index (BMI) = ---------Kg/M²

Neck circumference = --------- Cm

Waist circumference = --------- Cm

Body fat % = ---------%

Laboratory Results:

Systolic BP	----------		Cholesterol	----------	
Diastolic BP	----------		Triglycerides (TG)	----------	
Fasting glucose	----------		High-density lipoprotein (HDL)	----------	
Fasting Insulin	----------		Low-density lipoprotein (LDL)	----------	

Appendix 3C

Coding Sample

Do you concern to eat fruit daily? . . . . . | | |

(1) Don't eat [code=1] (2) Not every day [code=2] (3) Every day [code=3]

Do you concern to eat two serving of vegetables daily (Do you ensure that your meals contain vegetables daily)? | | |

(1) Never[code=1] (2) Sometimes[code=2] (3) Always[code=3]

What sweeteners do you use usually? . . . . . | | |

(0) Don't use [code=3] (1) Regular sugar [code=1] (2) Honey [code=2]
(3) Fruit sugar [code=2] (4) Artificial sweeteners [code=3] (5) Other [code= decide later], in our sample, no one responded "Other"

The way that you usually cook with: . . . . . | | |

(1) Grilled, boiled [code=3] (2) Cooks in the oven with out fats [code=3]
(3) Cooks in a pan with little fat [code=2] (4) Cooks in a pan with fat [code=1]
(5) Frying [code=1]
(6) Don't know [code= decide later] in our sample, no one responded "don't know"

Appendix 4

UNIVERSITY OF MARYLAND
INSTITUTIONAL REVIEW BOARD

1204 Marie Mount Hall
College Park, MD 20742-5125
TEL 301.405.4212
FAX 301.314.1475
irb@umd.edu
www.umresearch.umd.edu/IRB

DATE:	June 15, 2015
TO:	David Lei, Ph.D. OBJ OBJ OBJ OBJ OBJ OBJ OBJ OBJ OBJ OBJ Professor
FROM:	University of Maryland College Park (UMCP) IRB
PROJECT TITLE:	[411873-6] The development of a novel anthropometric tool for assessing overweight and obesity in Saudi adult population.
REFERENCE #:	
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
APPROVAL DATE:	June 15, 2015
EXPIRATION DATE:	June 11, 2016
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *4 & 7*

Thank you for your submission of Continuing Review/Progress Report materials for this project. The University of Maryland College Park (UMCP) IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a project design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

Prior to submission to the IRB Office, this project received scientific review from the departmental IRB Liaison.

This submission has received Expedited Review based on the applicable federal regulations.

This project has been determined to be a More than Minimal Risk project. Based on the risks, this project requires continuing review by this committee on an annual basis. Please use the appropriate forms for this procedure. Your documentation for continuing review must be received with sufficient time for review and continued approval before the expiration date of June 11, 2016.

Please remember that informed consent is a process beginning with a description of the project and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the project via a dialogue between the researcher and research participant. Unless a consent waiver or alteration has been approved, Federal regulations require that each participant receives a copy of the consent document.

Please note that any revision to previously approved materials must be approved by this committee prior to initiation. Please use the appropriate revision forms for this procedure.

All UNANTICIPATED PROBLEMS involving risks to subjects or others (UPIRSOs) and SERIOUS and UNEXPECTED adverse events must be reported promptly to this office. Please use the appropriate reporting forms for this procedure. All FDA and sponsor reporting requirements should also be followed.

All NON-COMPLIANCE issues or COMPLAINTS regarding this project must be reported promptly to this office.

Appendix 4

Please note that all research records must be retained for a minimum of seven years after the completion of the project.

If you have any questions, please contact the IRB Office at 301-405-4212 or irb@umd.edu. Please include your project title and reference number in all correspondence with this committee.

This letter has been electronically signed in accordance with all applicable regulations, and a copy is retained within University of Maryland College Park (UMCP) IRB's records.

Appendix 4

المملكة العربية السعودية
وزارة التعليم العالي
جامعة الملك سعود
رمزها ٠٣٤
كلية العلوم

بسم الله الرحمن الرحيم

الرقم: ٤/٦٧/٤٥٩٦٧٩
التاريخ: ١٩/ ١٢ /١٤٣٥هـ
المرفقات: .....
الموضوع: .....

سعادة الباحثة/ ريم البسام **حفظها الله**

السلام عليكم ورحمة الله وبركاته

نفيد سعادتكم بأن لجنة أخلاقيات البحوث العلمية الحيوية بكلية العلوم ناقشت في الاجتماع الرابع يوم الخميس 1435/07/16هـ، الموافق 2014/05/15 م البحث المرسل من سعادتكم تحت عنوان:

" The development of a novel anthropometric tool for assessing Overweight and Obesity in Saudi adult population."

وقد وافقت اللجنة على التعديل الذي تم من قبلكم بشأن تصويب الأخطاء اللغوية باللغة العربية وإزالة المقطع الذي يشير إلى موافقة المشاركين السعوديين بالبحث شفهياً والاستعاضة عنها بموافقة خطية كما جرت العادة على أن يعمل بهذا التغيير في النسخة الأصلية المقدمة للجنة.

القرار: الموافقة.

وتقبلوا خالص تحياتي وتقديري،،،

رئيس لجنة أخلاقيات البحوث الحيوية العلمية

بكلية العلوم

أ.د. ناصر بن محمد الداغري

P. O. Box 2455, Riyadh 11451 Tel 4674447 – Fax.: 4674253
ص. ب ٢٤٥٥ الرياض ١١٤٥١ هاتف: ٤٦٧٤٤٤٧ – فاكس: ٤٦٧٤٢٥٣
E-mail: cscience@ksu.edu.sa

Appendix 5

Measures of additive interaction

Since we are interested in the joint exposure effects of 2 factors (large neck and large waist; large neck and high BMI) on disease risk, I calculated the additive interaction. For the calculations of the measures of additive interaction between two dichotomous risk factors, we have four possible combinations and, thus, four exposure categories. As suggested by Rothman et al, and Andersson et al. (193, 194), I computed new composite variables, indicating a variable of joint exposure to both risk factors (11), a variable of exposure to one of the risk factors only (10 or 01), and the joint reference variable of no exposure (00).

Syntax

```
IF (Neck cutoff= 2 and Other measure= 2) ind11 = 1 .
EXECUTE.
IF ((Neck cutoff = 2 and Other measure = 1) or
(Neck cutoff = 1 and Other measure = 2) or
(Neck cutoff = 1 and Other measure = 1)) ind11 = 0.
EXECUTE.
IF (Neck cutoff = 2 and Other measure = 1) ind10 = 1.
EXECUTE.
IF ((Neck cutoff = 2 and Other measure = 2) or
(Neck cutoff = 1 and Other measure = 2) or
(Neck cutoff = 1 and Other measure = 1)) ind10 = 0.
EXECUTE.
IF (Neck cutoff = 1 and Other measure = 2) ind01 = 1.
EXECUTE.
IF ((Neck cutoff = 2 and Other measure = 2) or
(Neck cutoff = 2 and Other measure = 1) or
(Neck cutoff = 1 and Other measure = 1))ind01 = 0.
EXECUTE.
```

Logistic regression analysis is then used to estimate the ORs using these new indicator variables. As for logistic regression, in cross-sectional study, we make the

common assumption that the odds ratio can be used instead of the relative risk. The model includes terms for three of the four possible combinations of exposure while the fourth category used as reference category (195).

Three different measures exist to quantify the amount of interaction on an additive scale (193):

1) **The Relative excess risk** due to interaction (RERI), which can be interpreted as the risk that is additional to the risk that is expected on the basis of the addition of the ORs under exposure, calculated as the difference between the expected risk and the observed risk: RERI=OR11 –OR10 –OR01 +1

2) **The Attributable proportion** due to interaction (AP), which is interpreted as the proportion of disease or mortality that is due to interaction among persons with both exposures: AP = RERI/OR11

3) **The Synergy index** (S), which can be interpreted as the excess risk from exposure to both exposures when there is interaction relative to the risk from exposure without interaction: S = [OR11 – 1]/[(OR10 – 1) + (OR01 – 1)]

Appendix 5

The steps of the CI 95% calculation:

If we let $h(\hat{0}_1)$, $h(\hat{0}_2)$, and $h(\hat{0}_3)$ denote the estimated coefficients for OR10, OR01, and OR11, respectively.

To find the variance of $h(\hat{0})$, I used the standard delta method based on a Taylor Series expansion of h about$(\hat{0})$, whereby the variance estimate is of the general form:

$$\widehat{Var}[h(\hat{0})] = h1^2\widehat{\sigma 1^2} + h2^2\widehat{\sigma 2^2} + h3^2\widehat{\sigma 3^2} + 2h1h2\hat{\sigma}12 + 2h1h3\hat{\sigma}13 + 2h2h3\hat{\sigma}23$$

To find $\hat{\sigma}$ in SPSS, I used the covariance matrix syntax:

```
REGRESSION
/DESCRIPTIVES MEAN STDDEV CORR SIG N COV
/MISSING LISTWISE
/CRITERIA=PIN(.05) POUT(.10)
/NOORIGIN
/DEPENDENT Metabolic Syndrome
/METHOD=ENTER AGE ind11 ind10 ind01
```

As per Hosmer and Lemeshow (195) I used the following denotations

- **In calculation CI 95% for RERI**
  h1= -10 coefficient
  h2= -01 coefficient
  h3= 11 coefficient

- **In calculation CI 95% for AP**
  h1= 10coefficient ÷ 11coefficient
  h2= 01coefficient ÷ 11coefficient
  h3= (10coefficient + 01coefficient − 1) ÷11coefficient

- **In calculation CI 95% for S**
  h1= -10coefficient ÷ (10coefficient + 01coefficient −2)
  h2= -01coefficient ÷ (10coefficient + 01coefficient −2)
  h3= -11coefficient ÷ (11coefficient −1)

In the absence of an interaction effect, RERI and AP equal 0 and S equals 1 (193, 194, 195, 1).

[1] De Mutsert R, Jager KJ, Zoccali C, Dekker FW: The effect of joint exposures: examining the presence of interaction. Kidney Int; 2009 Apr;75(7):677-861.

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