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DEPARTMENT OF BIOCHEMISTRY AND BIOTECHNOLOGY

PREDOMINANT COMPONENTS OF METABOLIC SYNDROME AMONG PRE- AND POSTMENOPAUSAL GHANAIAN WOMEN: A CASE STUDY IN KUMASI METROPOLIS

THIS THESIS IS PRESENTED TO THE DEPARTMENT OF BIOCHEMISTRY AND BIOTECHNOLOGY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF THE MASTER OF PHILOSOPHY DEGREE IN BIOCHEMISTRY

BY

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DECLARATION

I hereby declare that this submission is my own work towards the MPhil and that, to the best of my knowledge, it contains no material previously published by another person nor material which has been accepted for the award of any other degree of the University, except where due acknowledgement has been made in text.

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ABSTRACT

MetS (MetS) is an important health condition which puts individuals at risk of cardiovascular diseases and type 2 diabetes as well as obesity-related cancers such as colon and renal cell in men, and endometrial and oesophageal in women. Menopause and age are thought to predispose women to the development of MetS. This study aimed to estimate the prevalence of MetS and identify its predominant components among pre- and postmenopausal Ghanaian women receiving healthcare at Suntreso and Seventh Day Adventist Hospitals in Kumasi, Ghana. It also sought to examine the influence of atherogenic and obesity indicators on the related determinants of MetS, and how these indicators could be used to predict MetS and its cut-offs in postmenopausal Ghanaian women. A cross-sectional study was conducted among pre- and postmenopausal women attending the out-patient departments of the two hospitals between May and July, 2011. Two hundred and fifty (250) Ghanaian women with one hundred and forty-three (143) being premenopausal women (control) and one hundred and seven (107) postmenopausal women were recruited for the study. Information on socio-demographic characteristics, medical history and menopausal status were obtained by questionnaire. Blood pressure, anthropometric measurements and blood sample were taken for some biochemical analyses. The women were evaluated for the prevalence of MetS using the World Health Organization (WHO), National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), International Diabetes Federation (IDF) and Harmonization (H_MS) criteria. Generally, MetS was significantly higher among postmenopausal women ($p < 0.05$ by all criteria) compared to their premenopausal cohort, but with marked inter-criteria variations. Central obesity, higher blood pressure and raised fasting blood glucose were the predominant components that contributed to MetS in Ghanaian women. The predominant anthropometric marker that significantly influenced metabolic risk factors among the premenopausal was waist-to-hip ratio for fasting blood glucose (FBG) [p- 0.004], systolic blood pressure (SBP)[p-0.026] and high density lipoprotein cholesterol (HDL-C) [p- 0.002] respectively whilst in postmenopausal it influenced diastolic blood pressure (DBP)[p-0.012], FBG [p-0.048], triglyceride (TG) [p-0.007] and HDL-C [p-0.0061] respectively. The appropriate cut-off values of waist circumference, WHR, TG/HDL-C and HDL-C/TC to predict the presence of MetS were 80.5 cm, 0.84, 0.61 and 0.34 respectively. The prevalence and its predominant components of MetS were more common among postmenopausal women than their premenopausal cohort.

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LIST OF ABBREVIATIONS

ATP	Adenosine triphosphate
ADP	Adenosine diphosphate
BMI	Body Mass Index
CETP	Cholesterol Ester Transfer Protein
CM	Chylomicrons
DAP	Dihydroxyacetone Phosphate
DBP	Diastolic Blood Pressure
F-DAOS	N-ethyl-N-(2-hydroxy-3-sulfopropyl)-3,5-dimethoxy-4 fluoro-analine, sodium salt
Gly-3-P	Glycerol -3- phosphate
GK	Glycerol Kinase
GPO	Glycerophosphate Oxidase
HDL-C	High Density Lipoprotein Cholesterol
HDL-C/TC	High Density Lipoprotein Cholesterol-Total Cholesterol ratio
H_MS	Harmonization
IDF	International Diabetes Federation
LDL-C	Low Density Lipoprotein Cholesterol
LP	Lipoprotein
MetS	Metabolic Syndrome
NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III
POD	Peroxidase

PP	Pulse Pressure
SBP	Systolic Blood Pressure
SDA	Seventh Day Adventist
TC	Total Cholesterol
TG	Triglyceride
TG/HDL-C	Triglyceride -High Density Lipoprotein Cholesterol ratio
THC	Thigh circumference
VLDL-C	Very Low Density Lipoprotein Cholesterol
WC	Waist Circumference
WHO	World Health Organization
WHR	Waist-to-hip ratio
WHtR	Waist-to-height ratio
WTR	Waist-to-thigh ratio

THESIS ASSOCIATED RESEARCH MANUSCRIPT

The manuscript below was prepared in conjunction with the thesis.

Arthur FKN, **Adu-Frimpong., M**, Osei-Yeboah J, Mensah FO and Owusu L. **Prediction of MetS among Postmenopausal Ghanaian Women using Obesity and Atherogenic Markers**. *Lipid in Health and Disease*. 2012, **11**:101-114

CHAPTER ONE

1.0 INTRODUCTION

1.1 BACKGROUND INFORMATION

Metabolic syndrome (MetS) which was first coined by Haller, (1977) has now become a powerful risk factor for cardiovascular diseases and type 2 diabetes in women. Generally, women develop cardiovascular diseases ten years later than men but among women of 50 to 64 years, the risk is higher (Ford *et al.*, 1998; Ouyang *et al.*, 2002). Similarly, the risk of cardiovascular diseases ascribed to MetS appears to be particularly high in women (Chu *et al.*, 2005) and it has been approximated that half of all cardiovascular events in women are related to MetS (Wilson *et al.*, 1999). Likewise, MetS and cardiovascular disease had been identified to be common in American women above 55 years of age with significant increase in individual risk factors in the postmenopausal phase compared to premenopausal cohorts (Mesch *et al.*, 2006; Lejskova *et al.*, 2011). It is also an important independent predictor of cardiovascular disease, type 2 diabetes and its incidence increases with age and menopause in Brazilian women (Mesch *et al.*, 2006). Even though central obesity and insulin resistance are regarded as significant causative factors of MetS, other factors like raised blood pressure, raised triglycerides (TG), reduced high density lipoprotein cholesterol (HDL-C) and raised fasting plasma glucose (FPG) also predispose women to MetS (Alberti *et al.*, 2006).

The prevalence of MetS has been identified to be superjacent in postmenopausal women than in premenopausal women (Neto *et al.*, 2010). A comparison of the various components of MetS between premenopausal and postmenopausal women

revealed that there was lower incidence of dyslipidaemia, hypertension, abdominal obesity, and diabetes in the former than in the latter (Rossi *et al.*, 2008; Neto *et al.*, 2010). The higher prevalence of MetS and its components among postmenopausal women than their premenopausal counterparts are due to ethnic variations, different criteria used for its definition, study design and sample size (Pandey *et al.*, 2010). The most widely accepted criteria for MetS were produced by World Health Organization (WHO), International diabetes Federation (IDF), the European Group for the Study of Insulin Resistance (EGIR) and the National Cholesterol Education programme-Third Adult Treatment Panel (NCEP ATP III) (Alberti and Zimmet, 1999; Balkau and Charles, 1999; NCEP, 2001).

In Ghana, the prevalence of MetS has been identified to vary greatly between active and sedentary subjects (Owiredu *et al.*, 2011). There is however, scarcity of statistics on the prevalence of MetS and its predominant components among pre- and postmenopausal Ghanaian women.

1.2 PROBLEM STATEMENT

Body composition changes become evident in women during menopause, especially an increase in central adiposity which is a major risk factor for developing insulin resistance (Lee *et al.*, 2004), atherosclerotic cardiovascular disease (Carr, 2003), dyslipidaemia (Schnatz and Schnatz, 2006), hypertension (Reckelhoff and Fortepiani, 2004), and breast cancer (Sellers *et al.*, 1992). MetS is a common condition that predisposes individuals to the risk of developing cardiovascular disease and type 2 diabetes (Ford *et al.*, 1998; Eckel *et al.*, 2005). It is estimated that about 20-25 percent of the world's population have MetS and are three times more likely to die from heart attack or stroke compared with people without MetS (Alberti *et al.*, 2006). In

addition, people including women with MetS have a quintuple risk of developing type 2 diabetes (Stern *et al.*, 2004). The risk of developing cardiovascular disease and type 2 diabetes appears to be higher in women than men and it is thought that these events in women are related to MetS (Rossi *et al.*, 2008).

The statistics of MetS and its predominant components among Ghanaian postmenopausal women is not known.

1.3 JUSTIFICATION

The early detection of any clinical condition is very paramount in its management. Since MetS has been identified as the predisposing factor of cardiovascular disease and type 2 diabetes, it is important for Ghana to identify those individuals with MetS so that lifestyle interventions and treatment may be used to minimize the development of diabetes and cardiovascular disease. It is also significant to determine the predominant indicators among the vulnerable groups so that the factors can be monitored earlier in life.

This study sought to determine the predominant components of MetS among pre- and postmenopausal Ghanaian women. The components found to be highly associated with MetS can be recommended to be added to routine test carried out by physicians.

1.4 RESEARCH HYPOTHESIS

This study thus, hypothesizes that the prevalence and the predominant components of MetS is higher among postmenopausal women than their premenopausal counterparts.

1.5 GENERAL OBJECTIVE

The main objective for this study was to determine the predominant components of MetS among pre- and postmenopausal Ghanaian women.

1.5.1 Specific Objectives

1. To evaluate the prevalence of MetS and its predominant components among pre- and postmenopausal Ghanaian women.

2. To examine the influence of atherogenic and obesity indicators on the related determinants of MetS, and how the factors can be used to predict MetS and its cut-offs in pre- and postmenopausal Ghanaian women.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 CRITERIA OF METS

Many definitions for MetS have been put forward by various authorities and the most widely accepted criteria for MetS were issued by World Health Organization (WHO), International Diabetes Federation (IDF), the European Group for the Study of Insulin Resistance (EGIR) and the National Cholesterol Education programme-Third Adult Treatment Panel (NCEP ATP III) (Alberti and Zimmet, 1999; Balkau and Charles, 1999; NCEP, 2001). These definitions though similar, vary slightly but it is expected that all the different criteria would identify the same persons as having MetS.

2.1.1 The NCEP ATP III Criteria

According to this definition an individual has MetS if she presents with three or more of the following (Grundy *et al.*, 2005):

- Abdominal obesity: ≥88cm;
- Hypertriglyceridaemia: ≥ 1.7 mmol/l
- Low HDL cholesterol: < 1.3 mmol/l
- High blood pressure: ≥130/85 mmHg
- High fasting glucose: ≥6.1 mmol/l

2.1.2 The WHO Criteria

The WHO criterion defines women with MetS as having diabetes mellitus, impaired glucose tolerance or insulin resistance in addition to two or more of the following abnormalities (Alberti *et al.*, 2005):

- High blood pressure: ≥140/90 mmHg
- Triglyceride concentration ≥ 1.70 mmol/l
- HDL≤1.01 mmol/l
- Body mass index (BMI) ≥30 kg/m²
- Waist-to-hip ratio >0.85
- Diabetes ≥6.1 mmol/l

2.1.3 The IDF Criteria

The IDF criterion diagnoses a woman with MetS if she has central obesity ≥80 cm plus two or more of the following abnormalities (Alberti *et al.*, 2006):

- Triglyceride concentration ≥1.7 mmol/l
- HDL cholesterol lower than 1.29 mmol/l
- Blood Pressure ≥130/85 mm Hg
- Fasting blood glucose (FBG) ≥5.6 mmol/l

2.1.4 The Harmonization (H_MS) Criteria

As indicated by H_MS criterion, a subject has MetS if she presents any three of the following abnormalities (Alberti *et al.*, 2009; Vaidya *et al.*, 2011):

- Waist measurement >80 cm for women
- Triglyceride concentration ≥1.7 mmol/ L
- HDL cholesterol lower than 1.29 mmol/ L
- Blood pressure ≥130/85 mm Hg
- Fasting blood glucose ≥5.6 mmol/L

2.2 MENOPAUSE AND METS

Menopause is a natural biologic event that affects every woman and it is technically defined as the last spontaneous menstruation (Neto *et al.*, 2010). Menopausal transition is characterized by ovarian failure and its consequent decrease in female sex steroid production (Soules *et al.*, 2001). The menopausal phase is often classified into premenopausal, perimenopausal and postmenopausal states. Premenopause is the period in which women still have menstrual cycles whether such cycles are regular or not (Neto *et al.*, 2010). Perimenopause or menopausal transition is the period that extends from two years before the last menstruation and until one year later (Neto *et al.*, 2010). Postmenopause is the period that starts one year after the last menstruation (Neto *et al.*, 2010). During the period of menopause, a lot of hormonal changes occur in the woman's body which gives rise to various problems like hot flushes, vaginal dryness, depression, night sweats, mental fatigue etc. Women also, face various psychological as well as physiological changes in the menopausal stage (Kaur and Mogra, 2006) and; there is often the tendency for weight gain which is a predisposing factor for several other chronic diseases like cardiovascular disease, hypertension, and diabetes.

Seventy percent of Indian women of age 45-54 years were overweight or obese as reported by (Kaur and Mogra, 2006). Before the age of 50, majority of the women tend to experience slow weight gain, whereas after menopause there appears to be an accelerated increase in fat mass and a preferential fat storage to a central part of body or the abdominal location (Kaur and Mogra, 2006). Most cross-sectional studies have established that postmenopausal European and American women are more likely to have higher triglyceride (Rexrode *et al.*, 1998; Schubert *et al.*, 2006; Heidari *et al.*,

2010) than their premenopausal counterparts as well as lower high-density lipoprotein cholesterol (HDL-C) levels independent of age because of oestrogen decline (Middleberg *et al.*, 2002; Carr, 2003; Kim *et al.*, 2007b) but some European studies showed no significant differences in triglyceride or HDL-C levels after adjustment for age (De Aloysio *et al.*, 1999; Peters *et al.*, 1999; Ushiroyama *et al.*, 2005). Other studies in Asia depicted no significant changes in HDL-C and triglyceride levels between premenopausal and postmenopausal women (Torng *et al.*, 2002; Janssen *et al.*, 2008). After adjusting for confounding variables, postmenopausal condition was linked with a 60% increased risk of MetS (Park *et al.*, 2003).

2.3 PREVALENCE OF METS AND ITS INDIVIDUAL COMPONENTS IN WOMEN

Variances in genetic makeup, eating habits, physical activity levels, gender, age and lifestyle influence the prevalence of MetS and its components (Cameron *et al.*, 2004). The prevalence of MetS in women varies depending on the characteristics of the population studied and the diagnostic criteria adopted. The prevalence ranges from 10.7% among Korean women above 30 years old by the NCEP ATP III criteria (Oh *et al.*, 2004; Hyun *et al.*, 2008) to 74% in postmenopausal women with coronary artery disease in Birmingham (USA) by IDF criteria (Oh *et al.*, 2004; Brown *et al.*, 2008; Hyun *et al.*, 2008).

A multicentre study conducted by Collaborative Group for Research of the Climacteric in Latin America (2007) with 3,965 menopausal women determined the prevalence of MetS to be 42.9% in postmenopausal women and 28.1% in premenopausal women. Deibert *et al.*, (2007) also established prevalence of 36.1% among postmenopausal women and 22.7% among premenopausal women. Similarly,

studies of menopausal women in Canada, Ecuador and South Korea estimated prevalence of 31% (Hidalgo *et al.*, 2006), 41.5% (Hidalgo *et al.*, 2006; Piche *et al.*, 2006; Kim *et al.*, 2007) and 54.6% (Kim *et al.*, 2007) respectively.

The prevalence of MetS in Chinese postmenopausal women was identified by Ruan *et al.*, (2010) to be 33.7%. The prevalence of MetS among Brazilian postmenopausal women was 44.4% (NCEP ATP III criterion) and 61.5% (IDF criterion) (Neto *et al.*, 2010). The same study estimated 24.0% (NCEP ATP III criterion) and 37.0% (IDF criterion) as the prevalence of MetS among premenopausal Brazilian women (Neto *et al.*, 2010). Low HDL-cholesterol, large waist circumference, hypertriglyceridaemia, and hyperglycaemia were identified as the predominant components (Neto *et al.*, 2010). Moreover there was a high prevalence of MetS in postmenopausal Asian and Ecuadorian women, which ranged from 13.9% to 52% (Chedraui *et al.*, 2007; Ding *et al.*, 2007; Ponholzer *et al.*, 2008).

Several studies (Oliveira *et al.*, 2006; Salaroli *et al.*, 2007; Kelliny *et al.*, 2008) have indicated prevalence of MetS in women aged less than 45 as 18.2%, 45 to 54 years as 56.9% and 55 to 64 years as 68.0%. Cho *et al.*, (2008) detected that postmenopause status was an independent risk factor for MetS and all of its individual components. Women of African descent especially black women, have high metabolic components of systemic hypertension (at an early stage), obesity and type 2 diabetes (Oliveira *et al.*, 2006). A study by Oh *et al.*, (2004), low HDL-C, systemic hypertension, hypertriglyceridaemia, hyperglycaemia and abdominal obesity were identified as the most common components of MetS. The prevalence of MetS or any of its constituents rises after menopause in relation to duration of menopause and sedentary lifestyle (Hidalgo *et al.*, 2006; Cho *et al.*, 2008; Janssen *et al.*, 2008). A study in the USA

estimated the overall prevalence for the women to be 22.6% and increases with age of which 40-50% were postmenopausal women (Park *et al.*, 2003). Predominant components of MetS particularly waist circumference contributed to an increase in weight of postmenopausal American women (Park *et al.*, 2003). Blood pressure was also established to be higher in menopausal and older women than premenopausal and younger women (Staessen *et al.*, 1998).

Fuchs *et al.*, (2008) also demonstrated that women with a cluster of four to five risk factors of MetS as well as a combination of high blood pressure and diabetes are prone to cardiovascular disease. The overall prevalence of MetS of 42% was established among Ecuadorian postmenopausal women with hypertension, abdominal obesity and low HDL-cholesterol as the predominant components (Hidalgo *et al.*, 2006). Similarly, Ainy *et al.*, (2007) established the prevalence of MetS to be significantly higher in postmenopausal women than premenopausal women with low HDL-cholesterol and high diastolic blood pressure discovered as most components in comparison to other factors.

2.4 BIOCHEMICAL INDICES

2.4.1 Dyslipidaemia and MetS in Women

The incidence of MetS in women may be present with elevated triglyceride levels and/or low HDL-C levels (Wilson and Grundy, 2003). Diabetic patients with cardiovascular disease normally have the coalition of raised triglyceride and low HDL than raised total cholesterol and LDL cholesterol levels (Rubins *et al.*, 1995). Moreover, elevated levels of small dense LDL cholesterol in type 2 diabetic and cardiovascular disease patients result from increased VLDL-cholesterol secretions, abnormal cholesterol and triglyceride transfer between VLDL and LDL (Reaven *et*

al., 1993; Tan *et al.*, 1995). An increase in VLDL cholesterol in diabetic patients is due to raised amount of glucose for VLDL synthesis and decrease in lipoprotein lipase activity leading to decrease of VLDL removal from peripheral circulation (Arora *et al.*, 2007).

An abnormal lipid profile or dyslipidaemia is defined by elevated levels of plasma cholesterol, LDL-cholesterol (LDL-C) and/or triglycerides or a low HDL-cholesterol (HDL-C) level (Fredrickson and Lees, 1965). Hormone levels influence lipoprotein levels and vary throughout the women lifespan. Cholesterol and other lipids can come from the diet as well as from endogenous synthesis, and triglycerides are synthesized from fatty acids or from glucose, hence, the modification in the levels of lipids in body makes the individuals more prone to developing type 2 diabetes and cardiovascular disease (Arora *et al.*, 2007). Distinguishing abnormalities in the lipid profile in type 2 diabetes and cardiovascular disease include elevated triglyceride levels, decreased atheroprotective high-density lipoprotein cholesterol (HDL-C) levels and increased levels of low density lipoprotein cholesterol (LDL-C) (Beckman *et al.*, 2002). The lipoprotein abnormalities of MetS are an excessive number of atherogenic ApoB lipoprotein particles, accompanied by reduced numbers, as well as dysfunction, of HDL particles (Pokrywka, 2007). Overproduction of large triglyceride-rich ApoB-containing VLDLs, which are associated with fasting and postprandial hypertriglyceridaemia because of their marred clearance by lipoprotein lipase leads to cardiovascular disease and type 2 diabetes (Sniderman *et al.*, 2001). The triglyceride-rich VLDLs are highly atherogenic and are subject to altered lipolysis, which creates smaller VLDL particles (remnants), small dense LDL and HDL particles (Pokrywka, 2007). HDL-cholesterol levels are lowered by raised levels

of triglyceride- rich lipoproteins promoting exchanges of cholesterol from HDL to VLDL through cholesterol ester transfer protein (CETP) (Beckman *et al.*, 2002). Moreover, decreased levels of HDL-C due to increase in hepatic lipase activity result in decreased VLDL clearances which are metabolic abnormalities relating to MetS (Arora *et al.*, 2007). The prevention of oxidative modification of plasma low density lipoprotein-cholesterol by HDL-C plays a major role in the pathogenesis of atherosclerosis (Parthasarathy *et al.*, 1990; Lopes *et al.*, 2003; Lewis and Rader, 2005; Jaichander *et al.*, 2008). The mechanism of this protection is not well understood due to paucity of studies, hence attention has been shifted to the potential antioxidant activity of serum enzymes associated with HDL-C. One of these enzymes, paraoxonase (PON1), which is co-associated with HDL-C and apolipoproteins A-1 (Apo-A1) in circulation has been claimed to play a crucial role in protecting LDL-C oxidation, thus forestalling vascular injury and atherosclerosis (Parthasarathy *et al.*, 1990; Lopes *et al.*, 2003; Jaichander *et al.*, 2008).

MetS is normally associated with dyslipidaemia (hypertriglyceridaemia, high small dense LDL-C and reduced HDL-C). Hypertriglyceridaemia and lowered HDL-cholesterol levels were determined to be the predominant components of MetS in several studies (Gaillard *et al.*, 1997; Carnethon *et al.*, 2004; Crossrow and Falkner, 2004; Grundy, 2004). Moreover, Escobedo *et al.*, (2009) identified the association between MetS, low HDL-cholesterol and high triglycerides levels whilst Titty *et al.*, (2008) classified low HDL-C as the commonest constituent in Ghanaian diabetic patients. The Jackson Heart Study also found that low serum HDL cholesterol according to NCEP ATP III criteria was a major determinant of MetS while serum triglycerides were least predictive in African Americans (Gaillard *et al.*, 2009). A

study conducted by Meis *et al*., (2006) revealed that serum total cholesterol and LDL-cholesterol were two to three times greater in MetS group than non-MetS group. Finally, triglyceride was pinpointed as the risk factor of MetS for postmenopausal women, with HDL-C as the protective factor (Ruan *et al*., 2010).

Menopause is associated with an increase in total cholesterol and LDL-cholesterol and triglycerides levels, (Rexrode *et al*., 1998; Schubert *et al*., 2006) and a decrease in HDL-cholesterol levels (Middleberg *et al*., 2002; Carr, 2003). Premenopausal women however, have favourable serum lipoproteins profile like low LDL-C and high HDL-C compared to their postmenopausal counterpart hence they have low risk of developing cardiovascular diseases (Zhang *et al*., 2007). Usoro *et al*., (2006) observed significantly higher total cholesterol (TC), LDL-C, TC/HDL-C ratio (atherogenic index) and lower HDL-C among Nigerian postmenopausal cohorts than their premenopausal counterparts. In contrast, mean HDL-cholesterol levels were identified to be similar in Chinese premenopausal and postmenopausal women (Kim *et al*., 2007). Moreover, Hall *et al*., (2002) determined reduced HDL-C and elevated TC, LDL-C and TG in postmenopausal women than their premenopausal counterpart. Similarly, Berg *et al*., (2004) also demonstrated higher TC, LDL-C and triglycerides in menopausal transition and postmenopausal women in comparison with premenopausal women. Furthermore, higher concentrations of total cholesterol, triglycerides and low levels of HDL-C were determined among Bulgarian women by Boyanov and Christov, (2005). Alternatively, Sidsel *et al*., (2008) identified increased concentrations of TC, TG and TC/HDL-C in postmenopausal women than premenopausal cohorts. Igweh *et al*., (2005) also detected significant reduction in cardio-protective HDL-C and significant increase in the atherosclerotic VLDL-C and

LDL-C in Nigerian females. Nielsen *et al.*, (2000) also established significant increase in TG and VLDL-cholesterol as well as low levels of HDL-cholesterol among postmenopausal women with unstable coronary artery disease. Presently, elevated plasma TG/HDL-C and HDL-C/TC ratios are more predictive to cardiovascular diseases especially in postmenopausal women as compared to the premenopausal group (Igweh *et al.*, 2005; Hussain *et al.*, 2007).

Since lipid alterations such as increase in serum TC, serum LDL-cholesterol and triglycerides can cause an increased risk of coronary heart disease and other complications (Stevenson *et al.*, 1993; Abbey *et al.*, 1999; Godsland, 2001; Hall *et al.*, 2002; Jensen *et al.*, 1990), Wannamethee *et al.*, (2001) suggested that the risk to the above diseases in women could be reduced through weight loss, exercise, smoking and alcohol cessation, and dietary alterations.

2.4.2 Hyperglycaemia and MetS in Women

Insulin resistance occurs when cells in the body (liver, skeletal muscle and adipose tissue) become less sensitive and ultimately resistant to insulin, the hormone produced by the beta cells in the pancreas to promote glucose absorption (Wilcox, 2005). In this state, glucose can no longer be absorbed by cells but remains in blood, triggering the need for more and more insulin (hyperinsulinaemia) to be produced in attempt to utilize glucose. Reaven's hypothesis is that the failure of insulin's hypoglycaemic action causes glucose intolerance which may be severe enough to be type 2 diabetes mellitus (Frayn and Stanner, 2005). However, there are contrasting views on how insulin resistance contribute to the pathogenesis of MetS in women. Paul and Smith (2005) suggested that insulin resistance has greater impact on the pathogenesis of MetS than obesity. They, (2005) also showed that weight gain in

women is a stronger prognosticator of impaired glucose tolerance than menopausal status. Visceral fat and fat deposits around the waistline, are more resistant to insulin which leads to hepatic glucose over-production and hyperglycaemia (Allende-Vigo, 2008). Diets high in carbohydrate can negatively affect the lipid profile and glucose tolerance, worsening the metabolic abnormalities in women with or predisposed to MetS (Ludwig *et al.*, 1999). Ruan *et al.*, (2010) identified abnormal fasting plasma glucose as the most common cause of abnormal metabolism in postmenopausal women. Contrarily, Godsland *et al.*, (1995) identified no difference in fasting plasma glucose between healthy postmenopausal women and those with MetS. Fasting plasma glucose was postulated to be higher in premenopausal obese women with low sex-hormone binding globulin (SHBG) (Akin *et al.*, 2008). Impaired glucose tolerance has been demonstrated to be elevated in females than male college students indicating that females have higher incidence of insulin resistance (Huang *et al.*, 2007). Furthermore, postmenopausal women are more likely to be identified with visceral obesity and related metabolic disturbances, such as type 2 diabetes, than premenopausal women (Piche *et al.*, 2005). Chronic hyperinsulinaemia, hyperglycaemia and impaired glucose tolerance lead to type 2 diabetes and have been shown to influence cardiovascular disease as well as MetS in women (Stratton *et al.*, 2000).

Pradhan, (2007) established an increased fasting glucose concentrations associated with diminished insulin action, obesity, and MetS in women. Fasting blood glucose level was demonstrated to increase progressively in postmenopausal women far exceeding normal range (Koskova *et al.*, 2009). Contrastingly, Rosano *et al.*, (2006)

postulated that menopause does not seem to affect fasting glucose but rather associated it with a progressive decline in glucose-stimulated insulin secretion.

2.4.3 Obesity and MetS in Women

Obesity is characterized by excess amount of adipose tissue as a result of long-term positive energy in balance. Expert Panel on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults (1998) defined obesity as a chronic disease that is complex and multifactorial in its nature and includes an interaction of genotype with environment in its development. The WHO also defined obesity as a condition with excessive fat accumulation in the body to the extent that health and well-being are adversely affected (WHO., 1998). People have different tendencies to gain weight in different locations of the body, such as the abdomen, which is referred to as abdominal or visceral obesity. Body mass index (BMI) is calculated as weight in kilograms divided by height in squared meters (kg/m^2). It is highly correlated with body weight and is a surrogate measure of total body fat content but is also affected by muscle mass. Waist-to-hip ratio is a measure of abdominal fat and is calculated as the ratio of waist and hip circumferences. Waist girth is measured at the midpoint between iliac crest and lowest rib and hip girth is assessed at the widest part of pelvis.

2.4.3.1 Effect of Obesity Indices on MetS among Women

Overweight, overall obesity and abdominal obesity are typically measured in epidemiological studies by using ratios of body weight and height or body circumferences, such as body mass index (BMI), waist circumference, waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) (Despres *et al.*, 2001; Seidell *et al.*, 2001; Seidell *et al.*, 2001).

Obesity is a major health problem in developing countries and its prevalence, especially in women, is assuming epidemic proportions worldwide (Lissner *et al.*, 2000; WHO., 2000; NCEP., 2001; Coitinho *et al.*, 2001; Lee *et al.*, 2005). Overweight and obesity are the root causes of MetS (National Cholesterol Education Program, 2002). They are independent risk factors for hypertriglyceridaemia (Stone, 1994) and low HDL-cholesterol level (Chait and Brunzell, 1990).

Previous studies have shown that health risks are positively associated with waist circumference but inversely related to hip circumference after adjustment for possible confounders (Lissner *et al.*, 2001; Seidell *et al.*, 2001). Body composition changes among women occur frequently after menopause, in which age-related increases in obesity occur more often (Flegal *et al.*, 2002). In premenopausal women, fat accumulates in lower extremities mainly as a result of oestrogen secretion whereas during menopause the pattern of hormone secretion changes and gradually causes fat deposition in visceral tissues of abdomen and this subsequently leads to central obesity (Poehlman, 2002).

Misra *et al.*, (2005) identified high waist circumference (>88 cm) as the most predominant risk factor for MetS among women. According to Carr, (2003) body changes that occur during premature menopause may result in increased abdominal visceral adiposity. Carr *et al.*, (2004) also postulated that women with increased deposition of visceral adipose tissue are more likely to develop MetS than those with increase in subcutaneous adipose tissue. In addition, studies conducted by Carr and Brunzell, (2004) and Mokdad *et al.*, (2003) reiterated the point that visceral fat accumulation often goes with obesity which in turn leads to a cascade of metabolic

disturbances. Central adiposity is common in postmenopausal women and it is a major risk factor for developing insulin resistance (Lee.*et al.*, 2004), atherosclerotic cardiovascular disease (CVD) (Carr, 2003), dyslipidaemia (Schnatz and Schnatz, 2006) and hypertension (Reckelhoff and Fortepiani, 2004). Postmenopausal Chinese women with abdominal obesity (as assessed by waist circumference) convey a higher risk of cardiovascular diseases and are more prone to insulin resistance than those without abdominal obesity (Hwu *et al.*, 2003). Similarly, most studies have shown an independent consequence of abdominal obesity on CVD risk factors, most often evaluated via waist circumference (Seidell *et al.*, 1990; Seidell *et al.*, 1992; Iwao *et al.*, 2001; Ardern *et al.*, 2003; Zhu *et al.*, 2004).

The influence of BMI on blood pressure, lipid profile and its ability to predict hypertension and dyslipidaemia was reported by Kawada, (2002). Whilst BMI is recognised to be linked to MetS, the relationship may not invariably be straightforward (Meigs *et al.*, 2006). Premenopausal women were estimated to have similar mean BMI to that of postmenopausal women, but the latter had large waist circumference after adjusting for age (Kim *et al.*, 2007).

Large waist circumference was described as sensitive index of risk of MetS in postmenopausal women (Pelt *et al.*, 2001). Body composition changes frequently among women following menopause leading to age-related increases in obesity (Flegal *et al.*, 2002). A study conducted by Lahti-Koski *et al.*, (2000) reported that abdominal obesity [was measured using waist to hip ratio (WHR)], was shown to be a strong risk factor for type 2 diabetes mellitus. In other studies, abdominal adiposity was proposed to be an independent predictor of changes in the plasma lipid,

lipoprotein and plasma glucose concentrations (Brochou *et al.*, 2000; Enino *et al.*, 2001). Moreover, several studies have established that the connection between WHR or WTR and glucose metabolism of type 2 diabetes was not only due to a larger waist circumference but also due to a smaller hip or thigh circumference (Seidell *et al.*, 1997; Lissner *et al.*, 2001; Seidell *et al.*, 2001; Snijder *et al.*, 2003a; Snijder *et al.*, 2003b). Oral *et al.*, (2002) found a higher subcutaneous adipose tissue in the thigh linked with lower prevalence of MetS among women.

2.4.4 High Blood Pressure and MetS in Women

Arterial hypertension is an important health problem worldwide (Kearney *et al.*, 2004). Hypertension is a major cardiovascular risk factor primarily responsible for mortality and cardiovascular morbidity (Grigore *et al.*, 2010). Blood pressure is a measurement of the force against the walls of arteries as heart pumps blood through the body. Blood pressure readings are usually given as two numbers, for example, 120 over 80 (written as 120/80 mmHg). One or both of these numbers can be very high. The top number is called the systolic blood pressure (SBP) and the bottom number is called the diastolic blood pressure (DBP). Systolic pressure is the force that pushes blood from the heart into the arteries and the rest of the body. In contrast, diastolic pressure is the force which allows the blood to flow back into the heart as it relaxes. Pulse pressure (PP) is the difference between systolic and diastolic blood pressures. Normal blood pressure is when the blood pressure is lower than or equal to 120/80 mmHg most of the time.

- High blood pressure (hypertension) is when the blood pressure is 140/90 mmHg or above most of the time.

- If the blood pressure numbers are 120/80 mmHg or higher, but below 140/90 mmHg, it is called pre-hypertension.

Women with pre-hypertension are more likely to develop high blood pressure. Premenopausal women tend to have lower blood pressure than age-matched men, with arterial blood pressure increasing after the cessation of menstrual cycle; hence menopausal women develop arterial hypertension often together with changes in lipid and glucose metabolism (Rosano *et al.*, 2006). The increase in blood pressure in postmenopausal women does not occur soon after the cessation of menstrual cycle or menstruation, but it becomes evident over a number of years. Although the mechanisms responsible for the increased blood pressure in women after menopause are not clear, it is believed that the fundamental mechanism may be lack of oestrogen which induces physiological changes leading to a greater prevalence of hypertension and MetS compared with the premenopausal period (Rosano *et al.*, 2006). A study by Staessen *et al.*, (1997) observed higher systolic and diastolic blood pressure in postmenopausal women than their premenopausal counterparts whilst other results from cross-sectional studies have been unclear (Staessen *et al.*, 1997; Reis *et al.*, 2006).

Furthermore, the connection between menopause and BP is difficult to elucidate because arterial stiffness and BP, as well as serum lipids and glucose tolerance, tend to get worse with increasing age (Kawecka-Jaszcz *et al.*, 2002). There seems to be a link between high blood pressure and obesity as indicated in a study by Lee., (2004) which postulated that both overall and abdominal obesity are related to cardiovascular disease, hence weight gain can increase the risk of developing hypertension independent of age and blood pressure. On the other hand, Kawada,

(2002) reported that BMI has an impact on blood pressure and lipid profile and is a good forecaster of hypertension and hyperlipidaemia. This was reiterated by Ishikawa, (2002) in his study which indicated that BMI above 22 kg/m^2 was associated with an increased risk for hypertension.

A similar study by Daniels *et al.*, (1999) stated that a greater accumulation of central fat is correlated with blood pressure whilst Giampaoli *et al.*, (2002) observed increased prevalence of hypertension with increasing age in Italian population. Staessen *et al.*, (1997) also specified that menopause was accompanied by a sheer rise in systolic blood pressure with age and diastolic blood pressure. High pulse pressure is a measure of the pulsatile constituent of blood pressure and has been confirmed to increase the risk of cardiovascular disease and total mortality as well as correlating to arterial stiffness (Domanski *et al.*, 1999; Blacher *et al.*, 2000; Glynn *et al.*, 2000; Pastor-Barriuso *et al.*, 2003). Likewise, higher pulse pressure, reflecting increased arterial stiffness, was detected in hypertensive women with MetS than those without (Mule *et al.*, 2007).

Recent data from a study using healthy women established that premenopausal systolic blood pressure (SBP) and pulse pressure (PP) were prognostic of arterial stiffness and plaque 5 to 8 years after menopause (Matthews *et al.*, 2001), implying that premenopausal levels of SBP and PP may identify high-risk younger women. Kim *et al.*, (2007) established that mean systolic blood pressure and pulse pressure were higher in postmenopausal women than premenopausal women. MetS has also been linked to increased arterial stiffness in women (Dell'Omo *et al.*, 2004; Lteif *et*

al., 2005; Lind, 2007). Similarly, accruing evidence buttress the concept of increased arterial stiffness in women with metabolic disruption (Yasuno *et al.*, 2010).

CHAPTER THREE

3.0 MATERIALS AND METHODS

3.1 RECRUITMENT OF SUBJECTS

This cross-sectional study was conducted between May and July, 2011 in the outpatient department of Suntreso and Seventh Day Adventist Government Hospitals in Kumasi, Ghana. Two hundred and fifty patients were randomly recruited of which one hundred and forty-three (143) were premenopausal women (control) and one hundred and seven (107) postmenopausal. Women who were still menstruating irrespective of the regularities of their menses were considered as premenopausal women while postmenopausal women were women who had ceased menstruation for at least one year (Oh *et al.*, 2004). The participation of the women was voluntary. Informed consent was obtained from each of them after thorough explanation about the study was done in a language they understand. All biochemical analyses were performed without knowledge of subject's clinical status by means of code numbering. This study was approved (CHRPE/ KNUST/ KATH/ 01_02_11) by the local Committee on Human Research Publication and Ethics.

3.1.1 Sample Size Consideration

The 250 participants were used after the estimation of minimum sample sizes for both pre- (98) and postmenopausal women (88) to achieve 80% power based on the method as suggested by (Fleiss. *et al.*, 1980; Van Belle, 2008). The parameters used were prevalence of MetS among pre- and postmenopausal women (Neto *et al.*, 2010); 24% and 44.4% respectively, confidence interval of 95%, relative sample size of 0.9, probability of type II error, 20% and probability of type I error 5%.

3.1.2 Inclusion Criteria

The eligible volūnteers were women with no signs of pregnancy, hypertension, type 2 diabetes, cancer, polycystic ovarian MetS, hepatitis and non-contraceptive users.

3.1.3 Exclusion Criteria

The exclusion criteria were any of the following: clinically confirmed pregnancy, known diabetics, hypertension, other heart diseases, polycystic ovarian MetS, contraceptive use and cancer.

3.1.4 Questionnaires

Self-reported questionnaires were administered to determine menopause status, smoking status, alcohol intake, educational level, physical activity levels, occupation and family medical history. Passive smokers were women who were exposed to cigarette smokes by their relatives and/ or husbands. Occupation was categorized into manual (traders, farmers and seamstress), non-manual (civil servants) and out of economically active population (unemployed).

3.2 MEASUREMENT OF ANTHROPOMETRIC VARIABLES

Anthropometric measurements included height to the nearest centimetre without shoes and weight to the nearest 0.1 kg in light clothing. Subjects were weighed on a bathroom scale (BR9012, Zhongshan Camry Electronic Co. Ltd, Guangdong, China) and their height measured with a wall-mounted ruler. Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m^2). Waist circumference was measured at the midpoint between the last rib and the iliac crest with the participants standing and wearing light cloths with a Gulick II spring-loaded measuring tape (Gay Mills, WI). The hip circumference was measured at the widest level over the greater

trochanters (WHO., 1995) and the waist-to-hip ratio (WHR) calculated by dividing the waist circumference (cm) by the hip circumference (cm). Thigh circumference (THC) on the other hand was measured on the left leg below the gluteal fold and waist-to-thigh ratio (WTR) calculated by dividing waist circumference (cm) by the thigh circumference (cm). Waist-to-height ratio was also calculated by dividing WC (cm) by height (cm). Waist-to-hip ratio (WHR), WHtR and WTR were recorded to the nearest 2 decimal places.

3.2.1 Blood Pressure (using Korotkoff 1 and 5)

Blood pressure was taken by trained personnel with participants in sitting position and having rested for at least 10 minutes using sphygmomanometer with appropriate cuff sizes and stethoscope in accordance with the recommendation of the American Heart Association (Kirkendall *et al.*, 1967). Triplicate readings were taken per subject, after two minutes intervals and the mean value was recorded to the nearest 2.0 mm Hg. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken at the 1st and 5th Korotkoff sounds respectively. Pulse pressure (PP) was calculated using SBP-DBP.

3.3 SAMPLE COLLECTION AND PREPARATION

Venous blood samples (5 ml from each woman) were collected between 7 am and 10 am after overnight fast (12-16 hours) and 4 ml dispensed into vacutainer ® plain tubes while 1 ml was dispensed into fluoride oxalate tubes. These were then taken to the laboratory and both were centrifuged at 500 g for 15 minutes; the plasma was used for the glucose assay and the serum for other biochemical assays.

3.3.1 Biochemical Analyses

Serum biochemistry was performed according to reagents manufacturer's specification (Fortress Diagnostics Limited, Unit 2C Antrim Technology Park, Antrim BT41 1QS, UK). Parameters that were determined included:

- Fasting blood glucose (FBG)
- Lipid Profile which includes:
    - Triglyceride (TG)
    - Total cholesterol (TC)
    - High density lipoprotein cholesterol (HDL-C)
    - Low density lipoprotein cholesterol (LDL-C)
    - Very low density lipoprotein (VLDL-C)

3.3.1.1 Fasting Blood Sugar Determination

Principle

The glucose determination is an enzymatic method based on a modification of Trinder colour reaction method (Barham and Trinder, 1972). Glucose is determined after enzymatic oxidation in the presence of glucose oxidase. The hydrogen peroxide formed reacts with phenol and 4-aminoantipyrine to form the colometric indicator, quinoneimine which is catalysed by peroxidase.

$$Glucose + O_2 + H_2O \xrightarrow{Glucose\ oxidase} Gluconic\ acid + H_2O_2$$

$$H_2O_2 + 4\text{-}aminoantipyrine + Phenol \xrightarrow{Peroxidase} Quinoneimine + 4\,H_2O$$

Procedure

The test tubes were labelled as blank, standard and sample. To the blank test tube

10 µl of distilled water along with 1000 µl of reagent were added. The standard test tube contained 10 µl of standard and 1000 µl of reagent. The content of sample test tube was also made up of 10 µl of the sample and 1000 µl of reagent. The contents in each of the test tubes were then mixed well and incubated in water bath for 5 minutes at 37°C. After completion of incubation, the absorbance of standard and samples was measured against reagent blank at 500 nm and calculations were done as follows;

Calculation:

$$\textit{Glucose concentration (mmol/l)} = \frac{\textit{Sample Absorbance}}{\textit{Standard Absorbance}} \textit{ X Standard Concentration}$$

3.3.1.2 Triglyceride Determination

Principle

The current method for triglyceride determination employs a modified Trinder (Trinder, 1969; Barham and Trinder, 1972) colour reaction to yield a fast, linear, endpoint reaction (Fossati and Prencipe, 1982; McGowan *et al.*, 1983). Triglycerides in the sample are hydrolyzed by lipase to glycerol and fatty acids. The glycerol is then phosphorylated by adenosine-5- triphosphate (ATP) to glycerol-3-phosphate (Gly-3-P) and adenosine-5-diphosphate (ADP) in a reaction catalyzed by glycerol kinase (GK). Gly-3-P is then converted to dihydroxyacetonephosphate (DHAP) and hydrogen peroxide by glycerophosphate oxidase (GPO). The hydrogen peroxide then reacts with 4-aminoantipyrine (4-AAP) and 3, 5-dichloro-2-hydroxybenzene (3, 5-DHBS) in a reaction catalyzed by peroxidase to yield a red coloured quinoneimine dye. The intensity of the colour produced is directly proportional to the concentration of triglycerides in the sample.

$$Triglycerides + 3H_2O \xrightarrow{Lipase} Glycerol + Fatty\ Acids$$

$$Glycerol + ATP \xrightarrow{GK,\ Mg^{2+}} Gly\text{-}3\text{-}P + ADP$$

$$Gly\text{-}3\text{-}P + O_2 \xrightarrow{GPO} DHAP + H_2O_2$$

$$2H_2O_2 + 4\text{-}aminoantipyrine + 4\text{-}chlorophenol \xrightarrow{POD} Quinoneimine + 4H_2O + HCl$$

Procedure

The test tubes were labelled as blank, standard and sample. To the blank test tube 10 µl of distilled water along with 1000 µl of reagent were added. The standard test tube contained 10 µl of standard and 1000 µl of reagent. The content of sample test tube was also made up of 10 µl of the sample and 1000 µl of reagent. The contents in each of the test tubes were then mixed well and incubated in water bath for 5 minutes at 37°C. After completion of incubation, absorbance of standard and samples was measured at 500 nm and calculations were done as follows;

$$Triglyceride\ concentration\ (mmol/l) = \frac{\Delta A\ Sample}{\Delta A\ Standard} X\ Standard\ Concentration$$

3.3.1.3 Total Cholesterol Determination

Principle

The method uses Trinder's (1969) colour system of peroxidase/phenol/4-aminoantipyrine. Cholesterol is present in serum as cholesterol ester and free cholesterol. The cholesterol esters present in serum are hydrolyzed by cholesterol esterase and the cholesterol is then measured by oxidizing with cholesterol oxidase to form hydrogen peroxide. The hydrogen peroxide in turn reacts with phenol and 4-aminoantipyrine present to form the red quinoneimine dye. The intensity of the dye

formed is directly proportional to the level of cholesterol present in the sample when read at 500 nm.

Cholesterol Esters + H_2O $\xrightarrow{\text{Cholesterol esterase}}$ Cholesterol + Fatty Acids

Cholesterol + O_2 $\xrightarrow{\text{Cholesterol oxidase}}$ Cholest-4-en-3-one + H_2O_2

$2H_2O_2$ + 4-Aminoantipyrine + Phenol $\xrightarrow{\text{Peroxidase}}$ Quinoneimine + 4 H_2O

Procedure

The test tubes were labelled as blank, standard and sample. To the blank test tube 10 µl of distilled water along with 1000 µl of reagent were added. The standard test tube contained 10 µl of standard and 1000 µl of reagent. The content of sample test tube was also made up of 10 µl of the sample and 1000 µl of reagent. The contents in each of the test tubes were then mixed well and incubated in water bath for 5 minutes at 37 °C. After completion of incubation, absorbance of standard and samples was measured at 500 nm and calculations were done as follows;

$$\textit{Total Cholesterol concentration (mmol/l)} = \frac{\Delta A \text{ sample} \times \text{Standard Concentration}}{\Delta A \text{ standard}}$$

3.3.1.4 High Density Lipoprotein Cholesterol Determination

Principle

The method employs an immunoinhibition reagent method which measures HDL-C directly (Castelli *et al.*, 1977). Two reagent were used in this method . Anti-human ß-lipoprotein antibody in Reagent 1 binds to lipoproteins (LDL, VLDL, and chylomicrons) other than HDL. The antigen-antibody complexes formed block enzyme reactions when Reagent 2 is added. Cholesterol esterase (CHE) and cholesterol oxidase (CO) in Reagent 2 react only with HDL-C. Hydrogen peroxide produced by the enzyme reactions with HDL-C yields a blue color complex upon

oxidase condensation with FDAOS [N-ethyl-N-(2-hydroxy-3-sulfopropyl)-3,5-dimethoxy-4 fluoro-analine, sodium salt] and 4-aminoantipyrine (4AA) in the presence of peroxidase (POD). By measuring the absorbance of the blue color complex produced, at approximately 593 nm, the HDL-C concentration in the sample can be calculated when compared with the absorbance of the HDL Calibrator.

Chylomicrons, LDL, VLDL $\xrightarrow{\textbf{\textit{Antihuman LP Antibody}}}$ ***Ag-Ab Complex***

$$\textit{HDL- C} + H_2O + O_2 \xrightarrow{\textit{Cholesterol Oxidase/Esterase}} \textit{Cholestenone} + H_2O_2 + \textit{FA}$$

$$H_2O_2 + \textit{4 –Aminoantipyrine} + \textit{F-DAOS} + H_2O \longrightarrow \textit{Blue Colour Complex}$$

Procedure

The test tubes labeled as blank, standard and sample were taken. In each test tube 5 µl of distilled water, standard and sample along with 450 µl of reagent 1 (R1) solution were added respectively. The contents in each of the test tubes were mixed well and incubated in water bath for 5 minutes at 37ºC. After completion of incubation, the first absorbance was measured at 593 nm of standard (Acal1) and sample (As1) against blank. Then 150 µl of reagent 2 (R2) was added in three tubes and after 5 minutes the second reading for standard (Acal2) and sample (As2) was also measured and calculations were done as follows;

$$\textit{HDL-C concentration (mmol/l)} = \frac{\textit{As2-As1}}{\textit{Acal2-Acal1}} \times \textit{Calibrator Concentration}$$

3.3.1.5 Low Density Lipoprotein Cholesterol (LDL- C) Determination

LDL-C was calculated according to Friedewald's formula (Friedewald *et al.*, 1972) in accordance to the manufacturers.

$$LDL\text{-}Cholesterol = Total\ cholesterol - \frac{Triglyceride}{2.2} - HDL\text{-}cholesterol$$

3.3.1.6 Very Low Density Lipoprotein Determination

VLDL-C was calculated according to the formula proposed by Wilson (DeLong *et al.*, 1986) in accordance to the manufacturers.

$$VLDL\text{-}Cholesterol = \frac{Triglycerides}{2.825}$$

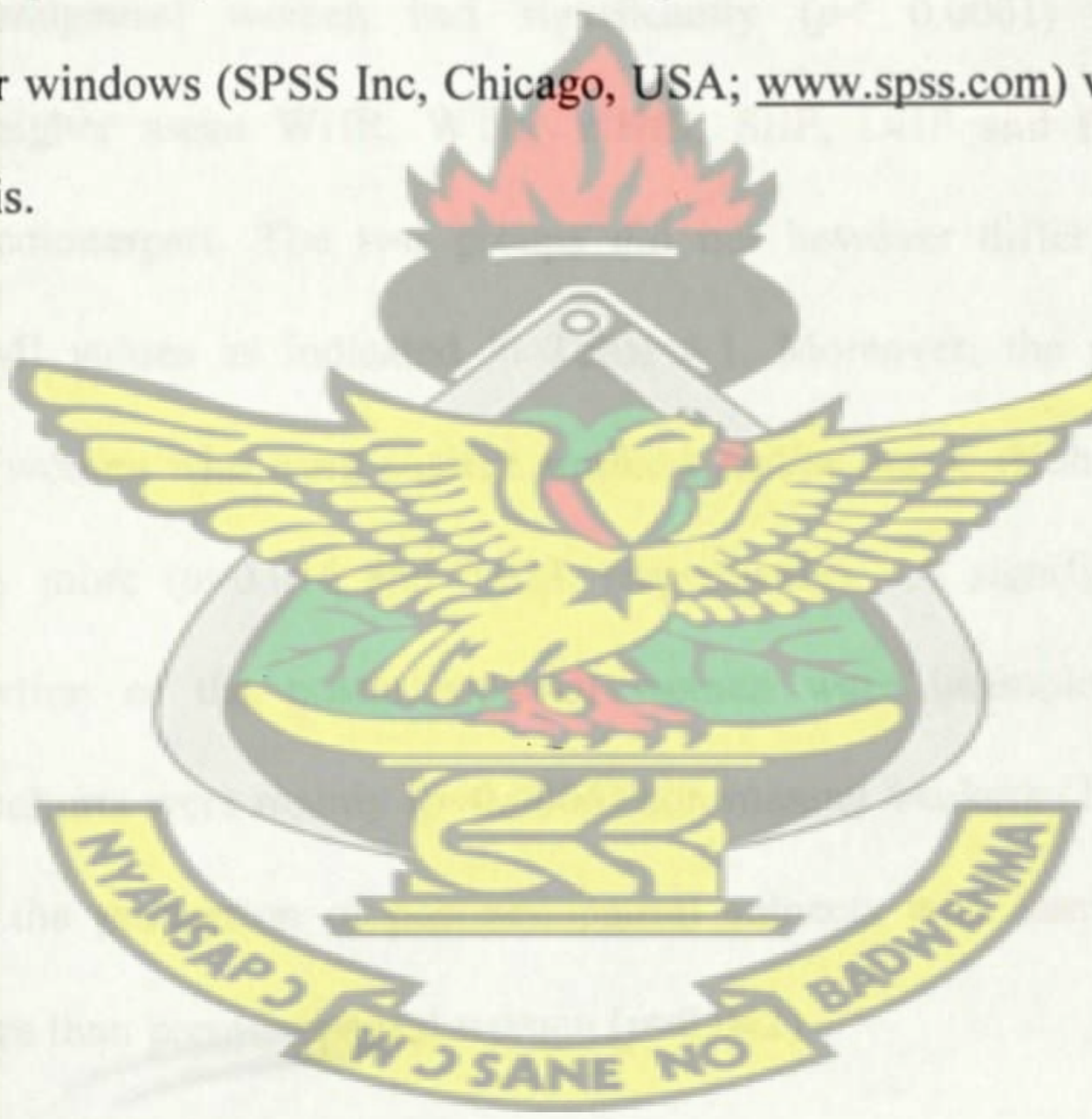
3.4 DETERMINATION OF METS AMONG SUBJECTS

Since no single definition for MetS has been accepted worldwide and to provide, the possibility for comparison with the majority of studies on the same topic, four widely used criteria were applied to examine the prevalence of MetS: the WHO, NCEP ATP III, IDF and H_MS panels. In this study MetS among pre- and postmenopausal Ghanaian women was determined using the WHO, NCEP ATP III, IDF and H_MS criteria as outlined under section 2.1.

3.5 STATISTICAL ANALYSIS

Normality of all variables were ascertained before being subjected to the statistical analyses using the D' Agostino-Pearson procedure. Continuous variables are expressed as their mean ± SEM, while categorical variables are expressed as proportion. Comparisons of the general characteristics of postmenopausal women against the premenopausal group were performed using unpaired *t* tests, χ^2 tests, or Fisher exact tests where appropriate. Areas under the Curve (AUC) for the atherogenic and obesity markers were measured through ROC curve analysis for the diagnosis of MetS amongst pre- and postmenopausal women. The diagnostic

performance characteristics in terms of sensitivity and specificity were calculated at different cut-offs for those markers which showed higher AUC. The significance of the difference between the areas that lie under the curves derived from pre- and postmenopausal samples were calculated using the formula suggested by (Hanley and McNeil, 1982). One way analysis of variance (ANOVA) followed by Tukey's multiple test was performed to compare metabolic indicators of pre- and postmenopausal women with and without MetS. All p values were two-sided and the level of significance of <0.05 was accepted after Bonferroni correction (Bonferroni, 1935). (GraphPad Prism version 5.00 (GraphPad software, San Diego California, USA; www.graphpad.com) and Statistical Package for the Social Sciences (SPSS) version 16.00 for windows (SPSS Inc, Chicago, USA; www.spss.com) were used for statistical analysis.



CHAPTER FOUR

4.0 RESULTS AND DISCUSSION

4.1 RESULTS

4.1.1 General Characteristics of the Population

Out of 250 women, 143 (57.2%) were premenopausal and 107 (42.8%) were postmenopausal. The general characteristics of the study population are shown in Table 4.1. The mean age of the postmenopausal women (57.25 ± 0.8) was significantly higher (p<0.0001) than the mean age of the premenopausal (34.48 ± 0.7) women. Postmenopausal women had significantly (p< 0.0001) larger waist circumference, higher mean WHR, WTR, WHtR, SBP, DBP and PP than their premenopausal counterpart. The two groups did not however differ significantly (p=0.415) in BMI values as indicated in Table 4.1. Moreover, the proportion of postmenopausal women who were passive smokers and/or drank alcoholic beverage was significantly more (p=0.016 and 0.023, respectively). A significantly higher (p=0010) proportion of the postmenopausal women were unemployed whereas premenopausal cohorts were mainly (p=0.0006) non-manual workers (Table 4.1). On the other hand, the proportion of postmenopausal subjects with family history of diabetes was more than premenopausal women (p=0.042).

Table 4.1: General Characteristics of Pre- and Postmenopausal Ghanaian Women

Parameters	Total (n=250)	Postmenopausal (n=107)	Premenopausal (n=143)	*P value*
Age (years)	44.23 ± 0.90	57.25 ± 0.80	34.48 ± 0.74	<0.0001
Anthropometric Parameters				
WC (cm)	92.41 ± 0.72	95.83 ± 0.93	89.85 ± 1.01	<0.0001
WHR	0.88 ± 0.00	0.91 ± 0.01	0.87 ± 0.01	<0.0001
WTR	1.67 ± 0.01	1.72 ± 0.01	1.62 ± 0.01	<0.0001
WHtR	0.58 ± 0.00	0.60 ± 0.01	0.56 ± 0.01	<0.0001
BMI (kg/m^2)	26.65 ± 0.32	26.92 ± 0.46	26.39 ± 0.44	0.415
Hemodynamic Parameters				
SBP (mmHg)	132.5 ± 1.20	140.6 ± 1.75	126.4 ± 1.44	<0.0001
DBP (mmHg)	86.3 ± 0.73	89.87 ± 1.09	83.62 ± 0.93	<0.0001
PP (mmHg)	46.2 ± 0.76	50.76 ± 1.12	42.73 ± 0.93	<0.0001
Socio-demographic Parameters				
Passive Smokers	35(14.0%)	22(20.6%)	13(9.1%)	0.0160
Alcoholics	89(35.6%)	47(43.9%)	42(29.4%)	0.0230
Married	148(59.2%)	61(57.0%)	87(60.8%)	0.6030
Occupation				
Manual	112(44.8%)	54(50.5%)	58(40.6%)	0.1252
Non-manual	118(47.2%)	37(34.6%)	81(56.6%)	0.0006
Outside of EAP	20(8.0%)	16(15.0%)	04(2.8%)	0.0010
High Education	73(29.2%)	27(25.2%)	46(32.2%)	0.2620
Physically Inactive	102(40.8%)	37(36.4%)	65(45.5%)	0.0920
Family History of Hypertension	95(38.0%)	41(38.3%)	54(37.8%)	1.0000
Family History of Diabetes	65(26.0%)	35(32.7%)	30(21%)	0.0420
Biochemical Assays				
TC (mmol/l)	4.40 ± 0.05	4.41 ± 0.08	4.40 ± 0.07	0.8500
TG (mmol/l)	1.20 ± 0.03	1.31 ± 0.06	1.12 ± 0.04	0.0060
HDL-C (mmol/l)	1.34 ± 0.02	1.31 ± 0.03	1.37 ± 0.02	0.0670
LDL-C (mmol/l)	2.51 ± 0.05	2.59 ± 0.08	2.52 ± 0.06	0.9130
VLDL-C (mmol/l)	0.42 ± 0.01	0.46 ± 0.02	0.40 ± 0.01	0.0060
HDL-C/TC	0.31 ± 0.00	0.30 ± 0.01	0.32 ± 0.01	0.0700
TG/HDL-C	0.91 ± 0.04	1.11 ± 0.08	0.86 ± 0.04	0.0040
FBG (mmol/l)	5.19 ± 0.08	5.60 ± 0.15	4.9 ± 0.07	<0.0001

Continuous data were presented as mean ± standard error of mean (SEM). Categorical data are presented as frequency with percentages in parenthesis. Continuous data were compared using unpaired t-test whilst categorical data were compared using Fischer's exact test. VLDL-C: Very Low Density Lipoprotein-Cholesterol, LDL-C: Low Density Lipoprotein-Cholesterol, HDL-C: High Density Lipoprotein, TC: Total Cholesterol, TG: Triglycerides, FBG: Fasting Blood Glucose, WHR: Waist-to-Hip Ratio, BMI: Body Mass Index, WC: Waist Circumference, WTR: Waist-to-Thigh Ratio, WHtR: Waist-to-Height Ratio, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, PP: Pulse Pressure, EAP: Economically active population.

Biochemical analyses point to a significant ($p< 0.05$) increase in the mean level of TG, VLDL cholesterol, and fasting blood glucose among postmenopausal participants as compared to the premenopausal subjects, and the mean TG/HDL-C ratio was also higher among the postmenopausal group (Table 4.1). Though these biochemical markers were significantly raised in postmenopausal women, they were within normal range. The postmenopausal women however had reduced HDL-C, though not statistically significant, compared to their premenopausal counterparts (Table 4.1).

4.1.2 Prevalence of MetS and Metabolic Score among Pre-and Postmenopausal Ghanaian Women

The percentage prevalence of MetS was 14.4%, 25.6%, 29.2% and 30.4% using WHO, NCEP ATP III, IDF and H_MS criteria respectively for the total population. The prevalence was higher among the postmenopausal group (i.e. 25.2%, 41.1%, 43.0% and 43.9% for WHO, NCEP ATP III, IDF and H_MS respectively) compared to the premenopausal population (i.e. 6.3%, 14.7%, 18.9% and 23.1% respectively for WHO, NCEP ATP III, IDF and H_MS criteria respectively) in Table 4.2.

In terms of proportion, women without any MetS risk factor (i.e. zero metabolic score) was significantly higher ($p<0.0001$ using WHO and NCEP ATP III criteria, and $p=0.001$ using the IDF and H_MS criteria respectively) among the premenopausal subjects as compared to the postmenopausal participants using all criteria. A metabolic score of 1 was found to be more associated with the premenopausal group than their postmenopausal counterparts (Table 4.2). However, the ratio of women who were about to traverse to MetS zone (i.e. metabolic score of 3) was similar between the postmenopausal group and the premenopausal individuals with the exception of WHO criteria (Table 4.2). There were some women who possessed three or more

MetS risk factors, yet they were not diagnosed of MetS according to WHO and IDF criteria. This small population was common among the premenopausal group, though not significant (Table 4.2).

Table 4.2: Prevalence of MetS and Metabolic Score among Pre- and Postmenopausal Ghanaian Women

Parameters	Total (n=250)	Postmenopausal (n=107)	Premenopausal (n=143)	*P value*
Prevalence of MetS				
WHO	36(14.4%)	27(25.2%)	09(6.3%)	<0.0001
NCEP ATP III	65(26.0%)	44(41.1%)	21(14.7%)	<0.0001
IDF	73(29.2%)	46(43.0%)	27(18.9%)	<0.0001
H_MS	76(30.4%)	47(43.9%)	29(20.3%)	<0.0001
Prevalence of clustering of one or two or more components of MetS				
WHO				
0	34(13.6%)	01(1.0%)	33(23.1%)	<0.0001
1	70(28.0%)	20(18.7%)	50(35.0%)	0.0050
2	76(30.4%)	45(42.1%)	31(21.7%)	0.0010
>2 without MetS	34(13.6%)	14(13.1%)	20(14.0%)	1.0000
NCEP ATP III				
0	30(12.0%)	03(2.8%)	27(18.9%)	<0.0001
1	57(22.8%)	13(12.1%)	44(30.8%)	0.0010
2	98(39.2)	47(43.9%)	51(35.7%)	0.1930
IDF				
0	13(5.2%)	00(0.0%)	13(9.1%)	0.0010
1	50(20.0%)	08(7.5%)	42(29.4%)	<0.0001
2	111(44.4%)	52(48.6%)	59(41.3%)	0.3030
>2 without MetS	03(1.2%)	01(1.0%)	02(1.4%)	1.0000
H_MS				
0	13(5.2%)	00(0.0%)	13(9.1%)	0.0010
1	50(20.0%)	08(7.5%)	42(29.4%)	<0.0001
2	111(44.4%)	52(48.6%)	59(41.3%)	0.3030

Data are presented as a proportion with corresponding percentages in parenthesis. The proportions were compared using Fischer's exact test. MetS: MetS

4.1.3 Prevalence of Determinant Components of MetS among Pre-and Postmenopausal Ghanaian Women

The prevalence of abdominal (central) obesity [87.9% in postmenopausal (WHO), 80.4% in postmenopausal (NCEP ATP III); 95.3% in postmenopausal (IDF and H_MS)]; raised fasting blood glucose [36.5% in postmenopausal]; and raised blood pressure [83.2% in postmenopausal)] were significantly higher (p<0.0001 for all) compared to the premenopausal population with [i.e. 56.0% (WHO), 51.7% (NCEP ATP III) and 79.0% (IDF and H_MS), 6.3% (WHO), 16.1% (NCEP, IDF &H_MS), 31.5% (WHO) and 49.7% (NCEP, IDF & H_MS)] for abdominal obesity, raised fasting blood glucose and raised blood pressure respectively as shown in Table 4.3. These components contributed to higher prevalence of MetS (about tenfold) among the postmenopausal group compared to the premenopausal individuals using these criteria.

On the other hand, using the NCEP criterion, the contributing factors were glucose and raised blood pressure , central obesity and raised fasting blood (Table 4.3). The percentage prevalence of these components was raised blood pressure (83.2%), central obesity (80.4%) and raised fasting blood glucose (36.5%) in postmenopausal women and were statistically significant (p<0.05) compared to premenopausal subjects (Table 4.3).

Table 4.3: Prevalence of the Predominant Components of MetS among Pre- and Postmenopausal Ghanaian Women

Parameters	Total (n=250)	Postmenopausal (n=107)	Premenopausal (n=143)	*P value*
WHO				
Central Obesity	177(70.8%)	94(87.9%)	83(58.0%)	<0.0001
Raised Fasting Glucose	39(15.6%)	30(28.0%)	9(6.3%)	<0.0001
Raised Triglyceride	24(9.6%)	15(14.0%)	9(6.3%)	0.0507
Raised Blood Pressure	109(43.6%)	64(59.8%)	45(31.5%)	<0.0001
Reduced HDL-C	47(18.8%)	26(24.3%)	21(14.7%)	0.0710
NCEP ATP III				
Abdominal Obesity	160(64.0%)	86(80.4%)	74(51.7%)	<0.0001
Raised Fasting Glucose	62(24.8%)	39(36.5%)	23(16.1%)	0.0003
Raised Triglyceride	24(9.6%)	15(14.0%)	9(6.3%)	0.0507
Raised Blood Pressure	160(64.0%)	89(83.2%)	71(49.7%)	<0.0001
Reduced HDL-C	91(36.4%)	45(42.1%)	46(32.2%)	0.1132
IDF				
Abdominal Obesity	215(86.0%)	102(95.3%)	113(79.0%)	0.0002
Raised Fasting Glucose	62(24.8%)	39(36.5%)	23(16.1%)	0.0003
Raised Triglyceride	24(9.6%)	15(14.0%)	9(6.3%)	0.0507
Raised Blood Pressure	160(64.0%)	89(83.2%)	71(49.7%)	<0.0001
Reduced HDL-C	91(36.4%)	45(42.1%)	46(32.2%)	0.1132
H_MS				
Abdominal Obesity	215(86.0%)	102(95.3%)	113(79.0%)	0.0002
Raised Fasting Glucose	62(24.8%)	39(36.5%)	23(16.1%)	0.0003
Raised Triglyceride	24(9.6%)	15(14.0%)	9(6.3%)	0.0507
Raised Blood Pressure	160(64.0%)	89(83.2%)	71(49.7%)	<0.0001
Reduced HDL-C	91(36.4%)	45(42.1%)	46(32.2%)	0.1132

Data are presented as proportion with corresponding percentages in parenthesis

4.1.4 Prevalence of Obesity, Hypertension, Diabetes and Dyslipidaemia among Population Classified by Menopause

The prevalence of BMI overweight, WHR obesity, WHtR obesity, hyperglycaemia, diabetes and hypertension were significantly (p<0.05) higher among postmenopausal group whilst WHR overweight, WHR obesity and WHtR normal were significantly (p<0.0001) higher among premenopausal subjects than their postmenopausal

counterparts (Table 4.4). BMI obesity was prevalent in premenopausal women than their postmenopaūsal cohorts though not significant.

Table 4.4: Prevalence of Obesity, Hypertension, Diabetes and Dyslipidaemia among Population Classified by Menopause

Parameters	Total (n=250)	Postmenopausal (n=107)	Premenopausal (n=143)	*P value*
BMI				
Underweight	23(9.2%)	07(6.5%)	16(11.2%)	0.2700
Normal	80(32.0%)	32(29.9%)	48(33.6%)	0.5850
Overweight	89(35.6%)	46(43.0%)	43(30.1%)	0.0450
Obese	58(23.2%)	22(20.6%)	36(25.2%)	0.4500
WHR				
Normal	16(6.4%)	01(1.0%)	15(10.5%)	0.0020
Overweight	42(16.8%)	06(5.6%)	36(25.2%)	<0.0001
Obese	192(76.8%)	100(93.5%)	92(64.3%)	<0.0001
WHtR				
Normal	66(26.4%)	18(16.8%)	48(33.6%)	0.0040
Obese	184(73.6%)	89(83.2%)	95(66.4%)	0.0040
FBG				
Hyperglycaemia	40(16.0%)	30(28.0%)	10(7.0%)	<0.0001
Impaired Glucose	12(4.8%)	06(5.6%)	06(4.2%)	0.7670
Hypertension	113(45.2%)	67(62.6%)	46(32.2%)	<0.0001
Dyslipidaemia	16(6.4%)	09(8.4%)	07(4.9%)	0.3020

n: number of subjects, Four categories of BMI (≤20, 20–24.9, 25–29.9, and ≥30 kg/m^2) were identified. The categories were selected according to WHO recommendations to define individuals with a healthy weight (BMI 20–25), overweight (BMI 25–29.9) and obese (BMI≥30). Individuals with a BMI ≤20 kg/m^2 were classified as underweight. Women with WHR < 0.80, 0.80–0.84 and ≥ 0.85 were classified as normal weight, overweight or obese respectively, women with WHtR = < 0.53 and > 0.53 were classified as normal and obese respectively; Hyperglycaemia = fasting blood sugar ≥ 6.1 mmol/l, Impaired Glucose = fasting blood sugar between 6.1 to 6.9 mmol/l, Diabetes = fasting blood glucose greater or equal to 7.0 mmol/l and Dyslipidaemia = TG ≥1.70 mmol/l and HDL-C ≤1.01 mmol/l

4.1.5 Prevalence of MetS Stratified by Menopausal Status and Age

The prevalence of MetS generally increased with age, using chi-square for trend, irrespective of the criteria applied, as shown in (Fig 4.1a and b). Using WHO as an example, the prevalence significantly ($\chi^2 = 25.75$; $p < 0.0001$) increased from 0.0% (0/52) among 20-29 years group to 4.9% (2/41) among 30-39 years group and through to 36.4% (12/33) in the greater or equal to 60 years group (Fig. 4.1a). The age specific distribution of MetS was usually higher among the postmenopausal group. The highest prevalence of MetS among the postmenopausal women was seen in 60 years group or older irrespective of the criteria with the exception of NCEP ATP III which was seen among 40-49 years group (Fig. 4.1a).

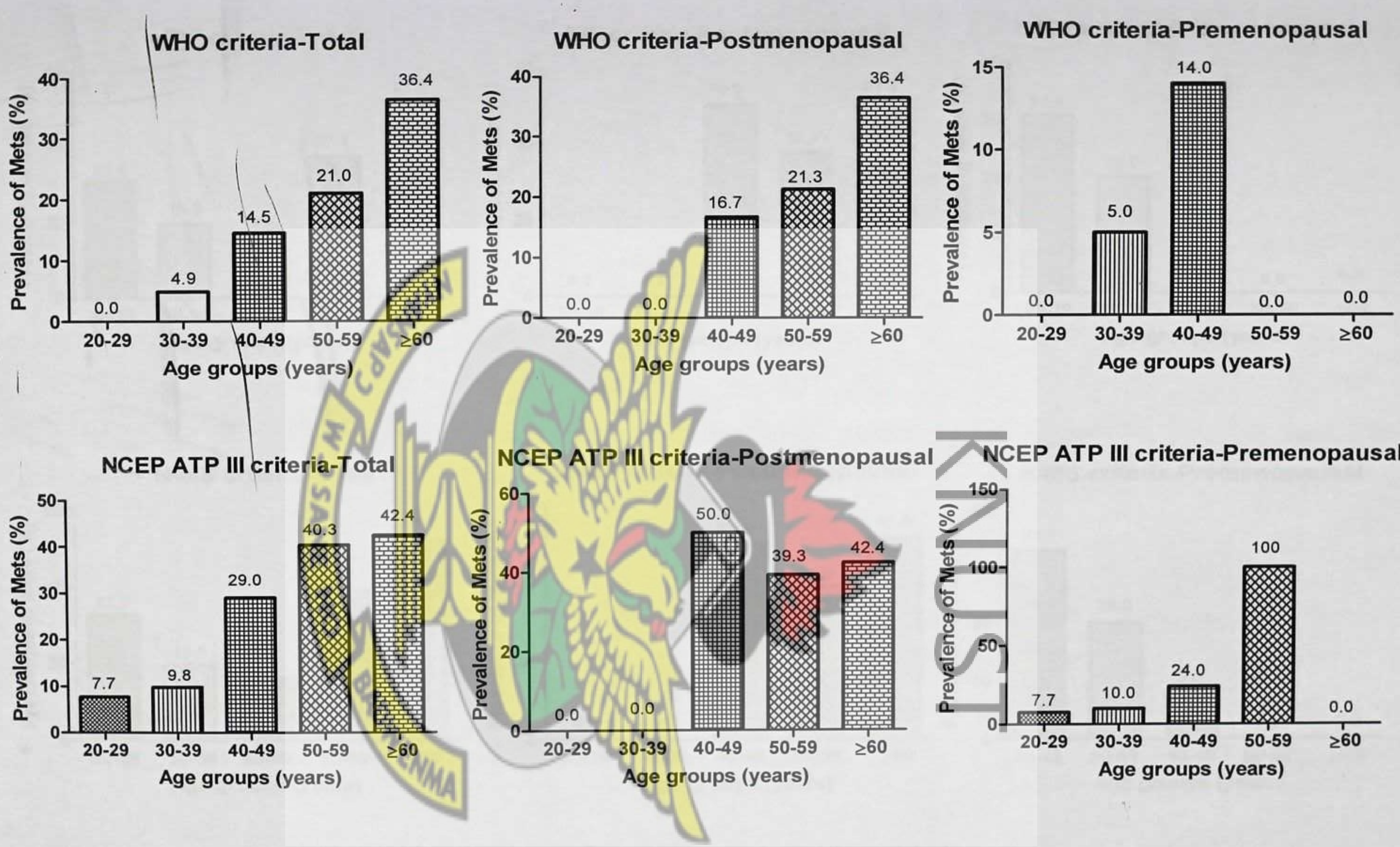


Figure 4.1a: Prevalence of MetS Stratified by Menopausal Status and Age. Percentages were calculated based on the number of women diagnosed of MetS expressed over the total number of the women in each age category for pre- and postmenopausal group.

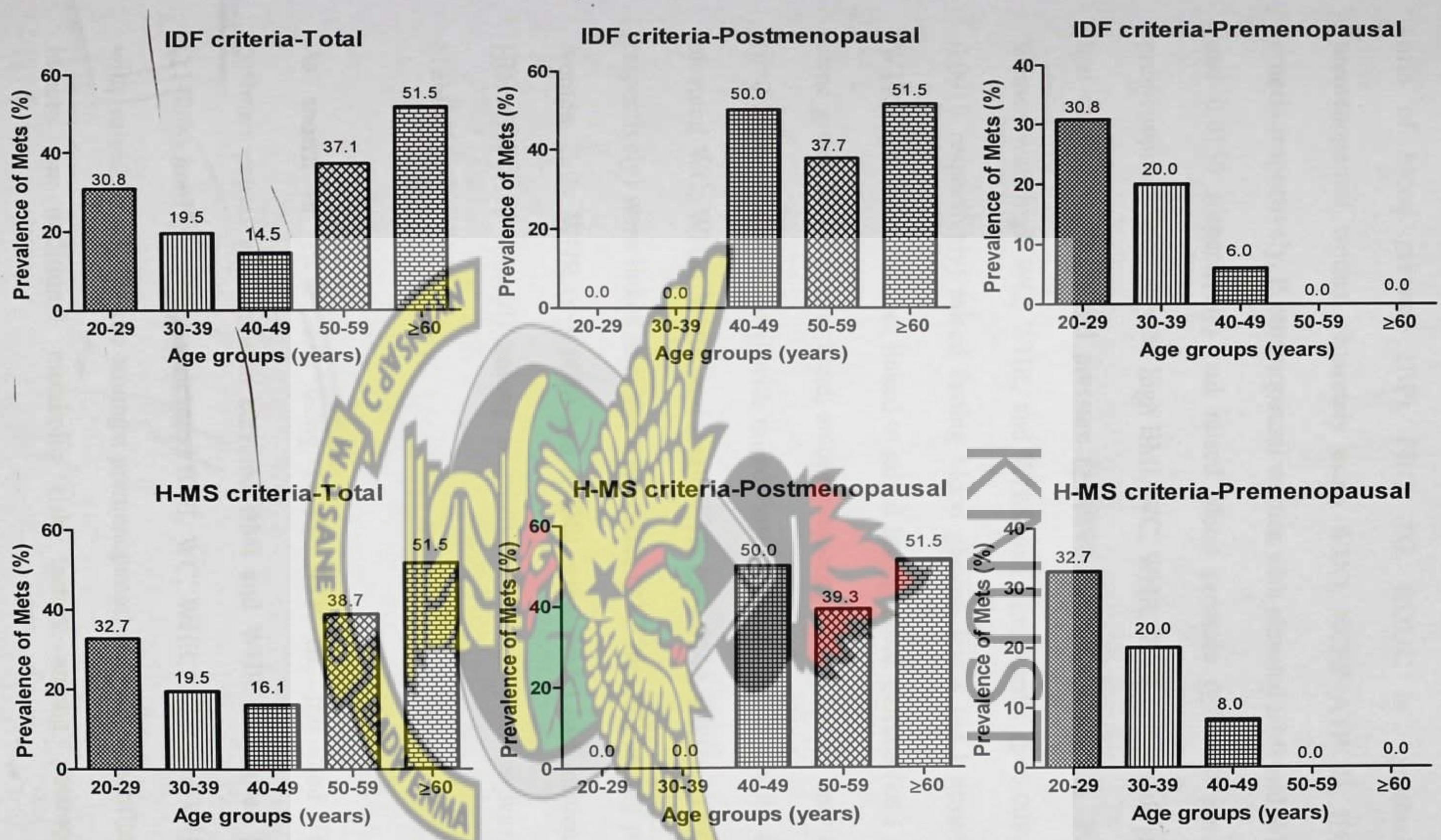


Figure 4.1b: Prevalence of MetS Stratified by Menopausal Status and Age. Percentages were calculated based on the number of women diagnosed of MetS expressed over the total number of the women in each age category for pre- and postmenopausal group

4.1.6 Influence of Obesity Markers on Metabolic Risk Factors

Tables 4.5 and 4.6 show the influence of BMI, WC, WTR, WHR, WHtR on the cut-offs of blood pressure (BP), FBG, TG, HDL-C in postmenopausal and premenopausal women separately using WHO, NCEP ATP III, IDF and H_MS criteria respectively. Postmenopausal women with elevated BMI and WHR (p=0.0440 and 0.0130 respectively) had raised blood pressure (≥140/90 mmHg), whereas premenopausal women with high BMI, WC, WHR, WTR and WHtR (p<0.05 for all) had raised systolic blood pressure (≥140/90 mmHg) (Table 4.5). Postmenopausal women with high WC, WHR, and WHtR had significantly (p=0.0080, 0.0300, and 0.0010 respectively) raised fasting blood glucose levels (≥6.1 mmol/l) but small WTR (0.0030) was rather linked to raised fasting blood glucose (<6.1 mmol/l) in the same group. On the other hand, among premenopausal subjects, only elevated WHR (p=0.0040) was associated with raised fasting blood glucose (Table 4.5). Similarly, elevated WC, WHR, WHtR and small WTR (p=0.0040, 0.0070, 0.0320 and 0.0070 respectively) were linked to raised triglyceride (≥1.7 mmol/l) among postmenopausal women. Only WHR (p=0.0070 and 0.0040 respectively) had influence on reduced HDL-C (<1.30 mmol/l) among postmenopausal and premenopausal populations (Table 4.5).

As shown in Table 4.6, using NCEP ATP III, IDF and H_MS criteria, postmenopausal women with elevated BMI and WHR had raised blood pressure (≥140/90 mmHg), whereas elevated BMI, WC, WHR, WTR and WHtR associated with raised blood pressure amongst premenopausal subjects. The influence of obesity indices on traditional metabolic risk factors among postmenopausal and

premenopausal populations was similar to what was detected when WHO criterion was applied (Table 4.6).

Table 4.5: BMI, WC, WHR and WHtR values According to the Various Cut-off of Different Metabolic Risk Factors in Pre- and Postmenopausal Ghanaian Women using WHO Criterion

Parameters	Postmenopausal					Premenopausal				
	BMI	WC	WHR	WTR	WHtR	BMI	WC	WHR	WTR	WHtR
WHO										
Systolic Blood Pressure										
<140 mmHg	25.96±0.6	95.24±1.3	0.92±0.01	1.71±0.2	0.60±0.01	25.73±0.4	88.10±1.0	0.86±0.01	1.60±0.01	0.55±0.01
≥140 mmHg	27.79±0.7	96.38±1.4	0.91±0.07	1.73±0.2	0.60±0.01	29.18±1.3	96.76±2.7	0.90±0.01	1.70±0.03	0.60±0.02
P value	0.0440	0.5420	0.1870	0.3800	0.9420	0.0020	0.0010	<0.0001	0.0004	0.0010
Diastolic Blood Pressure										
<90 mmHg	25.75±0.6	94.45±1.2	0.92±0.01	1.72±0.02	0.60±0.01	25.48±0.5	87.55±1.1	0.86±0.01	1.61±0.01	0.54±0.01
≥90 mmHg	27.99±0.7	97.19±1.4	0.91±0.01	1.72±0.02	0.61±0.01	28.83±1.0	95.59±2.1	0.89±0.01	1.67±0.02	0.60±0.01
P value	0.0130	0.1420	0.1700	0.9200	0.5380	0.0010	0.0003	0.0080	0.0300	0.0003
Fasting Blood Glucose										
<6.1 mmol/l	26.8±0.6	94.31±1.1	0.91±0.01	1.80±0.02	0.59±0.01	26.51±0.5	89.64±1.1	0.86±0.01	1.62±0.01	0.56±0.01
≥6.1 mmol/l	26.88±0.7	99.73±1.5	0.93±0.01	1.70±0.01	0.64±0.01	26.53±0.7	92.70±3.6	0.91±0.01	1.66±0.02	0.59±0.02
P value	0.9330	0.0080	0.0300	0.0030	0.0010	0.9900	0.4430	0.0040	0.4710	0.2980
Triglyceride										
<1.7 mmol/l	26.62±0.50	94.76±1.01	0.91±0.01	1.73±0.01	0.59±0.01	26.30±0.5	89.37±1.04	0.87±0.01	1.62±0.01	0.56±0.01
≥1.7 mmol/l	28.32±1.03	102.4±1.5	0.95±0.01	1.65±0.02	0.64±0.01	28.21±1.7	97.00±3.6	0.89±0.02	1.64±0.01	0.60±0.03
P value	0.1930	0.0040	0.0070	0.0320	0.0070	0.2970	0.0670	0.1540	0.7600	0.0890
HDL-C										
<1.01 mmol/l	25.52±0.7	95.92±1.7	0.94±0.01	1.68±0.02	0.60±0.01	25.77±1.0	91.29±2.8	0.90±0.01	1.62±0.01	0.57±0.01
≥1.01 mmol/l	27.19±0.6	95.80±1.1	0.91±0.01	1.73±0.02	0.60±0.01	26.56±0.5	89.61±1.1	0.86±0.01	1.62±0.01	0.56±0.01
p value	0.1220	0.9560	0.0070	0.0730	0.9820	0.5280	0.5590	0.0040	0.9990	0.6850

Data are presented as mean ± SEM. Continuous data were compared using unpaired t-test. HDL-C: High Density Lipoprotein, FBG: Fasting Blood Glucose, WHR: Waist-to-Hip Ratio, BMI: Body Mass Index, WC: waist Circumference, WTR: Waist-to-Thigh Ratio, WHtR: Waist-to-Height

Table 4.6: BMI, WC, WTR, WHR and WHtR values According to the Various Cut-off of different Metabolic Risk Factors in Pre- and Postmenopausal Ghanaian Women using NCEP ATP III, IDF and H_MS Criteria

Parameters	Postmenopausal					Premenopausal				
	BMI	WC	WHR	WTR	WHtR	BMI	WC	WHR	WTR	WHtR
NCEP ATP III, IDF & H_MS										
Systolic Blood Pressure										
<130 mmHg	24.19±0.8	92.50±1.8	0.92±0.01	1.70±0.02	0.58±0.01	25.37±0.5	87.10±1.1	0.85±0.01	1.60±0.01	0.54±0.01
≥130 mmHg	27.65±0.5	96.80±1.1	0.91±0.01	1.73±0.02	0.61±0.01	28.11±0.8	94.39±1.9	0.89±0.01	1.67±0.02	0.59±0.01
P value	0.0010	0.0530	0.5830	0.2540	0.1360	0.0030	0.0004	0.0004	0.0030	0.0010
Diastolic Blood Pressure										
<85 mmHg	24.59±0.7	94.00±1.6	0.93±0.01	1.70±0.02	0.59±0.01	25.10±0.5	86.96±1.1	0.86±0.01	1.62±0.01	0.54±0.01
≥85 mmHg	27.86±0.6	96.61±1.1	0.91±0.01	1.73±0.02	0.60±0.01	28.34±0.8	93.97±1.8	0.87±0.01	1.65±0.02	0.59±0.01
P value	0.0010	0.1990	0.0120	0.3430	0.7580	0.0002	0.0010	0.1180	0.2040	0.0010
Fasting Blood Glucose										
<5.6 mmol/l	26.64±0.6	93.91±1.2	0.91±0.01	1.76±0.02	0.58±0.01	26.81±0.5	90.04±1.1	0.86±0.01	1.62±0.01	0.56±0.01
≥5.6 mmol/l	27.13±0.7	99.18±1.5	0.93±0.01	1.66±0.01	0.63±0.01	24.98±0.9	88.87±2.3	0.89±0.01	1.63±0.02	0.55±0.02
P value	0.6060	0.0060	0.0480	<0.0001	0.0003	0.1400	0.6720	0.0260	0.7090	0.7290
Triglyceride										
<1.7 mmol/l	26.62±0.5	94.76±1.0	0.91±0.01	1.73±0.01	0.59±0.01	26.30±0.5	89.37±1.04	0.87±0.01	1.62±0.01	0.56±0.01
≥1.7 mmol/l	28.32±1.0	102.4±1.5	0.95±0.01	1.65±0.02	0.64±0.01	28.21±1.7	97.00±3.6	0.89±0.02	1.64±0.01	0.60±0.03
P value	0.1930	0.0040	0.0070	0.0320	0.0070	0.2970	0.0670	0.1540	0.7600	0.0890
HDL-C										
<1.30 mmol/l	26.41±0.6	96.76±1.4	0.93±0.01	1.69±0.02	0.61±0.01	26.09±0.8	90.97±2.0	0.89±0.01	1.62±0.01	0.57±0.01
≥1.30 mmol/l	26.98±0.6	95.34±1.2	0.90±0.01	1.74±0.02	0.59±0.01	26.56±0.5	89.49±1.2	0.86±0.01	1.62±0.01	0.56±0.01
P value	0.5530	0.4710	0.0061	0.0690	0.3450	0.6510	0.5310	0.0020	0.9820	0.4920

4.1.7 Influence of Atherogenic Indices on Metabolic Risk Factors

The influence of atherogenic indices such as TG/HDL-C, HDL-C/TC and HDL-C/LDLC on traditional metabolic risk factors is shown in Table 4.7. Premenopausal women with raised blood pressure (≥140/90 mmHg) had increased TG/HDL-C and HDL-C/LDL-C ratios ($p<0.0001$ and 0.0120 respectively) (Table 4.7). Among postmenopausal women, raised fasting blood glucose were common coupled with higher TG/HDL-C, HDL-C/TC and HDL-C/LDL-C ratios ($p<0.0001$, 0.0260 and 0.0420 respectively). Similarly, raised triglyceride levels were also significantly ($p<0.0001$ and 0.0010 respectively) influenced by higher TG/HDL-C and HDL-C/LDL-C ratios in the same group. Among premenopausal cohorts, TG/HDL-C and HDL-C/TC ratios significantly ($p<0.0001$ and 0.0200 respectively) influenced raised fasting blood glucose (Table 4.7). Finally, reduced levels of HDL-C were noticeable in higher TG/HDL-C ratio ($p<0.0001$) and decreased HDL-C/TC ratio ($p<0.0001$) in postmenopausal group whereas it was apparent in higher TG/HDL-C ratio ($p<0.0001$) but in lower HDL-C/TC and HDL-C/LDL-C ratios ($p<0.0001$ and 0.0200 respectively) among premenopausal subjects (Table 4.7). A similar result was observed when the other criteria were applied as shown in Table 4.8.

Table 4.7: TG/HDL-C, HDL-C/TC and HDL-C/LDL-C values according to the Various Cut-off of Different Metabolic Risk Factors in Pre- and Postmenopausal Ghanaian Women using WHO Criterion

Parameters	Postmenopausal			Premenopausal		
	TG/HDL-C	HDL-C/TC	HDL-C/LDL-C	TG/HDL-C	HDL-C/TC	HDL-C/LDL-C
Systolic Blood Pressure						
<140 mmHg	1.11±0.091	0.31±0.013	1.01±0.250	0.74±0.021	0.32±0.007	0.60±0.026
≥140 mmHg	1.08±0.132	0.32± 0.014	0.67±0.074	1.34±0.148	0.34±0.021	0.82±0.144
P value	0.8380	0.9580	0.1840	<0.0001	0.2360	0.0120
Diastolic Blood Pressure						
<90 mmHg	1.04±0.078	0.33± 0.014	1.04±0.240	0.73±0.023	0.32±0.008	0.59±0.027
≥90 mmHg	1.15±0.142	0.30± 0.014	0.63±0.074	1.19±0.111	0.34± 0.016	0.83±0.116
P value	0.5000	0.1750	0.0980	<0.0001	0.2310	0.0050
Fasting Blood Glucose						
<6.1 mmol/l	0.74±0.018	0.33± 0.010	0.67±0.057	0.76±0.020	0.33±0.007	0.65±0.038
≥6.1 mmol/l	2.01±0.211	0.28±0.0215	1.24±0.420	2.21±0.247	0.26±0.032	0.53±0.114
P value	<0.0001	0.0260	0.0420	<0.0001	0.0220	0.3850
Triglyceride						
<1.7 mmol/l	0.84±0.033	0.32 ± 0.010	0.66 ± 0.053	0.77 ± 0.021	0.33 ± 0.007	0.65 ± 0.038
≥1.7 mmol/l	2.69±0.324	0.28 ± 0.030	1.87 ± 0.807	2.26± 0.270	0.28 ± 0.031	0.56 ± 0.121
P value	<0.0001	0.1850	0.0010	<0.0001	0.1040	0.5550
HDL-C						
<1.01 mmol/l	1.20±0.263	0.21±0.012	0.54±0.194	1.59±0.188	0.24±0.018	0.44±0.066
≥1.01 mmol/l	0.83± 0.034	0.35±0.010	0.92±0.152	0.74±0.016	0.34±0.007	0.68±0.041
p value	<0.0001	<0.0001	0.1960	<0.0001	<0.0001	0.0200

Continuous data were presented as mean ± standard error of mean (SEM). LDL-C: Low Density Lipoprotein-Cholesterol, HDL-C: High Density Lipoprotein, TC: Total Cholesterol, TG: Triglycerides.

Table 4.8: TG/HDL-C, HDL-C/TC and HDL-C/LDL-C values According to the Various Cut-off of Different Metabolic Risk Factors in Pre- and Postmenopausal Ghanaian women using NCEP ATP III, IDF and H_MS Criteria

Parameters	Postmenopausal			Premenopausal		
	TG/HDL-C	HDL-C/TC	HDL-C/LDL-C	TG/HDL-C	HDL-C/TC	HDL-C/LDL-C
NCEP ATP III, IDF and H_MS Criteria						
Systolic Blood Pressure						
<130 mmHg	1.06±0.105	0.33±0.023	1.17±0.48	0.71±0.022	0.31±0.008	0.57±0.029
≥130 mmHg	1.11±0.101	0.31±0.011	0.74±0.087	1.13±0.088	0.34±0.014	0.76±0.082
P value	0.8290	0.5800	0.1490	<0.0001	0.0980	0.0140
Diastolic Blood Pressure						
<85 mmHg	1.12±0.097	0.33±0.018	1.14±0.368	0.71±0.023	0.32±0.008	0.58±0.031
≥85 mmHg	1.09±0.109	0.31±0.012	0.70±0.086	1.09±0.082	0.33±0.012	0.77±0.083
P value	0.8640	0.2410	0.1070	<0.0001	0.2290	0.0210
Fasting Blood Glucose						
<5.6 mmol/l	0.72±0.017	0.33±0.011	0.64±0.047	0.75±0.020	0.32±0.007	0.63±0.041
≥5.6 mmol/l	1.76±0.178	0.29±0.019	1.16±0.331	1.47±0.176	0.33±0.022	0.66±0.094
P value	<0.0001	0.0880	0.0470	<0.0001	0.8380	0.7730
Triglyceride						
<1.7 mmol/l	0.84±0.033	0.32±0.010	0.66±0.053	0.77±0.021	0.33±0.007	0.65±0.038
≥1.7 mmol/l	2.69±0.324	0.28±0.030	1.87±0.807	2.26±0.270	0.28±0.031	0.56±0.121
P value	<0.0001	0.1850	0.0010	<0.0001	0.1040	0.5550
HDL-C						
<1.30 mmol/l	1.74±0.198	0.24±0.013	0.65±0.170	1.26±0.136	0.25±0.012	0.44±0.041
≥1.30 mmol/l	0.77±0.025	0.36±0.010	0.93±0.169	0.74±0.015	0.35±0.007	0.72±0.045
P value	<0.0001	<0.0001	0.2990	<0.0001	<0.0001	0.0010

Continuous data were presented as mean ± standard error of mean (SEM). LDL-C: Low Density Lipoprotein-Cholesterol, HDL-C: High Density Lipoprotein, TC: Total Cholesterol, TG: Triglycerides.

4.1.8 Comparison of Metabolic Indicators among Pre- and Postmenopausal Women with and without MetS

Table 4.9 presents the comparison of metabolic indicators among premenopausal with and without Mets (PRWM & PRWtM) and postmenopausal women with and without MetS (POWM & POWtM). Systolic blood pressure was significantly higher in both postmenopausal group and PRWM than PRWtM. Also fasting blood glucose levels of POWM and PRWM were significantly higher than POWtM and PRWtM (Table 4.9). Postmenopausal women with MetS had significantly raised triglyceride levels as compared to POWtM and PRWtM groups. High density lipoprotein cholesterol (HDL-C) levels, however, were significantly reduced among POWM and PRWM than their counterparts without MetS. The ratios of HDL-C/VLDL-C and HDL-C/TC were significantly lower in Ghanaian women with MetS than those without MetS. Finally, the values of WHR, WTR and WHtR were significantly higher in postmenopausal groups than those in premenopausal groups (Table 4.9).

Table 4.9: Comparison of Metabolic Indicators among Pre- and Postmenopausal Women with and without MetS

Parameters	POWtM (n=60)	POWM (n=47)	PRWM (n=29)	PRWtM (n=114)	*P value*
H_MS					
Age (yrs)	57.53 ± 1.13‡‡‡***	56.89 ± 1.13$^{###§§§}$	38.38 ± 1.64¶	33.49 ± 0.81	<0.0001
SBP (mmHg)	142.0 ± 2.56***	138.9 ± 2.26§§§	134.0 ± 4.02¶	124.4 ± 1.44	<0.0001
DBP (mmHg)	91.33 ± 1.64	88.00 ± 1.28$^{###}$	85.48 ± 2.48	83.19 ± 0.98	<0.0001
FBG (mmol/l)	4.78 ± 0.11‡‡‡	6.59 ± 0.23†††§§§	6.03 ± 0.21¶¶¶	4.61 ± 0.05	<0.0001
TG (mmol/l)	1.10 ± 0.02‡	1.57 ± 0.13†††§§§	1.46 ± 0.15¶¶	1.05 ± 0.02	<0.0001
HDL-C (mmol/l)	1.49 ± 0.02†††‡‡‡	1.08 ± 0.04	1.12 ± 0.04	1.43 ± 0.02§§§¶¶¶	<0.0001
HDL-C:TC ratio	0.33 ± 0.01†††	0.27 ± 0.01	0.29 ± 0.02	0.32 ± 0.01§§§	<0.0001
TG:HDL-C ratio	0.74 ± 0.01	1.58 ± 0.16†††§§§	1.34 ± 0.15‡‡‡¶¶¶	0.74 ± 0.02	<0.0001
HDL-C:LDL-C ratio	0.59 ± 0.01	0.57 ± 0.05	0.65 ± 0.09	0.58 ± 0.01	0.5519
HDL-C:VLDL-C ratio	3.89 ± 0.08†††‡‡‡	2.59 ± 0.22	2.82 ± 0.29	4.03 ± 0.09§§§¶¶¶	<0.0001
BMI (kg/m²)	26.52 ± 0.64	27.44 ± 0.64	26.40 ± 0.77	26.48 ± 0.52	0.7041
WHR	0.90 ± 0.01***	0.93 ± 0.01$^{##§§§}$	0.89 ± 0.01	0.86 ± 0.01	<0.0001
WTR	1.75 ± 0.02‡‡‡***	1.68 ± 0.02	1.63 ± 0.02	1.62 ± 0.01	<0.0001
WHtR	0.59 ± 0.01*	0.61 ± 0.01$^{##§§§}$	0.56 ± 0.01	0.55 ± 0.01	<0.0001

Data were presented as mean ± standard error of mean (SEM). POWtM: postmenopausal women without MetS, POWM: postmenopausal women with MetS, PRWM: premenopausal women with MetS, PRWtM: premenopausal women without MetS, LDL-C: Low Density Lipoprotein-Cholesterol, HDL-C: High Density Lipoprotein, TC: Total Cholesterol, TG: Triglycerides, FBG: Fasting Blood Glucose, WHR: Waist-to-Hip Ratio, BMI: Body Mass Index, WTR: Waist-to-Thigh Ratio, WHtR: Waist-to-Height Ratio, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, WHR: Waist-to-Hip Ratio, BMI: Body Mass Index, WC: Waist Circumference, THC: Thigh Circumference, WTR: Waist-to-Thigh Ratio, WHtR: Waist-to-Height Ratio, HTR: hip-to-thigh circumference. *Each comparison was performed between pre and postmenopausal women with and without MetS. .*p<0.05, **p<0.001, ***p<0.0001, comparison of POWtM with PRWtM; †p<0.05, †† p<0.001, ††† p<0.0001, comparison of POWtM with POWM; ‡ p<0.05, ‡‡ p<0.001, ‡‡‡ p<0.0001, comparison of POWtM with PRWM; ¶ p<0.05, ¶¶ p<0.001, ¶¶¶ p<0.0001, comparison of PRWM with PRWtM; § p<0.05, §§ p<0.001, §§§ p<0.0001, comparison of POWM with PRWtM; # p<0.05, ## p<0.001, ### p<0.0001, comparison of POWM with PRWM.

4.1.9 Prediction of MetS among Pre- and Postmenopausal Ghanaian Women using Atherogenic and Obesity Indices

The Area under Curves (AUCs) of those lipid and obesity-based markers which showed significant prediction of high blood pressure, fasting blood glucose, low HDL-C and MetS is shown in Table 4.10 and Figures 4.2, 4.3, 4.4 and 4.5. In postmenopausal subjects with the cut-off value of 23.1 kg/m² (for BMI), 1.58 (for WTR), 0.53 (for WHtR), the sensitivity and specificity were 81.8% and 57.9%, 93.2% and 84.2%, 88.6% and 73.7%, respectively, which were found to detect high blood pressure (Table 4.11). The cut-off values for detecting fasting blood glucose were 81.5 cm (for WC), 0.84 (for WHR), 0.51 (for WHtR), 0.60 (for TG/HDL-C), 0.34 (for HDL-C/TC) and the corresponding sensitivity and specificity were 94.9% and 89.7%, 97.4% and 97.1%, 97.4% and 89.7%, 97.4% and 89.7%, 79.5% and 67.6% respectively in postmenopausal women (Table 4.12). The cut-off values to detect low HDL-C were 0.85 for WHR (sensitivity and specificity were 97.4% and 89.9%), 0.63 for TG/HDL-C (sensitivity and specificity were 89.5% and 87%), 0.32 for HDL-C/TC (sensitivity and specificity were 81.6% and 36.2%) (Table 4.13). The cut-off values to detect MetS in postmenopausal women were 80.5 cm (for WC), 0.84 (for WHR), 0.61 (for TG/HDL-C), and the corresponding sensitivity and specificity were 95.7% and 91.7%, 97.9% and 93.3%, 87.2% and 80%, 91.5% and 88.3%, respectively (Table 4.14).

Based upon the studied data, the various cut-offs with their sensitivities and specificities for premenopausal women are presented in Tables 4.11, 4.12, 4.13 and 4.14 whereas Tables 4.15 and 4.16 show the comparison of area under ROC curves between pre- and postmenopausal women.

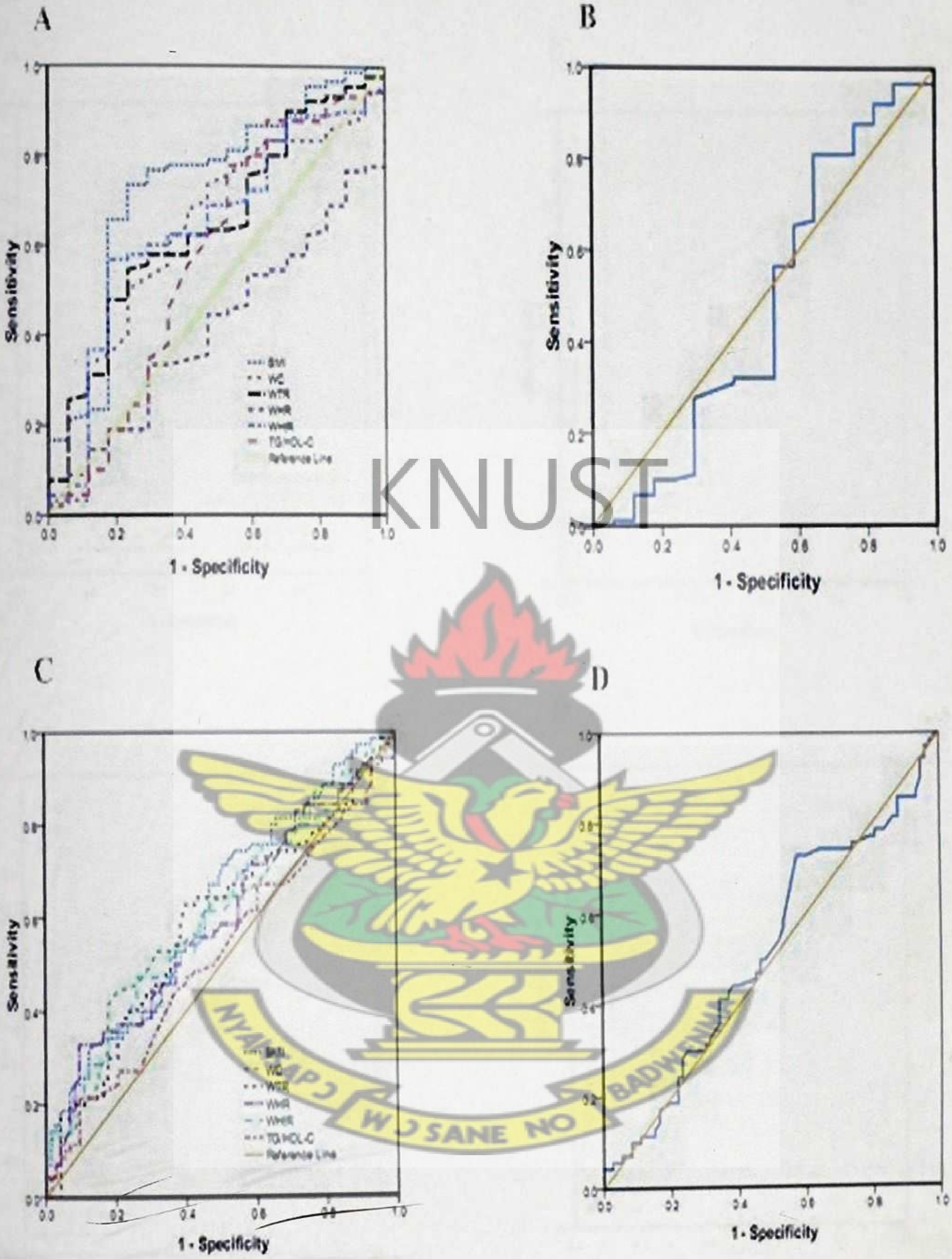


Figure 4.2: The ROC curves A, B, C, and D for BMI, WC, WHtR, WTR, WHR, TG/HDL-C and HDL-C/TC to detect High Blood Pressure in Postmenopausal and Premenopausal Ghanaian Women respectively

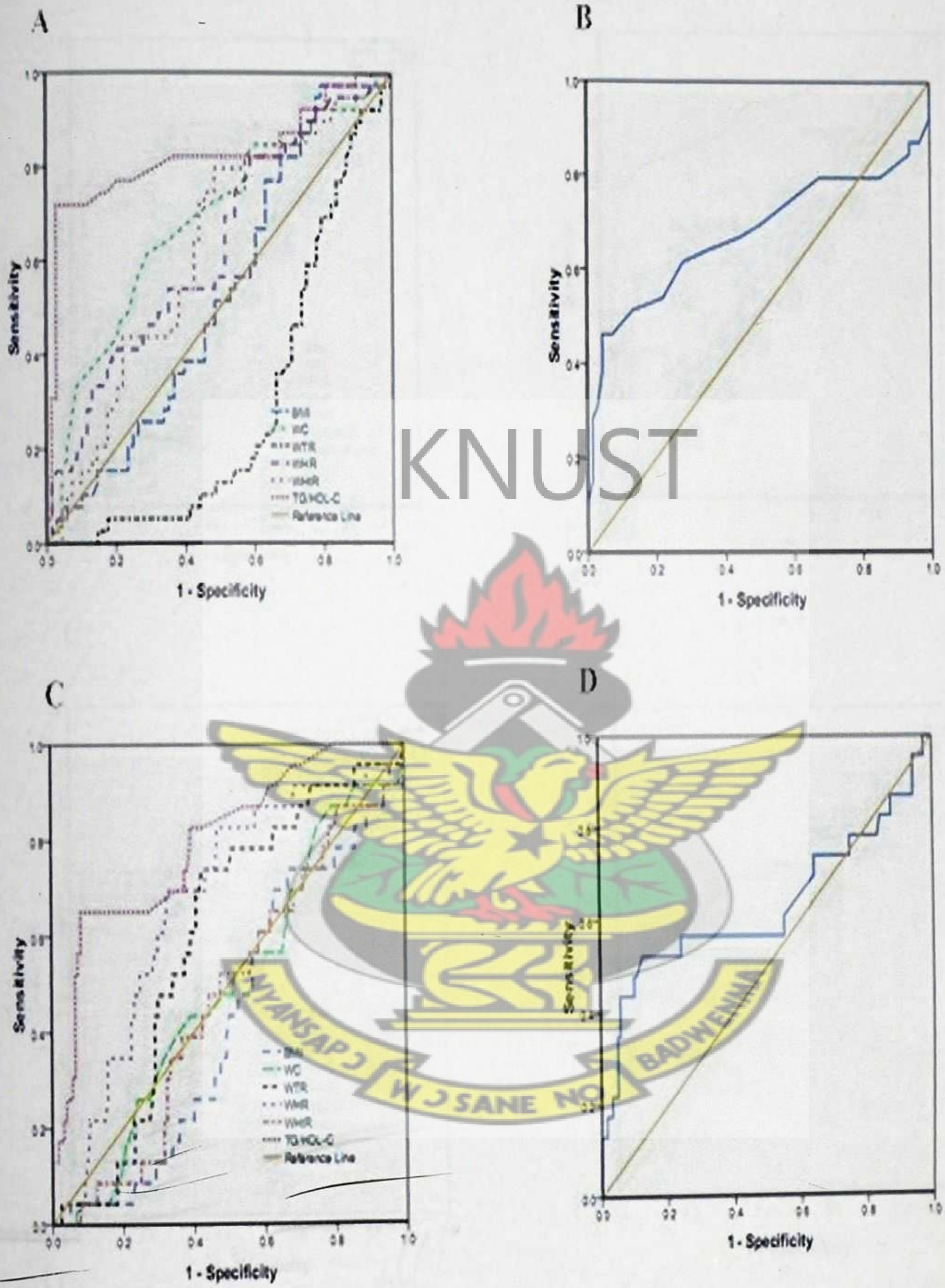


Figure 4.3: The ROC curves A, B, C, and D for BMI, WC, WHtR, WTR, WHR, TG/HDL-C and HDL-C/TC to detect High Blood Glucose Level in Postmenopausal and Premenopausal Ghanaian Women respectively

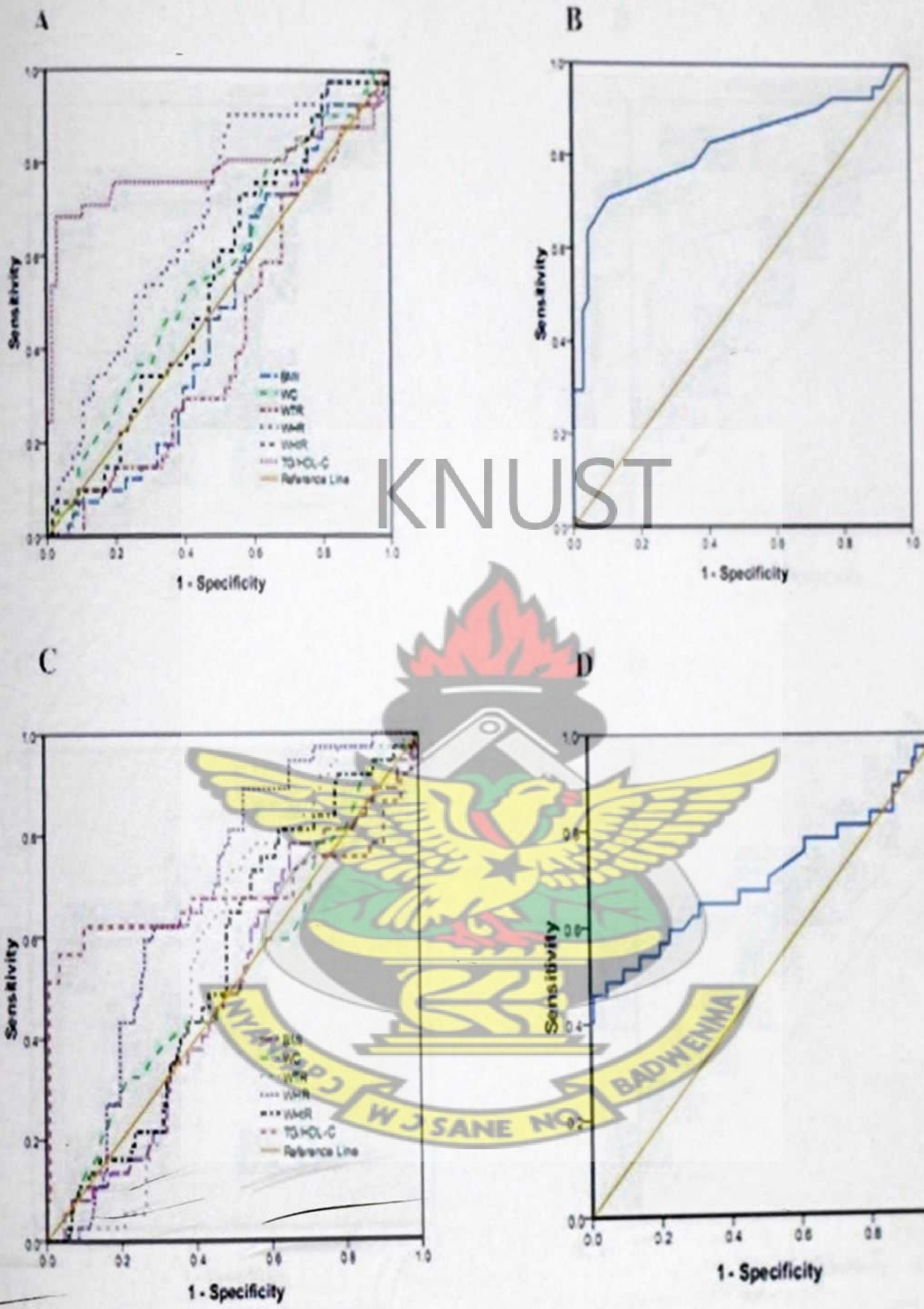


Figure 4.4: The ROC curves A, B, C, and D for BMI, WC, WHtR, WTR, WHR, TG/HDL-C and HDL-C/TC to detect Low HDL-C Level in Postmenopausal and Premenopausal Ghanaian Women respectively

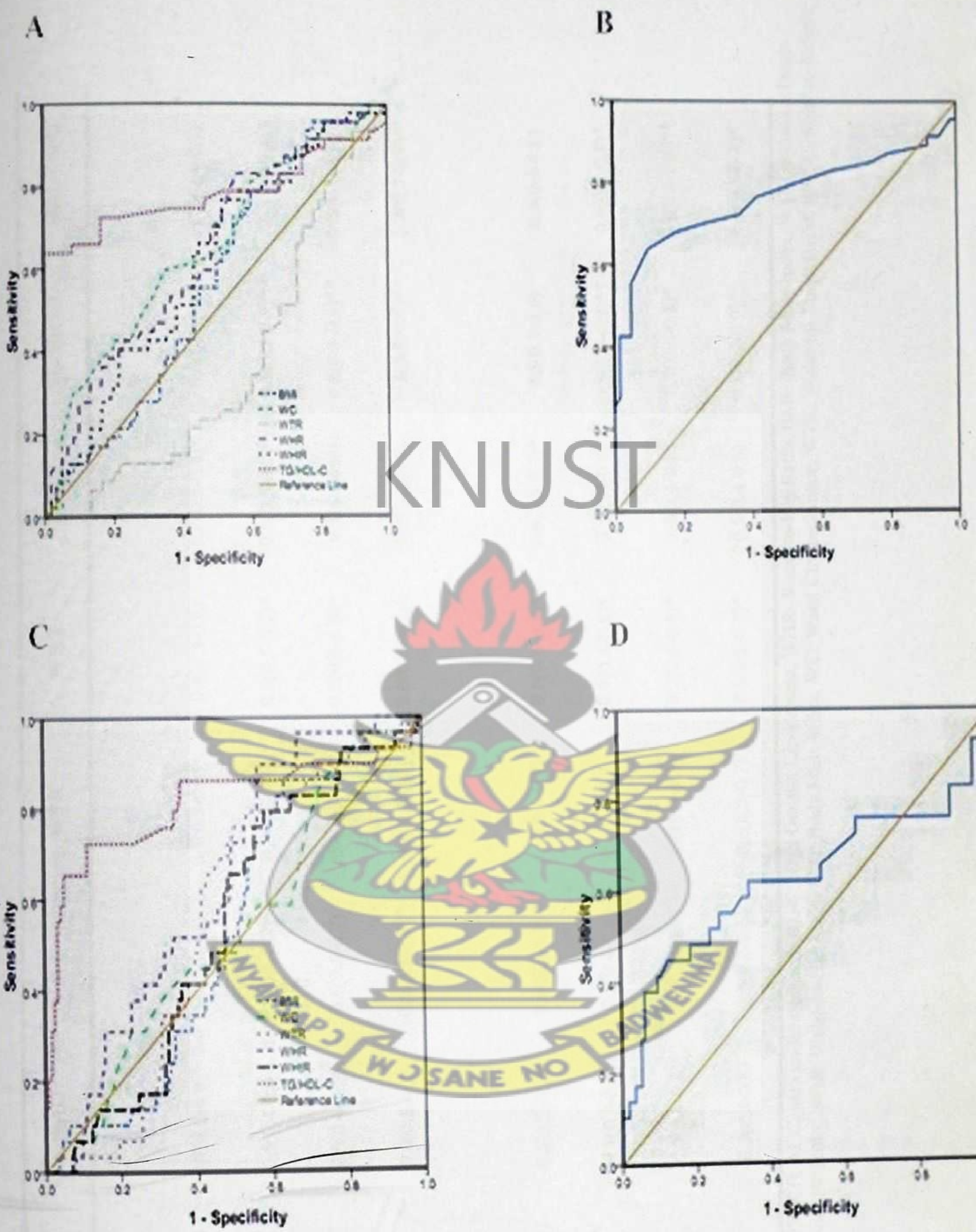


Figure 4.5: The ROC curves A, B, C, and D for BMI, WC, WHtR, WTR, WHR, TG/HDL-C and HDL-C/TC to detect MetS among Postmenopausal and Premenopausal Ghanaian Women respectively

Table 4.10: Area under Curves Values of BMI, WC, WTR, WHR, TG/HDL-C, HDL-C/TC and WHtR for MetS

	BMI	WC	WTR	WHR	WHtR	TG/HDL-C	HDL-C/TC
POSTMENOPAUSAL							
Blood Pressure (mmHg)	0.7(0.6-0.9)*	0.6(0.5-0.8)	0.7(0.5-0.8)*	0.4(0.3-0.6)	0.7(0.5-0.8)*	0.6(0.4-0.7)	0.5(0.4-0.7)
Glucose (mmol/l)	0.5(0.4-0.6)	0.7(0.6-0.8)*	0.3(0.2-0.4)	0.6(0.5-0.7)*	0.6(0.5-0.7)*	0.8(0.7-0.9)**	0.7(0.6-0.8)*
HDL-C (mmol/l)	0.5(0.4-0.6)	0.6(0.5-0.7)	0.4(0.3-0.5)	0.7(0.6-0.8)*	0.5(0.4-0.6)	0.8(0.7-0.9)**	0.8(0.7-0.9)**
MetS	0.6(0.5-0.7)	0.6(0.5-0.7)*	0.4(0.3-0.5)	0.6(0.5-0.7)*	0.6(0.5-0.7)	0.8(0.7-0.9)**	0.8(0.7-0.9)**
PREMENOPAUSAL							
Blood Pressure (mmHg)	0.6(0.5-0.7)*	0.6(0.5-0.7)*	0.6(0.5-0.7)	0.6(0.5-0.7)*	0.6(0.5-0.7)*	0.5(0.4-0.6)	0.5(0.4-0.6)
Glucose (mmol/l)	0.4(0.3-0.5)	0.5(0.4-0.6)	0.6(0.5-0.7)	0.7(0.6-0.8)*	0.5(0.4-0.6)	0.8(0.7-0.9)**	0.6(0.5-0.8)*
HDL-C (mmol/l)	0.5(0.4-0.6)	0.5(0.4-0.6)	0.6(0.5-0.7)	0.7(0.6-0.8)*	0.5(0.4-0.6)	0.7(0.6-0.8)*	0.7(0.6-0.8)**
MetS	0.5(0.4-0.6)	0.5(0.4-0.6)	0.6(0.5-0.7)	0.6(0.5-0.7)*	0.5(0.4-0.6)	0.8(0.7-0.9)**	0.6(0.5-0.8)*

All values were AUC (95%CI), AUC, area under curves; HDL-C: High Density Lipoprotein, WHR: Waist-to-Hip Ratio, BMI: Body Mass Index, WTR: Waist-to-Thigh Ratio, WHtR: Waist-to-Height Ratio, WHR: Waist-to-Hip Ratio, BMI: Body Mass Index, WC: Waist Circumference, WTR: Waist-to- Thigh Ratio, WHtR: Waist-to-Height; *P < 0.05. **P<0.001.

Table 4.11: Cut-off of the Atherogenic and Obesity Indicators to predict High Blood Pressure in Pre- and Postmenopausal Ghanaian Women

Parameters	Cut-off	Sensitivity	Specificity
POSTMENOPAUSAL			
BMI (kg/m²)	23.1	0.818	0.579
WTR	1.58	0.932	0.842
WHtR	0.53	0.886	0.737
PREMENOPAUSAL			
BMI (kg/m²)	22.9	0.817	0.681
WC (cm)	80.5	0.803	0.722
WHR	0.80	0.915	0.861
WHtR	0.50	0.817	0.778

Table 4.12: Cut-off of the Atherogenic and Obesity Indicators to Predict High Glucose Levels in Pre- and Postmenopausal Ghanaian Women

Parameters	Cut-off	Sensitivity	Specificity
POSTMENOPAUSAL			
WC (cm)	81.5	0.949	0.897
WHR	0.84	0.974	0.971
WHtR	0.51	0.974	0.897
TG/HDL-C	0.60	0.974	0.897
HDL-C/TC	0.34	0.795	0.676
PREMENOPAUSAL			
WHR	0.82	0.913	0.783
TG/HDL-C	0.65	0.957	0.708
HDL-C/TC	0.33	0.565	0.467

Table 4.13: Cut-off of the Atherogenic and Obesity Indicators to predict Low HDL-C Levels in Pre- and Postmenopausal Ghanaian Women

Parameters	Cut-off	Sensitivity	Specificity
POSTMENOPAUSAL			
WHR	0.85	0.974	0.899
TG/HDL-C	0.63	0.895	0.870
HDL-C/TC	0.32	0.816	0.362
PREMENOPAUSAL			
WHR	0.80	0.973	0.858
TG/HDL-C	0.58	0.865	0.906
HDL-C/TC	0.34	0.757	0.613

Table 4.14: Cut-off of the Atherogenic and Obesity Indicators to Predict MetS in Pre-and Postmenopausal Ghanaian Women

Parameters	Cut-off	Sensitivity	Specificity
POSTMENOPAUSAL			
WC (cm)	80.5cm	0.957	0.917
WHR	0.84	0.979	0.933
TG/HDL-C	0.61	0.872	0.800
HDL-C/TC	0.34	0.915	0.883
PREMENOPAUSAL			
WHR	0.81	0.966	0.833
TG/HDL-C	0.58	0.931	0.886
HDL-C/TC	0.34	0.724	0.632

Table 4.15: Comparison of ROC curves for Blood Pressure and Fasting Blood Glucose between Pre- and Postmenopausal Ghanaian Women.

Parameters	Premenopausal	Postmenopausal	*P value*
Blood Pressure			
BMI (kg/m²)	0.621	0.733	0.1339
WC (cm)	0.608	0.627	0.8225
WTR	0.587	0.646	0.4775
WHR	0.589	0.418	0.0617
WHTR	0.596	0.641	0.5873
TG/HDL-C	0.521	0.571	0.5691
HDL-C/TC	0.520	0.476	0.6299
Fasting Blood Glucose			
BMI (kg/m²)	0.427	0.524	0.2585
WC (cm)	0.492	0.680	0.0286
WTR	0.593	0.290	0.0003
WHR	0.669	0.629	0.6467
WHTR	0.468	0.623	0.0733
TG/HDL-C	0.796	0.824	0.7032
HDL-C/TC	0.631	0.674	0.6209

All values were area under the curve (AUC)

Table 4.16: Comparison of ROC Curves for High Density Lipoprotein Cholesterol and MetS between Pre- and Postmenopausal Ghanaian Women

Parameters	Premenopausal	Postmenopausal	*P value*
High Density Lipoprotein Cholesterol			
BMI (kg/m²)	0.499	0.474	0.7534
WC (cm)	0.523	0.569	0.5653
WTR	0.560	0.427	0.0932
WHR	0.675	0.681	0.9376
WHTR	0.549	0.547	0.9801
TG/HDL-C	0.685	0.782	0.1777
HDL-C/TC	0.704	0.818	0.0995
MetS			
BMI (kg/m²)	0.527	0.562	0.6725
WC (cm)	0.533	0.646	0.1655
WTR	0.563	0.364	0.0142
WHR	0.634	0.642	0.9217
WHTR	0.540	0.610	0.3950
TG/HDL-C	0.810	0.782	0.6840
HDL-C/TC	0.625	0.764	0.0716

All values were area under the curve (AUC)

4.2 DISCUSSION

4.2.1 Prevalence of MetS and its Predominant Components among Pre- and Postmenopausal Ghanaian Women

MetS has become a public health problem due to its link to diseases such as ischemic heart disease, stroke, dementia, non-alcoholic steatohepatitis, polycystic ovarian disease, haemochromatosis, endometrial and oesophageal cancers (Grundy *et al.*, 2005). Even though MetS concept was coined several decades ago, the comparison of prevalence between populations was made possible after the standardization of diagnostic criteria. The differences in genetic profile, lifestyle factors such as eating habits and level of physical activity, age, menopausal status and gender determine the prevalence and the predominant components of MetS in a population (Cameron *et al.*, 2004).

The present study assessed the prevalence of MetS and its predominant components among pre- and postmenopausal Ghanaian women. The prevalence of MetS as observed in this study increased from 14.4% through 25.6% to 29.2% and further to 30.4% when the WHO, NCEP ATP III, IDF and H_MS criteria respectively were used respectively (Table 4.2) [The prevalence of MetS varies among women and depends on the characteristics of the population as well as the diagnostic criteria applied (Hyun *et al.*, 2008; Oh, 2004)]. This study applied four different diagnostic criteria and each gave different degrees of prevalence and these results are in agreement with studies carried out among Brazilian, Chinese, German and Korean women which estimated the prevalence of MetS, to range from 10.7% through 20.9% and 33.7% to 36.1% (Oh *et al.*, 2004; Deibert *et al.*, 2007; Hyun *et al.*, 2008; Liu *et al.*, 2010; Neto *et al.*, 2010; Ruan *et al.*, 2010).

When WHO diagnostic criterion was used, the prevalence of MetS among postmenopausal women was higher (25.2%) compared to their premenopausal counterparts (6.3%) (Table 4.2). This finding is consistent with a study conducted in 2008 with 200 climacteric (menopausal) women in Pakistan, which found MetS in 21.0% of postmenopausal women against 7.0% of premenopausal women using the same criterion (Saira and Bashir, 2008). Piche and colleagues (2006) found prevalence of 29.6% among Canadian postmenopausal women using the WHO criterion. Applying the NCEP ATP III criterion, the prevalence of MetS was estimated to be higher among postmenopausal subjects in the present study (41.1%) than their premenopausal counterparts (14.7%). This implies that the prevalence of MetS can differ in a population depending on the criterion used. This observation is similar to studies carried out among premenopausal Korean and postmenopausal Ecuadorian women respectively which estimated the prevalence of MetS to range from 13.8% to 41.5% using the NCEP ATP III criterion (Hidalgo *et al.*, 2006; Kim *et al.*, 2007). Pandey and colleagues (2007) found prevalence of MetS among Indian women to be 56% using NCEP ATP III criterion whereas 33.7% prevalence rate of MetS was observed by Ruan *et al.*, (2010) using IDF criterion among Chinese women. Certainly, lifestyle and genetic characteristics of Ghanaian women are likely to be significantly different from women from China and India and these may explain the differences in prevalence rates of MetS obtained.

In addition, the prevalence of MetS was higher among postmenopausal women [(43.0% (IDF) and 43.9% (H_MS)] than premenopausal women [(18.9% (IDF) and 20.3% (H_MS)] (Table 4.2). Pandey *et al.*, (2010) used both criteria to estimate higher prevalence of MetS among postmenopausal Indian women compared to their

premenopausal counterparts. In their study, the prevalence of MetS among postmenopausal women was higher than that in premenopausal by both, IDF (premenopausal 45% and postmenopausal 55%) and H_MS criteria (premenopausal 44% and postmenopausal 56%).The differences in the prevalence rates in both present and Indian studies may be explained by difference in socio-cultural practices, lifestyle, as well as genetic compositions. The prevalence in the present study populations might increase in future as a great number of the women age, especially postmenopausal group, had metabolic scores of 2 when all the diagnostic criteria were applied. The findings from this study suggest that the prevalence of MetS is dependent on age regardless of the criteria used. The influence of age on MetS among pre- and postmenopausal women is important and this trend has been established in similar populations elsewhere (Neto *et al.*, 2010; Pandey *et al.*, 2010). This explains why postmenopausal women had higher age-specific prevalence of MetS than their premenopausal counterparts when all the four diagnostic criteria were applied (Figures 4.1a and 4.1b). The age-specific prevalence of MetS peaks at ≥60 years for postmenopausal women. These findings are in partial accordance with those observed in Seychellois (Kelliny *et al.*, 2008) women where the prevalence of MetS was highest among 55-64 years old. Physical activity and lean muscle mass naturally diminishes with age in women (Samaras *et al.*, 1999). The body composition of women shifts to more fat and less muscle which slows down the rate at which the body metabolises biomolecules which also results in weight gain especially central fatness culminating in metabolic abnormalities and higher MetS prevalence.

Premenopausal Ghanaian women develop MetS earlier (20-29 years) when NCEP ATP III, IDF and H_MS criteria were applied. This result is concurrent with the study

conducted by Kim *et al.*, (2007) which identified the onset of MetS to be 20-29 years among Korean pre- and postmenopausal women. The reason for marked increase in the prevalence of MetS among premenopausal individuals at the age group of 20-29 years (32.7%) and 30-39 (20.0%) is not known, though, it is possible these women might have kept positive caloric balance for some time and this had resulted to an increase in their obesity indices, blood pressure and lipid profile. Insulin sensitivity and glucose intolerance are not entirely explained by a woman's hormonal status. There are now data showing that weight gain in women is a stronger predictor of impaired glucose tolerance than menopausal status (Paul and Smith, 2005).

Examination of the Ghanaian women with MetS using the three diagnostic criteria identified central obesity, raised blood pressure and raised fasting glucose (WHO, IDF & H_MS) as the predominant components (Table 4.3). The components of MetS were common in the postmenopausal group when they were analyzed in relation to menopausal status. Oliveira *et al.*, (2006) found similar order of frequency of components respectively with the following proportions: central obesity (84.1%), raised blood pressure (53.6%), raised triglycerides (18.1%) and raised fasting glucose (16.7%). However, Oh *et al.*, (2004) in their study of 449 South Korean women listed the following predominant components: reduced HDL-C, raised blood pressure, raised triglycerides, raised fasting glucose and abdominal obesity. Contrarily, NCEP-ATP III criterion identified raised blood pressure, central obesity and raised fasting blood glucose as the predominant components in Ghanaian women. In premenopausal women, fat accumulates in lower extremities, to a greater extent, as a result of oestrogen secretion. After meals, the flow of blood containing high levels of chylomicrons to fat stored in the thighs and hips increased in women, but not in men

(Romanski *et al.*, 2000). On the other hand, the fats stored around the hips and thighs serve as storage form of energy during pregnancy as well as working as a defence for the reproductive organs (Romanski *et al.*, 2000). These could be the reasons why women store more fat in their lower body. However, during menopause the pattern of hormone secretion changes and gradually causes fat accumulation in visceral tissues of abdomen which results in central obesity (Poehlman, 2002). A lot of metabolic changes in postmenopausal women are related to the decrease in oestrogen secretion and consequent accumulation of abdominal fat. Moreover, central obesity is linked to a greater amount of visceral fat than to lower-body obesity, which is associated with more subcutaneous fat. Visceral fat produces free fatty acids and inflammatory cytokines which directly drains into the portal vein, and is thus likely to have a direct signalling and metabolic relation with the liver in comparison to subcutaneous fat (Zhang *et al.*, 1995; Johnson and Weinstock, 2006). Fat deposits in the liver are associated with the overproduction of very low-density lipoprotein predisposing women to atherogenic dyslipidaemia (elevated triglyceride, low HDL-cholesterol level, and small dense LDL cholesterol particles) (Johnson and Weinstock, 2006; Koh *et al.*, 2008). Elevated levels of small dense-LDL-cholesterol get entrapped in the endothelium of the arterial wall and are oxidized leading to arterial stiffness and atherosclerosis (Pohjantahti-Maaroos *et al.*, 2010) and these can culminate in high blood pressure and related conditions. Ghanaian women showed abdominal obesity and raised blood pressure especially among postmenopausal group and this may be due to the fact that they generally have adopted western lifestyle of consuming high-energy food whilst undertaking limited physical exercise.

Plasma TG and HDL-cholesterol are known to be inversely correlated from epidemiological studies (Despres *et al.*, 1989; Bruce., 1998). The enzyme cholesteryl ester transfer protein (CETP) balances the levels of TG and HDL-cholesterol by mediating the transfer of triglycerides (TGs) from TG-rich lipoproteins to HDL and LDL particles in exchange for cholesteryl. esters which leads to low HDL-C and small dense-LDL-C (Sandhofer *et al.*, 2006). It has been proposed that high CETP activity explains some of the high TG levels and low HDL-C levels (dyslipidaemia), observed in persons with MetS (Rashid *et al.*, 2002). In this study, menopause was associated with an increase in serum triglyceride but mean levels of HDL-cholesterol were similar between premenopausal and postmenopausal women (Table 4.1), which is consistent with the observation among Korean women by Kim *et al.*, (2007).

The present study also demonstrated that the prevalence of BMI overweight, WHR obesity, WHtR obesity, hyperglycaemia and hypertension were significantly higher among postmenopausal group compared to the premenopausal population whilst WHR overweight was the reverse. This finding is in disagreement with the study of Jaber *et al.*, (2004) which listed only low HDL cholesterol and raised fasting glucose as the predominant components of MetS among Arab American women. This could be attributed to differences in genetics and environment. Other studies have shown that the above components are predominant indicators of MetS (Kim *et al.*, 2007a; Ruan *et al.*, 2010; Liu *et al.*, 2011) however, menopause has been established to increase the risk of women to above-mentioned factors (Rexrode *et al.*, 1998; Schubert *et al.*, 2006). This further buttresses the point that postmenopause status is an independent risk factor for MetS and all of its individual components (Cho *et al.*, 2008). Moreover, postmenopausal women are thought to accumulate more fat in the

intra-abdominal depot than do premenopausal women and therefore have a greater risk of developing metabolic complications associated with obesity (Shi and Cleqq, 2009).

4.2.2 Prediction of MetS among Pre- and Postmenopausal Ghanaian Women using Obesity and Atherogenic Markers

Obesity and insulin resistance have been suggested to play important pathophysiological role in the aetiology of MetS as well as diseases associated with it (Ding *et al.*, 2007; Lobo, 2008). The accumulation of fat in the intra-abdominal depot is more common in postmenopausal women than their premenopausal counterparts and hence postmenopausal subjects have a greater risk of developing metabolic complications such as type 2 diabetes, hypertension, atherosclerosis and coronary artery disease (CAD) as well as obesity related cancers (Shi and Cleqq, 2009). Central obesity progressively increases hepatic and adipose-tissue insulin resistance and its resultant metabolic abnormalities like glucose intolerance, low HDL-C, elevated TG and hypertension (Pascot *et al.*, 2000; Hamdy *et al.*, 2006). Two hypotheses have been proposed in several studies (Walton *et al.*, 1995; Kahn and Flier, 2000; Després, 1993) to explain the strong relationship between intra-abdominal fat accumulation and insulin resistance. Foremost, intra-abdominal adiposities are more biologically active and are located near portal vein which carries blood from the intestinal area to the liver. Substances released by intra-abdominal fat, including free fatty acids enter the portal circulation and are transported to the liver where they subsequently influence glucose metabolism as well as blood lipids production (Bergman and Mittleman, 1998). Secondly, visceral adipose tissue and its resident macrophages produce more

inflammatory cytokines like tumour necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6) and less adiponectin (Yokota *et al.*, 2000). The change in levels of cytokines induces insulin resistance by depressing the synthesis of glucose transport protein, GLUT 4.

This present study demonstrates that WC, WHR, TG/HDL-C as well as HDL-C/TC values are significant indicators to identifying the presence of MetS in pre- and postmenopausal Ghanaian women (Tables 4.14). The cut-off values of the markers to predict MetS in postmenopausal Ghanaian women is 80.5 cm, 0.84, 0.61 and 0.34 for WC, WHR, HDL-C/TC and TG/HDL-C respectively. The 80.5 cm for WC observed in this study partially agrees with a similar study conducted among Chinese postmenopausal women by Ruan *et al.*, (2010) which identified cut-off for WC to be 80.75 cm. This study is also similar to the IDF and WHO recommended WC (80 cm and 88 cm respectively) and WHR [0.85 (WHO)] cut-off points for European women and other Eastern Mediterranean countries (Alberti *et al.*, 2006; Alberti *et al.*, 2009). Similarly, WC cut-off points of 72 cm, 82 cm, 85 cm, 86 cm and 88 cm provided the highest sensitivity for identifying hypertensives in Nigerian, Cameroonian, Jamaican, St Lucian and Barbadians women respectively (Okosun *et al.*, 2000).

Even though BMI and WHtR had been explored to predict MetS in several studies (WHO., 1998; Ruan *et al.*, 2010; Liu *et al.*, 2011), in this present study, the ROC analyses showed that BMI and WHtR could not be used to predict the presence of MetS among postmenopausal Ghanaian women (Table 4.10). In general most women in Ghana are defined as being overweight with BMI of 25 kg/ m² according to WHO criterion (WHO, 2000) but with a cut-off point of 23.1 kg/m² identified in both

groups, there is the possibility that Ghanaian women seem to develop MetS at lower anthropometric indices than the western populations. The accuracy of anthropometric variables as indicators of MetS was not high as Swets, (1988) had postulated that 0.5 > AUC < 0.7 is an indication of the diagnostic being less accurate when ROC curves are applied in the diagnosis of conditions.

The use of TG/HDL-C and HDL-C/TC ratios to predict the presence of MetS had not been studied in Ghana. These atherogenic ratios were able to predict the presence of MetS in postmenopausal Ghanaian women in this study. Since visceral adiposity is associated with hypertriglyceridaemia, reduced HDL-C as well as insulin resistance, there is the likelihood that TG/HDL-C and HDL-C/TC ratios play important role in the pathogenesis of MetS and atherosclerosis. Plasma TG, TC and HDL-C are inversely related (Rashid *et al.*, 2002). The enzyme Cholesterol-Ester Transfer Protein (CETP) balances the levels of TG and HDL-C, hence responsible for the joint exchange of TG and cholesterol ester between Apo-B containing lipoproteins (chylomicrons, VLDL and LDL) and HDL. It has been postulated that high CETP activity explains some of the high TG levels and low HDL-C levels as demonstrated in women with MetS (Rashid *et al.*, 2002).

Both obesity and atherogenic markers had influence on the traditional metabolic risk factors in Ghanaian women (Tables 4.5, 4.6, 4.7 & 4.8). Liu *et al.*, (2011) observed association between obesity indices (higher BMI, WC and WHtR values) and the traditional metabolic risk factors (high blood pressure, fasting blood glucose and triglyceride) among Chinese women. Visceral abdominal fat had been recognized to predict insulin resistance and the presence of related metabolic abnormalities through

overexposure of liver to free fatty acids (Lemieux *et al.*, 2001; Ross *et al.*, 2002; Nieves *et al.*, 2003; Mertens *et al.*, 2006; Pascot *et al.*, 2001). Body composition changes occur in women mostly after menopause due to decreased secretion of oestrogen (Lobo, 2008), resulting in age-related increases in obesity as well as metabolic disturbances (Flegal *et al.*, 2002). In the present study, small WTR values were related to high FBG and TG among postmenopausal women (Tables 4.5 and 4.6). This implies that Ghanaian postmenopausal women with smaller waist and larger thigh circumferences are at high risk of MetS. Contrarily, Snijder *et al*, (2003a) identified the association of lower risk of diabetes with larger thigh circumference among European women. Ryan *et al.*, (2002) also showed that African-American postmenopausal women had 34% greater midthigh low-density lean tissue area (a marker of intramuscular lipid content) than Caucasian postmenopausal women. The reason for small WTR values in Ghanaian postmenopausal women may be due to physical inactivity which could result in decrease and increase in muscle mass and intramyocellular lipid accumulation respectively in their thighs. African American postmenopausal women had greater intramyocellular lipids which are more insulin resistant than white women despite comparable fitness and relative body fat levels (Ryan *et al.*, 2002). Increased plasma free fatty acids lead to intramyocellular lipid accumulation in humans that has been proposed to play a significant role in the development of insulin resistance and type 2 diabetes (Griffin *et al.*, 1999). Intramyocellular lipid accumulation is associated with activation of protein kinase C (PKC) (Griffin *et al.*, 1999). Alterations in PKC activation may interfere with normal insulin signalling which result to insulin resistance and glucose intolerance (Schaffer, 2003). Despite paucity of Ghanaian studies on physical activity or inactivity and its relation to obesity, evidence of physical inactivity is obtained from the growing

problem of overweight (12.7%) and obesity (25.3%) especially among non-pregnant women aged 15-49 years (Ghana Statistical Service ., 2009). Visceral fat in thighs can affect the activity of lipoprotein lipase resulting in increase in exposure of muscles to free fatty acids through uptake and storage. One of the sites responsible for insulin resistance is muscle mass (Snijder *et al.*, 2003a). The ratios of TG/HDL-C, HDL-C/TC and HDL-C, LDL-C are associated with raised FBG, TG and low HDL-C among postmenopausal women in this study (Tables 4.7 and 4.8). This finding buttresses the point that the TG/HDL-C, HDL-C/TC and HDL-C/LDL-C can be explored as diagnostic tool for MetS as well as atherosclerosis.

In order to decrease the risk of MetS and atherosclerosis among premenopausal and postmenopausal Ghanaian women, in general, life style modification to control weight, lipid profile, blood pressure and blood glucose should be emphasized. Moreover, exercise and consumption of low caloric foods would improve plasma lipid concentrations by raising their HDL cholesterol concentrations (Leon and Sanchez, 2001) or decreasing triglycerides concentrations (Fahlman *et al.*, 2002) or both (Kraus *et al.*, 2002). Furthermore, physical activity is linked with lowered blood pressure, improved glucose intolerance, insulin sensitivity and lowered risk of type 2 diabetes (Owiredu *et al.*, 2011).

CHAPTER FIVE

5.0 CONCLUSION AND RECOMMENDATIONS

5.1 CONCLUSION

The findings in this study estimated the prevalence of MetS in Ghanaian women to be 14.4% (WHO), 26.0% (NCEP), 29.2% (IDF) and 30.4% (H_MS). MetS was higher among postmenopausal women, irrespective of the diagnostic criteria. Age had a major influence on the prevalence and the individual constituents of MetS. The predominant components identified were central obesity, raised blood pressure and raised fasting glucose in the order of frequency.

The present study also suggested that WC, WHR, WHtR, TG/HDL-C, HDL-C/TC and HDL-C/LDL-C values all had influence on traditional metabolic risk factors. Raised glucose and triglyceride values were influenced by Waist-to-thigh ratio. In Ghanaian pre- and postmenopausal women, waist circumference, WHR, HDL-C/TC and TG/HDL-C predicted the presence of MetS. MetS has become a significant health problem in the contemporary world and as such all efforts should be made to create local awareness, early diagnosis and prevention.

5.2 RECOMMENDATIONS

The following recommendations are suggested based on the knowledge gained through this work:

- It is important to conduct similar investigations in other regions in Ghana in order to obtain regional prevalence of MetS among pre- and postmenopausal Ghanaian women.

- The obesity and atherogenic indices that were shown to be associated with MetS should be confirmed in a larger prospective cohort study and once established should be made part of women's routine laboratory investigative panel.
- Biochemical markers like CETP and adipocytokines should be monitored prospectively in Ghanaian women in order to explicitly explain their contributions to the development of MetS.

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APPENDIX

Appendix A: Questionnaire for obtaining background information of the women

KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY
FACULTY OF BIOSCIENCES
DEPARTMENT OF BIOCHEMISTRY AND BIOTECHNOLOGY
QUESTIONAIRE / PATIENT'S DETAILS

Ref. Code: MS .....

A. PERSONAL DETAILS

Patient Identity:.....

Residence.....

Age:..... Sex:..... Marital Status.....

Body weight (BW).....Height (H).....BMI (BW/H).....

Waist Circ. (WC).....Hip Circ. (HC)..... WHR.....

Thigh Circ. (TC)..... WTR.....

Systolic Pressure (SP).....Diastolic Pressure (DP).....

Pulse Pressure (PP).....

How long have you been in your menopause? Months.....

Years.....

Do you exercise? (Y/N) If yes how often do you exercise? .....

Have you ever drunk alcohol before (Y/N) If yes for how long .....

Type of alcoholic beverage consume.....

How often do you drink: Social drinker □ Heavy drinker □ Moderate drinker □

Have you ever smoked? (Y/N) When did you stop?.....

Does your husband/ relative smoke?.....

Before menopause were you? Normal/overweight/obese

What type of food do you often eat? .....

B. OCCUPATION

Are you a. still working…….. b. retired……..

If still working what is the nature of your work? ……..

If retired what was the nature of your work?.....

How many hours do/did you work?.....

C. EDUCATION BACKGROUND

Non Formal □ Basic □ Secondary □ Tertiary □ Post graduate □

D. METS COMPONENTS

Fasting Blood Glucose……. Total Cholesterol……

Triglyceride…… HDL-Cholesterol……

LDL-Cholesterol…….. VLDL-Cholesterol……

Do you have any of these? a. Hypertension (Y/N) b. Diabetes (Y/N) c. Cardiac disease (Y/N) d. Others (specify) (Y/N)

Have you ever been diagnosed of the above diseases before menopause? (Y/N)

E. FAMILY HISTORY

Do you have a family history of the following?

a. hypertension b. Diabetes c. Cardiac disease d. Others (specify)

If yes how is the person related to you?.....