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Les valeurs anthropométriques ; mesures prédictives du risque cardio-métabolique et du syndrome métabolique au Kenya

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Résumé

Introduction : La prévalence mondiale des maladies cardiovasculaires et métaboliques (MCM) ainsi que du Syndrome métabolique (SM) est en constante augmentation, et ce plus drastiquement dans les pays en voie de développement. L'accumulation de gras corporel, communément estimé par des mesures anthropométriques, a été associé au SM et à un risque accru de développer des MCM. Cette relation demeure toutefois très peu étudiée parmi les populations de pays d'Afrique sub-Saharienne.

Objectif : L'objectif de cette étude était d'évaluer l'association entre les mesures anthropométriques et les facteurs de risque de MCM, en plus du SM, parmi des populations adultes rurales et urbaines du Kenya.

Méthodologie : Cette étude transversale comprenait 1401 participants de milieux ruraux et urbains. Les valeurs anthropométriques ont été mesurées, incluant le poids corporel, l'indice de masse corporelle (IMC), la circonférence abdominale (CA), le gras abdominal viscéral (VAT), le gras abdominal sous cutané (SAT) et le ratio de ces deux valeurs (VAT/SAT). Des valeurs de glycémies (à jeun, 2 heures post glucose), d'insuline et de lipides plasmatiques (Triglycérides, LDL-C, HDL-C, cholestérol total) ont été analysées. La résistance à l'insuline a été estimée par l'*Homeostatic model assessment of insulin resistance* (HOMA-IR). Des valeurs de tension artérielle systolique (TAS) et diastolique (TAD) ont été mesurées. Des analyses de régressions linéaires et logistiques multivariées ont été utilisées afin d'évaluer les forces d'association.

Résultats : Les participants de milieux urbains avaient des valeurs anthropométriques et des facteurs de risques de MCM plus élevés comparativement aux participants de milieux ruraux ($P<0.05$ pour le poids corporel, IMC, CA, SAT et VAT/SAT) ($P<0.05$ pour les triglycérides, LDL-C, cholesterol total, glycémie à jeun, insuline, HOMA-IR, TAS et TAD). L'ensemble des facteurs de risques de MCM et le SM étaient positivement et significativement associés aux valeurs anthropométriques, excepté pour les valeurs de HDL-C. VAT et SAT présentaient les associations les plus fortes.

Conclusion : Les valeurs anthropométriques d'accumulation du gras et particulièrement celles qui reflètent de l'obésité abdominale sont des indicateurs pertinents de la santé cardio-métaboliques des populations rurales et urbaines du Kenya.

Mots clés : Syndrome métabolique, anthropométrie, obésité, lipides, résistance à l'insuline, Afrique sub-saharienne.

Abstract

Background: The prevalence of cardio-metabolic diseases (CMD) and metabolic syndrome (MS) is drastically increasing in low and middle income countries. CMD and MS risk factors has been correlated with anthropometric measures of fat accumulation. However, very few studies have addressed by this association in rural and urban Sub-Saharan African (SSA) populations. It remains unclear which anthropometric features of fat accumulation are best associated with CMD risk factors and MS. This study aimed to investigate the association between anthropometric features, metabolic syndrome (MS) and other cardio-metabolic risk factors in a population from Kenya.

Methods: In this cross-sectional study, 1,401 rural and urban Kenyan men and women were examined. Anthropometric measurements were carried out, including body weight, body mass index (BMI), waist circumference(WC), visceral and subcutaneous abdominal adipose tissue (VAT and SAT). Measures of blood glucose (FBG, 2-h OGTT), fasting plasma insulin and plasma lipids were analyzed. Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated. Systolic and diastolic blood pressure (SBP and DBP) were measured. Adjusted multivariate linear regression analyses and adjusted multivariate logistic regression analysis were performed.

Results: Urban Kenyans had significantly higher anthropometric features ($p < 0.05$ for Weight, BMI, WC, SAT and VAT/SAT) and CMD risk factors ($p < 0.05$ for triglycerides, LDL-C, total cholesterol, FPG, FPI, HOMA-IR, OGTT, SBP and DBP) compared to rural. CMD risk factors and MS were associated with all anthropometric features of fat accumulation, except for HDL-C levels ($P<0.05$) and the strongest associations were seen with VAT and SAT.

Conclusions: Anthropometric measures of fat accumulation, especially features of central obesity, are relevant indicators of cardio-metabolic health in Kenyan rural and urban populations.

Key words : Metabolic syndrome, anthropometric measures, obesity, Kenya, lipids, insuline resistance, sub-Saharan Africa

Table des matières

Liste des tableaux

From the manuscript

Liste des figures

Liste des sigles

AHI/NHLB : American Heart Institute / National Heart Lung and Blood Institute

ATPIII : Adult Treatment Panel III

BMR : Basal metabolic rate

CMB : Cardio-metabolic diseases

CT : Computed Tomodensitometry

DBP : Diastolic blood pressure

DXA : Dual-energy X-ray absorptiometry

DSAT : Deep subcutaneous adipose tissue

EI : Energy intake

FA : fatty acids

FFA : free fatty acids

FPG : Fasting plasma glucose

GHO : Global Health Observatory

GIES : General intake estimation system

GWAS : Genome wide association studies

HbA1c : Glycated hemoglobin

HDL-C : High density lipoprotein cholesterol

HIV : Human immunodeficiency virus

HOMA-IR : Homeostasis model assessment of insulin resistance

HR : Heart rate

IDF : International Diabetes Federation

IFG : Impaired fasting glucose

IGT : Impaired glucose tolerance

LDL-C : Low density lipoprotein cholesterol

LPL : Lipoprotein lipase

MHO : Metabolically healthy obese

MS : Metabolic syndrome

MRI : Magnetic resonnance imaging

NAFL : Non alcoholic fatty liver

NCEP : National cholesterol education program

NCD : Non communicable diseases

OGTT : Oral Glucose Tolerance Test

RAAS : renin-angiotensin aldosterone system

SAT : Subcutaneous adipose tissue

SBP : Systolic blood pressure

SNS : Sympathetic nervous system

SSA : Sub-saharan Africa

SSAT : Superficial subcutaneous adipose tissue

TG : Triglycerides

UNICEF : United Nation International Children's emergency found

UK : United Kingdom

US : Ultrasonography

USA : United States of America

VAT : Visceral adipose tissue

VLDL : Very-low density lipoproteins

WHO : World Health Organization

WC : Waist circumference

Liste des abréviations

et al. : and collaborators

L'humanité est constamment aux prises avec deux processus contradictoires dont l'un tend à instaurer l'unification, tandis que l'autre vise à maintenir ou à rétablir la diversification.

- *Claude- Lévis-Strauss*

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Introduction

Chapter 1

The cardio-metabolic risk worldwide and in sub-Saharan Africa

1.1 The Metabolic Syndrome

1.1.1 Definition

The metabolic syndrome (MS) is generally defined as a cluster of four traditional cardiovascular risk factors: abdominal obesity, dyslipidemia, hypertension and hyperglycemia. The ultimate objective of this association is to better identify individuals at risk of developing both cardiovascular diseases and type II diabetes (1). As cardiovascular and metabolic diseases are increasing worldwide, there has been a recent growing interest in this constellation of risk factors to better define and understand their mutual interactions.

Since 1988, when Gerald Reaven first described this clustering and named it the "Syndrome X" (2), a number of expert groups have suggested different definitions. In 1999, a World Health Organization's (WHO) diabetes working group established new criteria defined by impaired glucose tolerance or type II diabetes with at least two of the following diagnoses: hypertension, hypertriglyceridemia, obesity (defined by body mass index (BMI) or waist circumference(WC)), low levels of high-density lipoprotein cholesterol (HDL-C), and microalbuminuria (3). Two years later, the Third Report of the U.S. National Cholesterol Education Program (NCEP) on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (ATPIII) suggested a new approach, more focused on an individual's cardiovascular risk than on insulin resistance (4). To be diagnosed with MS, one had to present three of the following five criteria: central obesity, raised blood pressure, raised triglycerides, low levels of HDL-C, and fasting hyperglycemia. In 2004, a consensus group from the International Diabetes Federation (IDF) published a review in which it recommended that

central obesity become an obligatory component for MS diagnosis (1). So far, there is no clear consensus on whether MS is representing a unique cluster of cardiovascular risks, a syndrome caused by obesity or the ultimate cardiometabolic consequence of insulin resistance.

One of the main criticisms of the international community was that the MS cut-offs, which were originally set for Caucasian populations, appeared to be less applicable to other ethnic groups. Indeed, several studies have shown that ethnicity influences cardiometabolic disorders associated with obesity (5, 6). Moreover, differences between the various definitions of MS were leading to some confusion among clinicians regarding the identification of their patients (7). In response, a consensus group from the IDF and the American Heart Association /National Heart, Lung, and Blood Institute (AHA/NHLBI) met in 2009 (7). Its objectives were to harmonize the various definitions and establish new recommendations, which are shown in Table 1.

Table 1. Criteria for clinical diagnosis of MS

Measures	Cut points
Raised triglycerides	≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality
Reduced HDL-C	< 40 mg/dL (1.03 mmol/L) in males < 50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality
Raised blood pressure	systolic BP ≥ 130 mm Hg or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension
Raised fasting plasma glucose (FPG)	(FPG) ≥ 100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes if above 5.6 mmol/L or 100 mg/dL Oral glucose tolerance test (OGTT) is strongly recommended but is not necessary to define presence of the syndrome.
Elevated waist circumference	Population and country specific definitions

According to this consensus, the presence of any 3 of these 5 risk factors constitutes a diagnosis of MS. Also, a single set of cut points should be used worldwide for all components, except for WC. Ethnic-specific cut-offs for WC were included in the definition (Table 2), however due to paucity of data, European cut-offs are still recommended for sub-Saharan African populations (7).

Table 2. IDF criteria for ethnic or country specific values of WC

Country or ethnic group	Sex	WC (cm)
Europid	Men Women	>94 cm >80 cm
South Asian	Men Women	>90 cm >80 cm
Chinese	Men Women	>90 cm >80 cm
Japanese	Men Women	>90 cm >80 cm
Ethnic groups from South and Central America		Use South Asian data until more specific data are available
Sub-Saharan African		Use European data until more specific data are available
Eastern Mediterranean and Middle East population		Use European data until more specific data are available

1.1.2 Epidemiology

IDF's most recent report characterized MS as the main driving force of the current cardiovascular diseases epidemic. The authors estimate that 20% to 25% of the current worldwide adult population suffers from MS (8). In sub-Saharan Africa, the increasing burden of cardiovascular diseases linked to urbanization and lifestyle modifications has led to a growing interest for MS prevalence in these countries. Effectively, the data suggest that by 2030, more than 27% of SSA adults would have a BMI ≥25 kg/m^2 (9). In 2012, Kaduka et al. published a study revealing MS prevalence in a population of 539 adults living in Nairobi's area in Kenya

(10). A total of 34.6% (40.2% of women and 29.0% of men) of Kenyan adults presented 3 of the 5 risk factors identified in IDF's most recent definition (7). Another study made in rural and urban communities of Benin found a respective MS prevalence of 5.0% and 17.0% in men and women living in urban areas, and of 4.7% and 8.2% in men and women living in semi-rural areas (11). However, the authors used the 2004 IDF definition, which included WC as an obligatory parameter for MS diagnosis. Jennings et al., who studied the presentation of MS in black South African women, found a prevalence of 13% using WHO's definition compared to 10% when using the ATPIII criteria (12). Differences between the prevalence of MS in sub-Saharan Africa might partly be explained by the variety of definitions used in the last decade by the international scientific community.

1.1.3 Pathophysiology

As it is highlighted in the IDF consensus on the worldwide definition of MS, its main causes are complex and remain to be elucidated (13). According to Reaven and the 1999 WHO definition, insulin resistance plays a central role in MS (2, 3). On the other hand, obesity and hypertriglyceridemia have both been independently associated with increased cardiovascular and metabolic risks (3, 14, 15). Indeed, obesity contributes to hypertension, dyslipidemia, high-serum cholesterol, hyperglycemia, and insulin resistance itself.

Although MS pathophysiology remains controversial, it is now commonly accepted that both insulin resistance and abdominal obesity increase cardiovascular risk (7) . However, several other predisposing factors should be considered. Genetic and environmental factors, aging, hormonal changes, and pro-inflammatory state all seem to have a causal effect on MS. The following sections will try to present the main components of MS, their characteristics, their interactions, and the diverse factors that might regulate them.

1.2 Obesity

1.2.1 Definition and Diagnosis

Obesity is defined as a state of excessive adipose tissue mass resulting from a chronic positive energy balance. Excessive body fat is usually classified into overweight or obesity, according to BMI and perhaps WC. As it is highlighted in WHO's Global status report on non-communicable diseases (NCDs), overweight and obesity in adult populations are defined by a BMI superior to 25 km/m^2 and 30 km/m^2, respectively (9).

1.2.2 Epidemiology

WHO refers to obesity as one of the most neglected public health problems that threatens to deeply affect both developed and developing countries. According to WHO's Global Health Observatory (GHO) report published in 2014, data show that at least 2.8 million people die each year from being overweight or obese (16).

As it is highlighted in the GHO report, the prevalence of obesity and overweight is highest in the Americas (27% obese and 61% overweight in both sexes) and seems to increase along with the countries' income level (16). Indeed, low-income countries such as sub-Saharan African countries (excluding South Africa) still present the lowest prevalence of obesity. However, these countries currently have the fastest rise in prevalence of obesity and overweight, as it is estimated that by 2025 three-quarter of the obese population worldwide will live in developing countries (16). A study by Zibara et al. showed that the prevalence of obesity and overweight in women from sub-Saharan countries had increased by one-third between 1992 and 2005 (17).

1.2.3 Pathophysiology

Obesity seems to be the result of a heterogeneous group of disorders, and it has been difficult to identify and quantify all the causes and parameters involved. The neuroendocrine

and metabolic systems that regulate energy intake and storage, which are mediated by environmental conditions and genetic predisposition are complex systems.

Genetic Predisposition

Different methods have been used in obesity research to detect the effects of the gene-environment interaction in humans. In 1990, Bouchard and Pérusse proposed an innovative method to detect the effects of the gene-environment interaction by submitting both members of a pair of monozygotic twins to a standardized hypercaloric regime in a controlled environment. Significant within-pair similarities were observed, suggesting that the genotype plays an important role in the physiological responsiveness to an excess in calorie (18). In 1995, Heitmann et al. have investigated dietary fat intake and weight gain in 361 women during a 6-year follow-up period. Taking into account their family history, they showed that a high dietary fat intake (defined as more than 40% of energy intake coming from fat) was significantly associated with an increased BMI, but only among participants with a familial predisposition (19). Genetic predispositions to develop obesity are now studied at a molecular level, and the most recent genetic mapping of obesity has shown that more than 100 genes or loci are associated with a potential effect on weight gain (20, 21).

Environmental Factors

The association between physical inactivity and weight gain is well known and has been extensively studied. More than 50 years ago, Morris and al. published a study which suggested the benefits of vigorous physical activity on cardiovascular health (22). Since then, many epidemiological studies have examined the association between physical activity and obesity in different ethnic groups.

In 2010, Mbalilaki et al. studied obesity and predisposing factors in a population of 985 Tanzanian men and women (rural Maasai and urban Bantu). The authors found that Tanzanian Maasai presented an extremely high self reported level of energy expenditure, corresponding to 2,556 kcal a day over the basal rate. Despite its high in fat atherogenic diet, the Maasai population had a low body weight and a very low rate of obesity compared to urban Bantu. Leading a traditional African lifestyle, working and commuting were Masaai's main sources of

daily physical energy expenditure. According to the authors, these findings provided some support for the hypothesis that time spent doing light to moderate physical activity such as walking might be beneficial to reduce cardiovascular risk factors in sub-Saharan populations (23). On the other hand, other studies suggested that a decrease in body fat and visceral adipose tissue might only be obtained with a certain level of intensity in physical activity (24, 25). In a systematic review, Vissiere et al. investigated the independent effect of exercise without diet in an overweight and obese population of men and women. They found that a moderate to high intensity aerobic training had more effect on body fat and visceral abdominal tissue (VAT) than a low intensity aerobic exercise (24). Because it has been largely associated with cardiometabolic disorders, VAT has been the subject of a growing interest in obesity research. In a review on the effect of exercise on fat distribution, Goedecke et al. suggested that a higher proportion of visceral fat was lost in response to moderate to high intensity exercise compared to overall body fat (26).

Over the past 30 years, BMI has been increasing dramatically in sub-Saharan African populations, as in a majority of low and middle-income countries (27). Some authors suggest that the dominant factor precipitating the obesity pandemic is diet rather than a sedentary lifestyle (27, 28). A study by Delisle et al. examining diets of 200 Beninese adults has concluded that two major types of diet exist in Benin. One, more traditional, was found to be healthier and more varied than the other diet, which was characterized as “transitional” and had a higher percentage of energy coming from fat, saturated fat and sugar (29). Rashcke et al. proposed that a nutrition transition had been taking place in Africa since the time of colonial occupation, with the progressive extinction of traditional food habits and the indigenous lifestyle (30). According to Steyn et al., who published a review on the interactions between obesity and nutrition transition in sub-Saharan Africa, the process rather started to take place in 1975 mainly because of the massive growth of the manufactured food industry and the subsequent popularization of soft drinks, fast food and other westernized products on the continent (31). Still, a majority of studies admits a general tendency in the nutrition transition affecting sub-Saharan African countries, characterized by an increased intake in saturated fat, high index sugar, and animal proteins, and a decreased intake in low index sugar, low fat and fibers (31, 32).

1.3 Hypertension

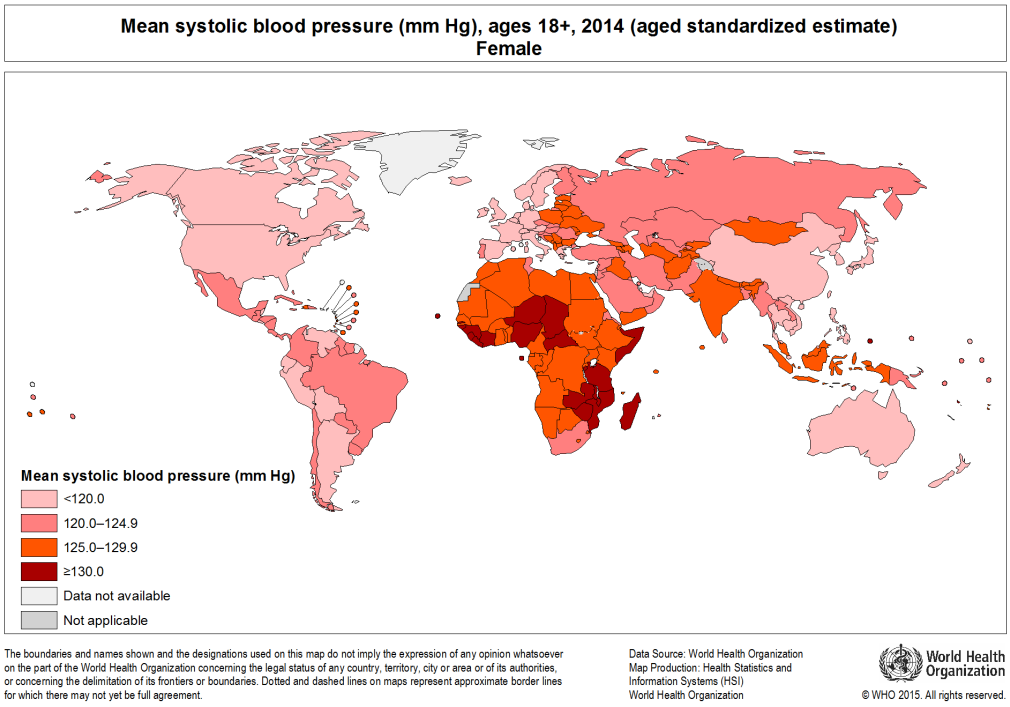
1.3.1 Definition and Diagnosis

In 2013, WHO published a global brief on hypertension in order to implement global policies to reduce death and disability caused by cardiovascular diseases. In this brief, hypertension was defined as a chronic disease in which blood vessels had a persistently raised pressure (33). Normal adult blood pressure is defined as a systolic blood pressure of 120 mmHg and a diastolic blood pressure of 80 mmHg. Hypertension is diagnosed when systolic blood pressure is equal to or above 140 mmHg and diastolic blood pressure is equal to or above 90 mmHg (33).

1.3.2 Epidemiology

In 2008, it was estimated that more than 40% of adults older than 25 years old had been diagnosed with hypertension worldwide (the highest rate being in Africa, with 46%, and the lowest in the Americas, with 35%) (33). Figure 1 and Figure 2 illustrate the mean systolic blood pressure of adult men and women worldwide (33).

Figure 1. Mean systolic blood pressure of adult females

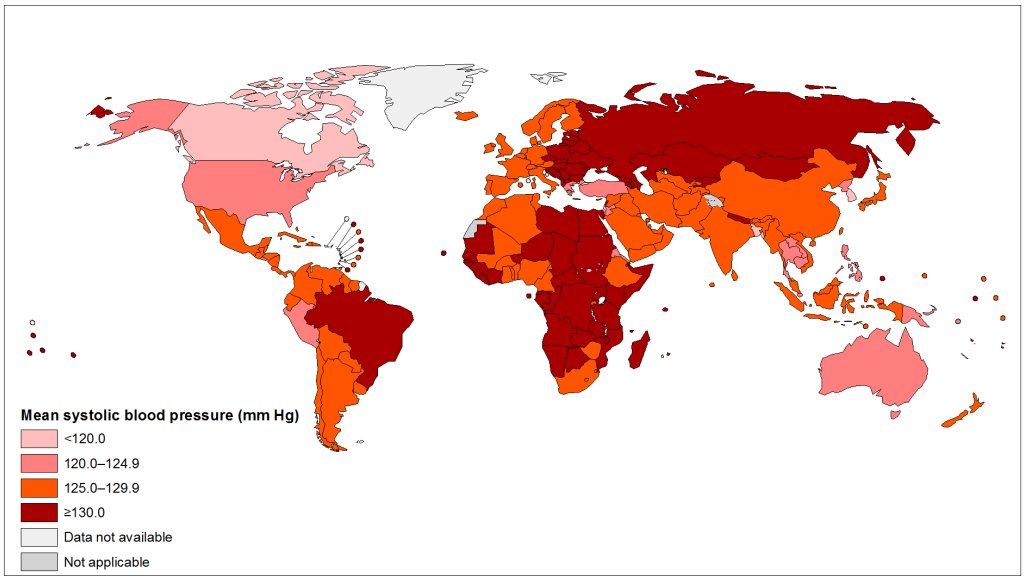


The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Health Statistics and Information Systems (HSI)
World Health Organization

World Health Organization

Figure 2. Mean systolic blood pressure of adult males



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Data Source: World Health Organization
Map Production: Health Statistics and Information Systems (HSI)
World Health Organization

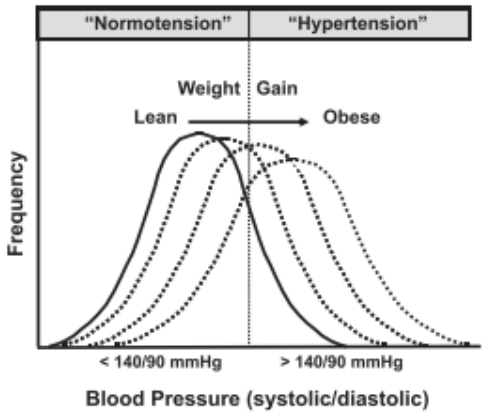
World Health Organization

Statistics on prevalence of hypertension in sub-Saharan Africa differs across literature, in particular for Kenya. In a population-based study directed in Nairobi conduced in 2014, Joshi et al. established the prevalence of hypertension (systolic blood pressure (SBP) >140 mmHg and/or diastolic blood pressure (DBP) >90 mmHg and/or use of anti-hypertensive medication) at 22.8% among their 2,031 participants (34). On the same year, Bloomfield et al. who studied cardiovascular risk factors among 4,092 rural participants living in Bugoma district, a western province of Kenya, reported hypertension (self reported diagnosis of hypertension) in 3% of men and 6% of women (35). Beyond differences in both methodologies, level of urbanization might partly explain these differences in the prevalence within the country. According to the last WHO report on hypertension, the increasing prevalence of hypertension in sub-Saharan Africa is mainly attributed to aging, but also to unhealthy diet, lack of physical activity, use of alcohol, and chronic exposure to stress, all of which are more prevalent in urban areas (33).

1.3.3 Pathophysiology

Hypertension is a complex and multifactorial condition affected by both genetic and environmental factors. It is now commonly accepted that it is strongly correlated to weight gain and obesity, and a number of studies have shown that the relationship between BMI and blood pressure is nearly linear. Fat mass accumulation, especially in the visceral and retroperitoneal spaces, seems to have a direct effect on the vascular system and on the kidneys' constitution and function (36). Adipocyte dysfunction seen in excessive fat accumulation contributes to hypertension via different mechanisms such as insulin resistance, dysfunction of the sympathetic nervous system (SNS), inflammatory mechanisms, and alteration and stimulation of the renin-angiotensin-aldosterone system (RAAS) (37). In a recent review on hypertension induced by obesity, Hall et al. proposed that overweight and obese individuals who weren't hypertensive by definition tended to have a higher blood pressure than the one they would have at their normal weight (Figure 3) (36)

Figure 3. Effect of weight gain on the shift of the frequency distribution of blood pressure toward higher levels



In 2003, a large meta-analysis examined the interaction between weight change and blood pressure. Authors concluded that, for the most part, a weight reduction of 10% was enough to achieve a clinically significant reduction in blood pressure and cardiovascular mortality (-1.05 mmHg of systolic and -0.92 mmHg of diastolic blood pressure per kilogram of weight loss) (37).

Genetic Predisposition

Recent genome wide association studies (GWAS), mostly conducted in European and Asian populations, have linked more than 30 loci to blood pressure (38). In sub-Saharan Africa, one of the first Demographic and Health surveys "Determinants and treatment of hypertension in South Africans: the first Demographic and Health Survey" published by Steyn et al. in 2008 showed a significant association between hypertension and a positive family history of hypertension or stroke (39). As highlighted in a review by B. Rayner on hypertension in South Africa, the heritability of hypertension ranges from 30% to 60%, with various clinical presentations. According to Rayner, black Africans are generally at greater risk of developing salt-sensitive hypertension (40). In 2001, the same authors studied the levels of aldosterone and renin in South African black and white populations. They found that a large fraction of black normotensive participants had low renin and aldosterone plasmatic levels compared to white

participants, suggesting a salt-retaining tendency in black subjects despite comparable sodium intake (41). Similar results were found by Bochud et al. who studied hypertension in black and white South Africans living in Belgium (42).

Environmental Factors

Above genetics, the interplay between genetics and environmental factors such as physical activity and diet seems to contribute to hypertension's pathophysiology.

In 2015, Olack et al. published a cross-sectional study looking at the interactions between lifestyle and hypertension in a large cohort of sub-Saharan African participants living in Nairobi's slums in Kenya. Their results showed that moderately active participants were one and half time more at risk of developing hypertension than participants engaging in high levels of physical activity (43).

Consistent evidences have shown an association between salt intake and blood pressure. In 1990, Poulter et al. published a longitudinal observational study of migrants in Kenya examining the possible causes of change in blood pressure associated with the rural-urban migration process. The authors evaluated and followed 325 new adult migrants in Nairobi and compared them to 267 controls living in rural Kenya. They found that the ratio of dietary sodium to potassium (as assessed by urinary measurements) were significantly higher in the urban group compared to the control. They suggested that high dietary sodium and low dietary potassium intakes were possible determinants of blood pressure in urban Kenyan populations (44).These results are consistent with a study made in Papua New Guinea which showed an increased blood pressure level in participants exposed to a high sodium intake for no more than 10 days (45). Fat intake has also extensively been associated with high blood pressure. Recently, a study made in a large cohort of rural sub-Saharan adults from Malawi, Rwanda and Tanzania has shown that fat intake and meat consumption were associated with hypertension (participants at the highest quartile of frequency of eating high-fat food had a twofold higher odds of developing hypertension compared to the lowest quartile). Frequent consumption of fruits and vegetables was also correlated to lower blood pressure averages (lowest quartile of frequency of

consumption having an odd ratio of 0.75 (0.57 – 1.00) and the highest quartile having and OR of 0.64 (0.38-1.1)) (46).

As it is suggested in WHO's global brief on hypertension, social determinants of health might also influence the development and control of high blood pressure (33). Rapid urbanization found in most sub-Saharan African countries might lead to an environment which encourages fast food consumption, salty diet, sedentary behaviour, tobacco (47) and alcohol consumption (48), all of which are related to an increased risk of hypertension (33).

1.4 Insulin resistance and type II diabetes

Diabetes is a chronic disease in which the body can't produce or use properly an essential hormone produced by the pancreas: insulin. This dysfunction leads to the inability of muscle and tissue cells to absorb blood glucose, which causes a constant elevated level of blood glucose and, consequently, microvascular, cardiometabolic, and neurologic dysfunctions (8). Type 2 diabetes is the most prevalent form of diabetes worldwide and it is now commonly accepted as a comorbidity strongly associated with obesity and MS (8). Insulin resistance, which is a state were muscle cells, fat cells and hepatocytes do not respond adequately to insulin, might precipitate the development of type II diabetes and has also been associated with endocrine, metabolic, and cardiovascular complications (49).

1.4.1 Definition and Diagnosis

According to WHO and IDF's Technical Advisory Group's last recommendations, type 2 diabetes should be diagnosed using the OGTT or FPG. One who presents a venous FPG higher than 7.0 mmol/L (126 mg/dL) or a 2–h plasma glucose higher than 11.1 mmol/L (200 mg/dL) should be considered a type 2 diabetic (50). According to the Canadian Diabetes Association, type II diabetes can also be diagnosed with a random plasma glucose higher than 11.1 mmol/L, or a glycated hemoglobin (HbA1c) superior to 6.5%. HbA1c avoids day-to-day variability of blood glucose as it reflects an average blood glucose of the last 2 or 3 months (51). Impaired glucose tolerance (IGT), which is a pre-diabetic state of hyperglycemia, is as a FPG lower than 7.0 mmol/L and a 2-h plasma glucose higher than 7.8 mmol/L, but inferior to 11.1mmol/l. Impaired fasting glucose (IFG), a pre-diabetic state where fasting glucose is constantly higher

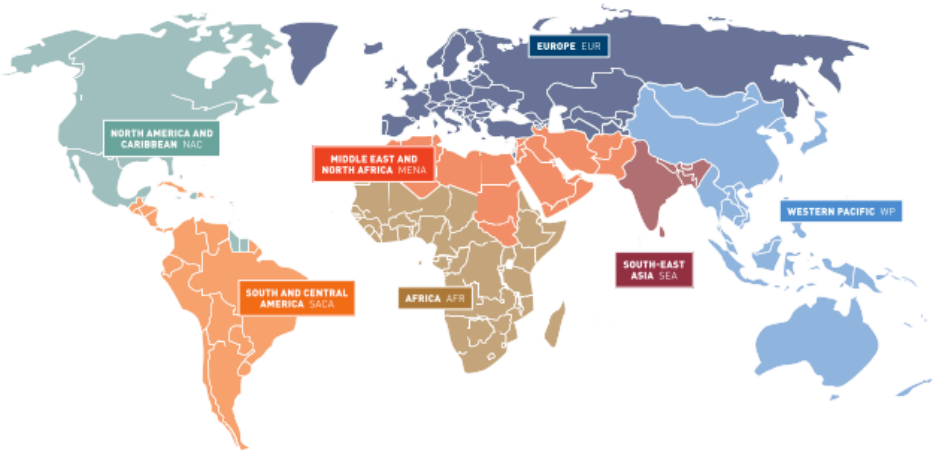
than normal, is defined as a FPG between 6.1 mmol/L and 6.9 mmol/L and a 2-h plasma glucose lower than 7.8 mmol/L (50).

1.4.2 Epidemiology

According to the 6th Edition of IDF's Diabetes Atlas, in 2014, 8.3% of adults worldwide were suffering from diabetes, and almost half of them were not aware of it (8). The majority (80%) of adults affected by the disease and aged between 39 and 59 years old were living in low or middle-income countries. In 2013, more than 5.1 million deaths were directly caused by diabetes, meaning that one person was dying from diabetes (either type 1 or 2) every six seconds.

Both type 1 and type 2 diabetes are increasing globally. Following the urban migration and a dramatic rise in predisposing factors including obesity, type 2 diabetes is expected to rise by 55% by 2035 (8). Figure 4 shows the global actual prevalence and the projections of type 2 diabetes across different regions of the world (8).

Figure 4. Global and regional IDF projections of the number of people with diabetes (20-79 years old), 2013 and 2035



IDF REGION	2013 MILLIONS	2035 MILLIONS	INCREASE %
Africa	19.8	41.4	109%
Middle East and North Africa	34.6	67.9	96%
South-East Asia	72.1	123	71%
South and Central America	24.1	38.5	60%
Western Pacific	138.2	201.8	46%
North America and Caribbean	36.7	50.4	37%
Europe	56.3	68.9	22%
World	**381.8**	**591.9**	**55%**

In sub-Saharan Africa, type 2 diabetes varies widely among regions, with prevalence ranging from 0.3% (rural Gambia) (52) to 8.27% (South Africa) (8) depending on ethnic groups, level of urbanization, difference in diet, lifestyle and studies' methodologies. One of the first studies to estimate the prevalence of type 2 diabetes in African populations was carried out in 1958. The authors found a prevalence of 0.4% studying rural Ghana's populations (53). However, as it is explained by Christensen et al. in an article studying the prevalence of glucose intolerance in Kenya, glycosuria has been largely used as a diagnostic tool in the past decades in sub-Saharan African studies (54). This technique might have led to underestimated prevalence rates in the past considering the poor sensitivity of this test. In 2005, the INTERHEART study showed that the global prevalence of diabetes in Africa was 7.6% (55). In 2009, Christensen et al. found a relatively low age-standardised prevalence of diabetes in Kenya (4.2%), with a concurrent prevalence of IGT (12.0%), based on OGTT results (54).

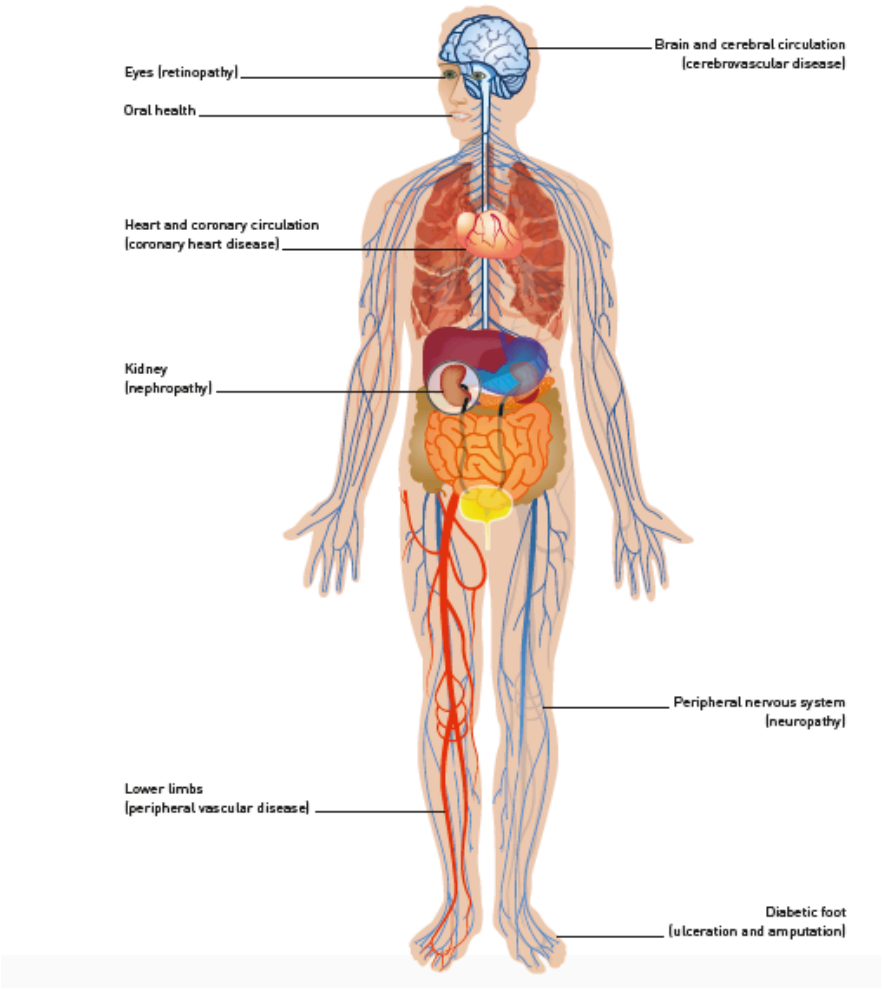
1.4.3 Pathophysiology

In type 2 diabetes, the pancreas is at first able to produce extra insulin, but it is either not sufficient or the peripheral tissues are unable to respond adequately to its effect (insulin resistance). Insulin resistance is indeed defined as a loss of response to insulin (impaired glucose uptake) by sensitive peripheral tissues and by an impaired ability to decrease hepatic glucose output (49). This phenomenon can later lead to pancreatic beta-cells exhaustion and their dysfunction (8). Insulin resistance is the primary cause of type 2 diabetes and usually occurs years before its onset.

It is now commonly accepted that obesity lead to metabolic dysfunction and to an increased risk of type 2 diabetes through insulin resistance. Interactions are complex and the cascade of events occurring during the development of insulin resistance induced by obesity still needs to be elucidated. In 2013, Jianping Ye published a manuscript describing the different mechanisms of insulin resistance in obesity. It is suggested that obesity could lead to insulin resistance through different phenomena such as adipose tissue dysfunction, hyperinsulinemia, and chronic inflammation (56). For example, the chronic low-grade state of systemic inflammation found in obese individuals would be associated with adipose tissue dysfunction. Through several mechanisms, inflammation would inhibit the insulin signaling activity of hepatocyte and adipocytes (56). Also, the number and function of β cells in pancreatic islets would enhance with weight gain (57). β cells are the only source of insulin. Obesity would thus be associated to a state of hyperinsulinemia. According to Ye, hyperinsulinemia could lead to insulin resistance. This hypothesis was supported Shanik et al., whom published in 2008 a review presenting 5 different studies from human and animal models where insulin level was considered as a quantitative contributor to insulin resistance (58). In another review published in 2007 by Jianping Ye, it is suggested that insulin resistance would result from a negative feed-back loop in the insulin signaling pathway, activated in state of hyperinsulinemia (57). Other factors such as sleep apnea, pregnancy, stress or genetic factors have also been outlined as involved phenomena (56).

Once type 2 diabetes has been diagnosed, a strict control is necessary in order to avoid a number of life-threatening conditions. As illustrated in Figure 5, a chronic elevated blood glucose level is known to damage blood vessels, nerves (diabetic neuropathy), kidneys and eyes (diabetic retinopathy), and is linked to serious cardiovascular complications (angina, stroke, myocardial infarction, cardiomyopathy, congestive heart failure, and peripheral artery diseases). It also increases the risk of infections, which can be a real challenge for low and middle-income countries given the importance of communicable diseases such as tuberculosis and human immunodeficiency virus (HIV) in these regions (8).

Figure 5. Major type 2 diabetes complications (8)



Genetic Predisposition

It is now commonly accepted that type 2 diabetes has a strong genetic component. In 1992, Kaprio et al. studied the concordance of type 2 diabetes in a population-based cohort of monozygotic and dizygotic twins in Finland (59). Results showed a concordance rate of 34% among monozygotic twins, and of 16% among dizygotic twins, highlighting the major role of genes in the pathophysiology of type 2 diabetes. Recent technological development in biomolecular medicine has permitted to identify more than 50 genes associated with the disease, but they would account for only 10% of the primary constitutional origin of type 2 diabetes (60).

However, as it was outlined by Yako et al. in a meta-analysis on the genetic risk of type 2 diabetes in the African continent, most of genome-wide association studies were conducted in European and Asian populations. Results can hardly be transposed to other ethnic groups, especially African populations which are known to harbour more inter-individual genetic variations (61). Further research is needed in order to better understand the specific genetic predisposition of sub-Saharan African populations to develop type 2 diabetes.

The Effect of Body Fat Distribution: An Ethnic Predisposition

In 2003, Nakagami et al. published a review looking at the effects of ethnicity on the association between age, BMI, and the prevalence of type 2 diabetes. They examined population-based studies carried out in different ethnic groups (Europeans, Maltese, Japanese, Indian, and Chinese) and concluded that the effects of weight gain on age-adjusted prevalence of type 2 diabetes are affected by ethnicity (62). Comparatively, Christensen et al. published a study looking at insulin resistance and beta-cell functions in different ethnic groups of Kenya (63). They demonstrated that Maasai participants, compared to Luo and Kamba, had a higher rate of insulin resistance and hyperinsulinemia. According to the authors, this ethnic difference can be partly caused by fat distribution, as Maasai have a higher VAT accumulation compared to the two other groups. Their results showed a significant interaction between ethnicity and VAT accumulation, suggesting an ethnic predisposition to stock fat viscerally, and thus to be at higher risk of insulin resistance and type 2 diabetes.

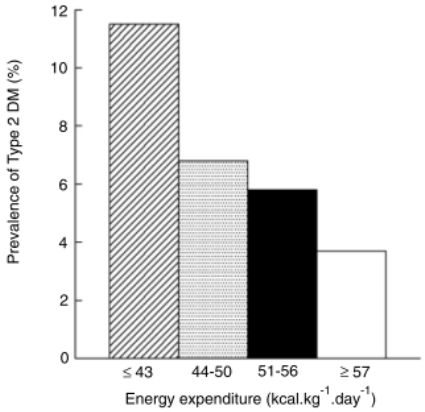
In 2014, Goedecke and Micklesfield published a review looking at the effects of exercise on body fat distribution and on the risk of developing type 2 diabetes (26). According to their review, body fat distribution, or the predisposition to stock fat viscerally instead of subcutaneously, can be associated with insulin resistance and type 2 diabetes. They suggested that VAT was more lipolytic and had a higher inflammatory profile compared to subcutaneous adipose tissue (SAT). Since free fatty acids (FFA) and adipokines from VAT are being released directly into the portal circulation, they have a greater effect on hepatic glucose homeostasis and can lead to insulin resistance (26). In a prospective study, Neelan et al. studied 732 obese adults and found that VAT, but neither total body fat or SAT, was associated with the incidence of insulin resistance and type 2 diabetes (64).

The role of VAT is also clearly demonstrated by the metabolically healthy obese phenotype (MHO) characterized by a diagnosis of obesity with the presence of only two or less components of MS. MHOs tend to be insulin sensitive, and studies have shown that they usually present a lower amount of VAT, liver, and intramuscular fat compared to obese subjects with associated cardiometabolic disorders (65). On the other hand, as it is highlighted in Goedecke's review, SAT accounts for more than 80% of FFA and adipokines released into the total bloodstream. Both abdominal tissue layers seem to have detrimental cardiometabolic effects and should be considered as risk factors for insulin resistance and type 2 diabetes (26).

Environmental Factors

Many studies have shown interest for the association between physical activity and type 2 diabetes and insulin resistance in low and middle-income countries. In 1999, Levitt et al. investigated the prevalence of type 2 diabetes and its predisposing risk factors in South Africa. In this cross-sectional study, the authors showed a negative association between both occupational and leisure physical activity and type 2 diabetes. They also demonstrated a dose-response effect between the intensity of physical activity (levels of energy expenditure) and the prevalence of insulin resistance and type 2 diabetes, as illustrated in Figure 6 (66).

Figure 6. Prevalence of type 2 diabetes according to level of physical activity expressed as quartile



In 2016, Gatimu et al. studied the prevalence and the determinants of diabetes among 5,565 Ghanaian adults (67). They found that respondents aged 50 to 59 years and those aged 60 to 69 years participating in low to moderate physical activity were respectively 67% and 117% more likely to be diabetic than their counterparts engaging in a high intensity level of physical activity. These results provide evidence on the association between the intensity of physical activity and the prevalence of type 2 diabetes, particularly among aging populations. Similar correlations were found in urban slums of Kenya (68).

There are epidemiological evidences for the association between dietary patterns and insulin resistance or type 2 diabetes. Indeed, nutrition has been identified as one of the major modifiable risk factor for type 2 diabetes. Nevertheless, food intake in low and middle-income countries, and particularly in sub-Saharan Africa, differs largely from dietary patterns in European, Asian or American populations. In 2016, Schulze et al. have studied the food habits of a large Ghanaian urban population (69). As expected, a low fat diet rich in fruits and vegetables was associated with a lower risk of developing type 2 diabetes. However, authors also found a negative association between red meat and type 2 diabetes, which was surprising but might be explained by the leaner types of meat found in sub-Saharan Africa compared to westernized countries. Cheng et al. recently studied the effects of food insecurity on type 2 diabetes in a Kenyan population (70). They assessed food security by questioning 1733 patients

presenting type 2 diabetes about their diet. The authors found a particularly high prevalence of food insecurity status (32%) in patients affected by type 2 diabetes (70). These results highlight the essential need for further research on the relation between nutrition and type 2 diabetes and insulin resistance in sub-Saharan Africa, which should include the entire spectrum of food intake.

1.5 Dyslipidemia

1.5.1 Definition

Dyslipidemia associated with obesity is characterized by increased triglycerides (TG), low HDL-C and/or elevated small-dense LDL particles (71). Such a profile usually predisposes to cardiovascular diseases. Table 3 shows a general classification of total cholesterol, LDL-C and TG levels, as suggested by the NCEP-ATPIII (72). Table 4 shows a similar classification for HDL-C levels (72).

Table 3. ATPIII classification for total cholesterol, LDL-C, and serum TG

Levels	Total Cholesterol (mg/dL: mmol/l)	LDL-C (mg/dL: mmol/l)	TG (mg/dL: mmol/l)
Desirable	<200: 5.18	<100: 2.59	<150:1.69
Borderline High	200-239: 5.18-6.19	100-159: 2.59-4.12	150-199: 1.69-2.25
High	>239: 6.19	159-189: 4.12-4.89	199-499: 2.25–5.64
Very High		>189: 4.89	>500: 5.64

Table 4. ATPIII classification for HDL-C

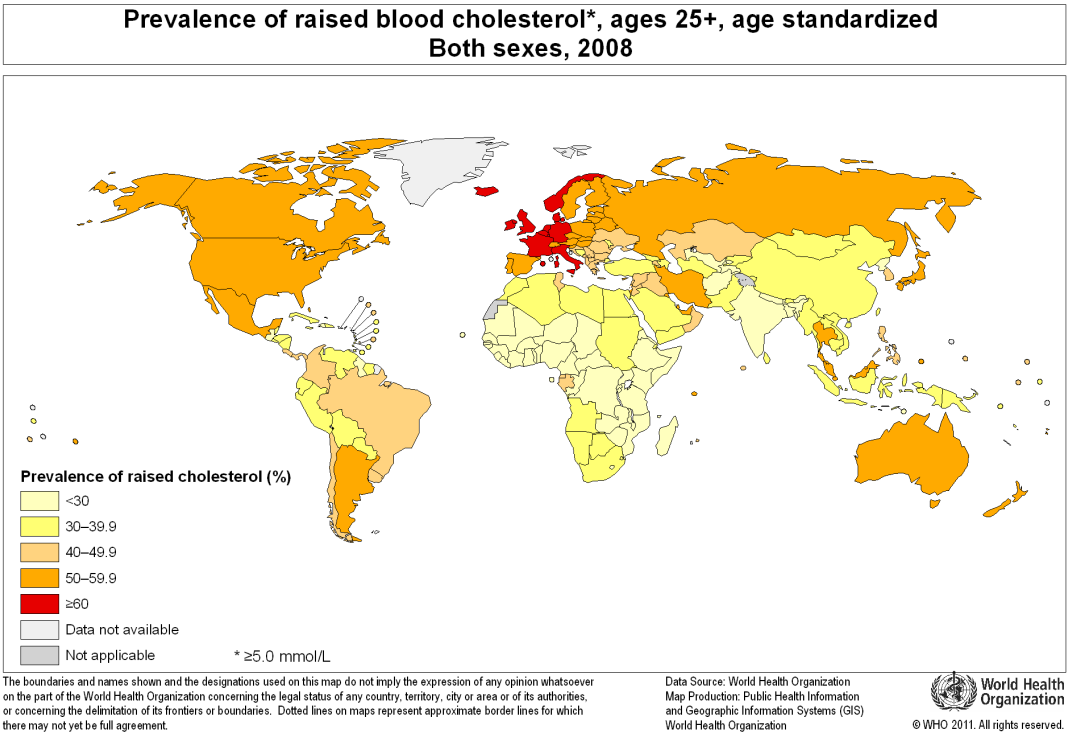
Levels	HDL-C (mg/dL: mmol/l)
Low	<40: 1.04
High	>59: 1.53

1.5.1 Epidemiology

According to WHO, in 2008, the global prevalence of dyslipidemia was 37.0% in men and 40% in women (9). They estimated that cholesterol levels had barely changed in the past 20 years, declining by less than 0.1 mmol/L per decade despite global health interventions. According to WHO's statistics, the African region had a dyslipidemia prevalence of 22.6%, while European and American regions presented a respective prevalence of 54.0% and 48.0% (9). The INTERHEART Africa study evaluating risk factors for myocardial infarction across the African continent concluded that dyslipidemia was the leading risk factor for ischemic heart

diseases (55). Figure 7 illustrates the worldwide prevalence of raised cholesterol in men and women.

Figure 7. Prevalence of raised cholesterol, age 25+, age standardized for male and female



In Kenya, very few studies have reported dyslipidemia prevalence in rural or urban populations. In a cross-sectional study published in 2015, Christensen et al. found a dyslipidemia prevalence of 37.3% in a rural Kenyan population of 1,139 men and women, of which only 6.1% had isolated high TG levels, 86.7% had isolated low HDL-C levels, and 7.3% had both (73). In 2016, Harengu et al. found a hypercholesterolemia prevalence of 10.3% and a hypertriglyceridemia prevalence of 17.3% in a cohort of 5,190 Kenyans living in the urban slums of Nairobi (74).

1.5.2 Pathophysiology

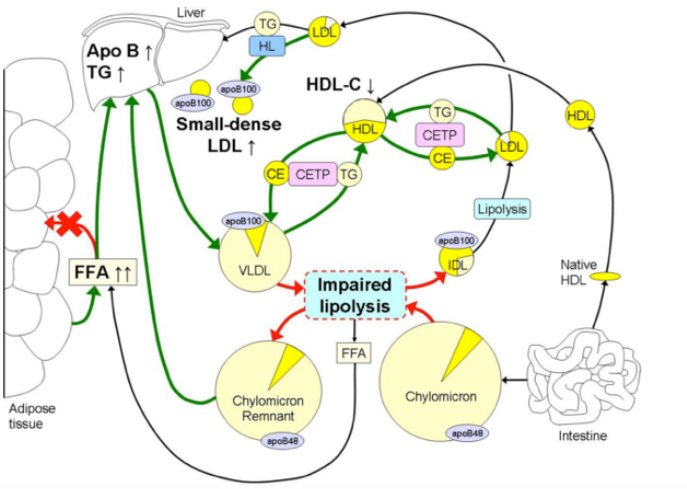
Obesity increases the risk of developing a variety of pathological conditions such as non-alcoholic fatty liver disease (NAFL) or dyslipidemia. Adipose tissue plays a major role in the pathogenesis of metabolic dysfunction as it is the major repository of FFA. In the bloodstream, fatty acids (FA) are either linked to albumin (FFA) or transported via chylomicrons and very low-density lipoproteins (VLDL). They are delivered to specific tissues for energy fuel or storage (75). Chylomicrons are large transport lipoproteins assembled in the intestinal mucosa which carry exogenous fat and cholesterol, whereas VLDL, synthetized by the liver, are another type of lipoproteins which transport endogenous TG, phospholipids, cholesterol, and cholesteryl esters (76). The amount of FA released from VLDL and chylomicrons depends on the activity of several lipases and apoproteins acting as co-factors. Lipoprotein lipase (LPL) is one of the main enzymes responsible for TG lipolysis. It is strongly expressed in skeletal muscles, the heart, and adipose tissues, which are all commonly known to require large quantities of FFA for energy expenditure or storage. LPL hydrolyzes TG from VLDL and chylomicrons and releases TG into specific tissue cells so these molecules can be used (76).

Insulin is a major regulator of FFA storage and mobilization (77). In a post-prandial state, the rapid rise in insulin allows FFA uptake by cardiomyocytes, adipose tissue cells, and myocytes. On the contrary, in a fasting state, FFA can be mobilized from the adipose tissue and redistributed in the most demanding tissues, such as cardiomyocytes (77). Following lipolysis by LPL, chylomicrons and VLDL are transformed into denser lipoproteins called chylomicrons remnants, VLDL remnants and low-density lipoproteins (LDL-C) (71). Both are then catabolized by hepatocytes through a receptor mediated pathway (78, 79). The liver also synthetizes beneficial transport proteins named high-density lipoproteins (HDL-C). HDL-C particles collect cholesterol from the peripheral tissues and the arterial walls and return it to the liver where it will be catabolized (71). Mature HDL-C particles, rich in cholesterol, can either be taken up by the liver or transfer their cholesterol content to other lipoproteins (80).

As it is highlighted in a review by Klop et al. on dyslipidemia and obesity published in 2013, obese individuals tend to present low HDL, small dense LDL-C, and elevated fasting and post-prandial TG levels (81). According to Klop's review, hypertriglyceridemia is the major

cause of other lipid abnormalities induced by obesity. Studies have shown that obese individuals present a reduction in LPL activity in skeletal muscles, which impairs the lipolysis of TG-rich lipoproteins and induces hypertriglyceridemia (71). Hypertriglyceridemia delays clearance of TG-rich lipoproteins such as VLDL and leads to an increased synthesis of small dense LDL-C, which are metabolised slowly and can cause atherosclerosis (82). Figure 8 illustrates the pathophysiological interactions between lipoproteins in dyslipidemia induced by obesity.

Figure 8. Interactions between lipoproteins in dyslipidemia induced by obesity



Genetic Predisposition

Ethnic differences in lipid profiles have been documented and attributed, in part, to genetic polymorphisms. However, most genetic studies are based entirely on European descents, and it remains unclear if the markers found in recent studies have a prognostic utility in other populations such as Africans or Hispanics (83). In 2009, Deo et al. published an interesting study whose objective was to genotype a panel of 12 new genetic variants known to predict lipid profiles in Europeans in a cohort of 4,464 African Americans (83). The authors did not found any significant association between these variants and LDL-C, HDL-C, and TG levels of African Americans. They concluded to a lower effect sizes for the 12 risk variants in African descent populations and highlighted the need for caution in the use of genetic variants for risk assessments across different ethnic groups.

In 2008, Sumner et al. published an interesting cross-sectional study where they used a cohort of 2804 participants from the American National Health and Nutrition Examination Survey (NHNES) to determine the prevalence of dyslipidaemia, obesity, hypertension and type 2 diabetes by ethnicity. Despite a higher level of obesity, hypertension, and type 2 diabetes, African Americans presented lower TG levels compared to their white and Hispanic counterparts. The authors' hypothesis was that an ethnic difference may exist in the production and clearance of TG rich lipoproteins, possibly linked to LPL activity (84). In 2000, Deprés et al. have compared body fatness, BMI, VAT, plasma lipids and LPL activity between a cohort of black and white men and women (85). They found that, for a greater body fat content compared to their white counterparts, black women had a significantly lower levels of VAT, reduced apolipoprotein B and higher HDL-C levels. A higher LPL activity level was found in black participants from both sexes. Nevertheless, the authors admitted that despite a significant difference in LPL activity between the two ethnic groups, results from their multiple regression analysis showed that ethnicity had only a modest effect on the variance of plasma lipoproteins levels. To a certain extent, variability in lipid levels across ethnicities might rather be explained by a propensity to stock fat viscerally or subcutaneously (85).

It is more and more accepted as a fact that black Africans and African Americans tend to present a better profile in plasma lipids (lower LDL-C and TG levels) compared to Caucasians and Asians (12, 29, 85). However, some studies have also found that black African descents and African populations present lower levels of HDL-C (12, 29, 86). In 2015, Asiki et al. studied dyslipidemia in a population of rural southwestern Uganda. They found that almost three quarter of the the population having dyslipidemia had isolated low HDL-C levels (71.3%), while only 6.0% of them presented isolated high TG levels (87). Similar results were found by Christensen et al., who studied the differences in blood pressure and lipid status according to age, ethnicity, and sex in a Kenyan population. They found that 86.7% of their participants affected by dyslipidemia had isolated low HDL-C, regardless of their insulin resistance or obesity status. As it is suggested by the authors, HDL-C levels might be a major and an independent cardiometabolic risk factor in black African populations (73). Another hypothesis is that HDL-C is not correlated to body fat accumulation in African populations, unlike other lipoproteins such as LDL-C and TG (85, 86).

Environmental Factors

According to Delisle et al., whereas genetic factors must contribute highly to dyslipidemia, environmental factors such as diet are also at play. The authors' hypothesis states that HDL-C levels found in African populations are significantly associated with nutrition, particularly with poor micronutrients intake and vitamin deficiency. From their cohort of 541 healthy adults from Benin, Delisle et al. found that HDL-C was significantly associated with either undernutrition or overnutrition and poor micronutrients intake (29). Asiki et al. who studied dyslipidemia in a rural Ugandan population have also associated low HDL-C levels to an insufficient consumption of fruits and vegetables (87). Populations from countries affected by nutrition transition such as most African countries are thus at risk of cardiometabolic diseases through low HDL-C levels.

Diet composition is undoubtedly associated with cardiovascular risk factors. High intakes of saturated FA, trans-unsaturated FA, and cholesterol have been shown to increase LDL-C levels, whereas high carbohydrates diets have been associated to lower HDL-C levels (88, 89). According to the most recent guidelines from the American Heart Association, increased intake of sugar, refined carbohydrates, and alcohol are also increasing TG and VLDL levels (89). Moreover, as it is suggested in the NCEP-ADPIII, antioxidant nutrients, folic acids, B-vitamins, and other micronutrients can also affect lipid profiles (72). Food quality might be an independent risk factor for cardiometabolic health.

According to the NCEP-ADPIII expert panel, physical activity has also been associated with an improvement of lipid profile (72). As it is explained in the NCEP-ADPIII, the mechanisms are not fully understood. However physical activity seems to play a beneficial role regarding fat accumulation. It reduces atherogenic lipids (small dense LDL-C particles and TG) by increasing daily energy expenditure and decreasing body fat mass (72). In 2007, Mbalilaki et al. published a study made on 985 rural and urban Tanzanian participants from various ethnic origins. They showed that rural populations presenting a higher physical activity level compared to urban populations were also having lower levels of LDL-C, total cholesterol, TG, and alipoprotein B. Unexpectedly, rural Tanzanians also presented lower HDL-C levels (86). In

2010, similar associations were found in another Masaai population from Tanzania. Mbalilaki et al investigated the association between dietary pattern, physical activity level and serum lipids in a population of 985 men and women from two different ethnic origins (Masaai and Bantu). Masaai presented an extremely high level of physical activity (2,565 kcal/day compared to 891 kcal/day for urban Bantu) and favourable lipid levels despite a diet rich in fat and carbohydrates (23).

Chapter 2

Anthropometric measures of body fat distribution

Advanced researches and technologies have led to an incremental knowledge on cardiovascular and metabolic diseases and their association with body composition and fat distribution. Technologies such as magnetic resonance imaging (MRI), computer tomography (CT) or dual-energy X-ray absorptiometry (DXA) have helped to understand the complex interactions between each individual body composition, adipose tissue compartment and health risks.

Since the late 40's, it is recognized that alterations in body mass composition are involved in the pathogenesis of many chronic and acute illnesses. One of the first reports on the association between obesity, fat distribution and health risks was published by French physician Jean Vague in 1947 (90). Since the 80's, it is commonly accepted that body mass and fat distribution have a significant influence on an individual's health, and the main consequences tend to affect the cardiovascular and the metabolic systems (91).

MRI and CT, the accepted gold standards to assess regional body composition, require important financial and technological resources and are difficult to include in routine health care situations. Moreover, such technologies remain rare in low and middle income countries, and almost inexistent in the majority of rural areas. Despite a crucial progress in biomedical technologies over the last decade, nutritional health is still based on anthropometry, the science that defines physical measures of a person's size, form and functional capacity (92). Although new medical imaging systems offer impressive possibilities, a number of studies have shown the reliability of anthropometric measurements (91). As a simple, inexpensive and safe process, anthropometry remains the most widely used method for quantifying body mass composition, and new potential applications are still being explored (91).

Anthropometry covers multiple non-invasive in vivo methods to evaluate body composition and its physiological and pathological states. Overall, fat accumulation is frequently defined by measurements such as body weight or BMI . The localisation of excess

adipose tissue can be strongly associated with cardiometabolic risk. Abdominal obesity, measured by WC, is known to be a strong predictor of mortality and morbidity (93). Adipose tissue compartments have also aroused considerable research interest. Compartments of abdominal fat, commonly referred as visceral and subcutaneous adipose tissues (VAT and SAT), have been largely studied for their possible relationship with metabolic and cardiovascular abnormalities (94). The propensity to stock fat viscerally or subcutaneously, measured by the visceral-to-subcutaneous adipose tissue ratio (VAT/SAT), has also been suggested as a potential correlate of cardiometabolic risk (94).

2.1 Body mass index

WHO promotes BMI as a measure to classify underweight, overweight and obesity in adult populations. It is defined as a person's weight (kg) divided by the square of its height (m^2). The following ranges, showed in Table 5, have been established according to the effect of excessive fat on comorbidities and mortality (95).

Table 5. Nutritional status by BMI (92)

BMI	Nutritional status
Below 18.5	Underweight
18.5–24.9	Normal weight
25.0–29.9	Pre-obesity
30.0–34.9	Obesity class I
35.0–39.9	Obesity class II
Above 40	Obesity class III

BMI is well correlated to total body adiposity, and numerous studies have shown its value for detecting increased mortality risk. However, as it is explained by Müller et. al in a

systematic review on the pathogenesis of obesity and MS, metabolic and cardiovascular consequences of fat accumulation vary among individuals (96). For example, in their review, Müller et al. reported that 50% of overweight (or pre-obese) and 30% of obese subjects present a favorable metabolic profile, i.e. the absence of inflammation, dyslipidemia, hypertension or cardiovascular and metabolic complications. These subjects, considered as "metabolically healthy obese" (MHO), differ from the "metabolically abnormal obese" by their fat distribution. As explained by Müller et al., for a comparable BMI, MHO tend to present lower VAT and fat infiltration in the liver and the skeletal muscles. At the opposite, other studies have reported the existence of a subgroup of normal-weight subjects with low SAT and increased VAT. Characterized as "thin-fat", these individuals are exposed to a greater risk of insulin resistance and cardiometabolic complications because of their adverse adipose tissue distribution (97).

As WHO already pointed out in its last report on obesity (95), BMI is a limited measure. It does not take into account differences in adipose tissue distribution based on age, gender, ethnicity or physical activity level. It may over or underestimate adiposity and its cardiometabolic consequences. As an example, in 2002, a WHO expert consultation panel proposed to lower BMI ranges for South Asian populations, known to present a relatively high prevalence of the "thin-fat" phenotype (95). They concluded that South Asians had different associations between BMI and health risks and recommended to use a BMI of 23 kg/m^2 as a trigger point for public health actions (98). Further researches are needed to evaluate the limitation of BMI in different ethnic groups.

2.2 Waist circumference

Increasing evidence suggests that abdominal fat is an important cardiometabolic risk factor. WHO now recommends WC as the official anthropometric measure to assess central obesity. Sex-specific cut-offs are promoted to identify the increased relative risk of Cardio-Metabolic Diseases (CMD). Based on a random sample of 2,183 men and 2,698 women, WHO has recently established a sex-specific table of recommended cut-off points (Table 6) (99). The IDF has also provided recommendations stratified by sex, population and geographic areas (Table 7) (13). There is still no agreement between WHO, IDF and the AHA/NHLBI on the

definition of abdominal obesity. While WHO and IDF recommend that the WC threshold for abdominal obesity in European populations should be ≥94 cm for men and ≥80 cm for women, the AHA/NHLBI rather recommends cut-off points superior to 102 cm for men and to 88 cm for women (7).

Table 6. WHO WC cut-offs for men and women

Sex	WC (cm)
Men	>94
Women	>80

Table 7. IDF criteria for ethnic or country-specific values of WC for men and women

Country or ethnic group	Sex	WC (cm)
Europid	Men Women	≥94 ≥80
Asian	Men Women	≥90 ≥80
Middle East and Mediterranean	Men Women	≥90 ≥80
Sub-Saharan African	Men Women	≥94 ≥80
Central and South America	Men Women	≥90 ≥80

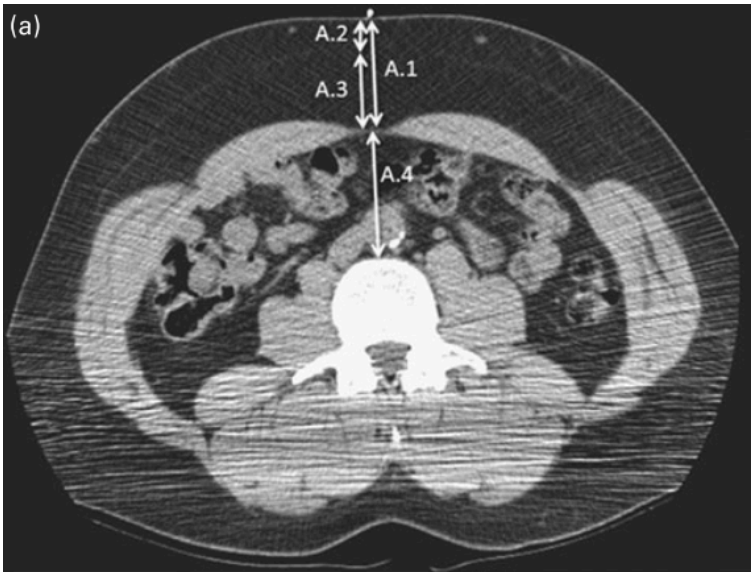
One of the main critics concerning WC cut-offs (as established by WHO) is that they are based on limited data from Caucasian subjects, mainly from European countries. Recent studies have shown that these cut-offs cannot be universally used across ethnic groups, particularly for individuals from Asian origin, known to be at a higher risk of CMD for lower WC values (7). On the other hand, according to WHO, limitation of data makes it difficult to specify cut-off points. Although WHO accepts the hypothesis that cardiometabolic risk may vary between ethnicity for a similar WC, there isn't sufficient evidence to recommend ethnic specific cut-offs values (99).

2.3 Adipose tissue Compartments

The role of adipose tissue has to be considered within the context of its physiological benefits versus its pathogenic consequences. Indeed, being overweight is not necessarily detrimental, and adipose tissue has diverse roles, pathogenic or not, depending on its location and function.

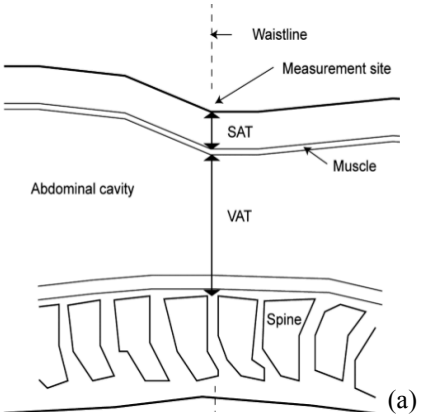
Adipose tissue compartments can be stratified in different levels based on their distribution within the body. Different classifications have been proposed, however it is commonly accepted that body fat is divided in three major zones: superficial subcutaneous adipose tissue (SSAT), deep subcutaneous adipose tissue (DSAT) and VAT (100-102). In the abdomen, abdominal muscle (the anterior line of the rectus abdominis muscle) constitute the anatomical separation of two distinct compartments: the primary compartment (SSAT and DSAT) and the secondary compartment (which only includes VAT). A fascial plane (*fascia superficialis*) divides SSAT and DSAT (101). All structures are easily recognized on CT and MRI, and even with ultrasonography (Figure 9, Figure 10).

Figure 9. CT references for abdominal adipose tissue compartment's thickness (100)

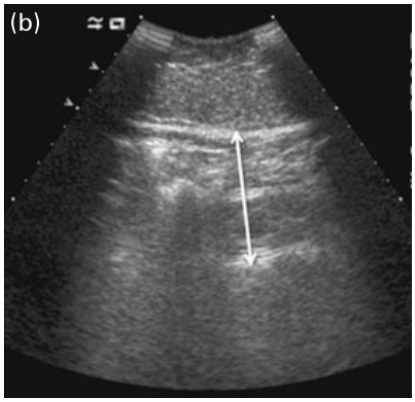


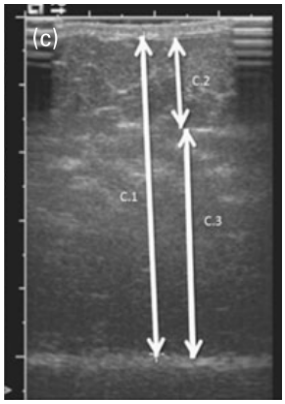
A.1 shows total subcutaneous fat thickness; A.2 shows superficial subcutaneous fat thickness; A.3 shows deep subcutaneous fat thickness; A.4 shows total visceral fat thickness. From (103)

Figure 10. US references for abdominal adipose tissue compartment's thickness



(a)





(a) shows abdominal adipose tissue and anatomical landmark used in US measurements (104) ; (b) shows total visceral fat thickness; (c) shows subcutaneous fat thickness: C.1 shows total subcutaneous fat thickness, C.2 shows superficial subcutaneous fat thickness, and C.3 shows deep subcutaneous fat thickness (103).

How Fat Is Stored

Each layer of adipose tissue possesses its own morphological and functional characteristics. Typically, adipose tissue is constituted of approximately 50% of adipocytes and 50% of stromal vasculature (fibroblasts, endothelial cells, macrophages and pre-adipocytes) (105). When the human body is exposed to a positive caloric intake balance, its adipose tissue will expand via a phenomenon named adipogenesis, or adipocyte hyperplasia, which is characterized by the transformation of pre-adipocytes, the cells from the stromal vasculature, into functional fat cells, the adipocytes. Adipogenesis allows an adequate storage of free fatty acids and prevents lipotoxicity that is defined as ectopic fat deposition into muscles and other organs such as the liver and the pancreas (105). Via adipogenesis, the human body has the functional capacity to increase its fat mass without any major pathological consequence. That procedure requires an orderly and appropriate production of transcriptional and modulating factors, with an extensive transformation of the adipose extracellular matrix. Any disruption in the adipogenesis process may lead to adipocyte hypertrophy, which is a phenomenon where fat cells increase in volume and become dysfunctional. Fat cell hypertrophy increases circulating free fatty acids and ectopic fat storage (105). The determination as whether adipose tissue will undergo adipogenesis or fat cell hypertrophy in response to a positive caloric intake balance depends of genetic predispositions and modulatory factors (105).

Where Fat Is Stored

The physiology of fat storage (hyperplasia/adipogenesis versus hypertrophy) is a major determinant in the onset of lipotoxicity. However, the layer of adipose tissue (DSAT, SSAT or VAT) where fat mass expansion occurs also has significant consequences.

As it has been previously discussed, an important number of overweight and obese subjects are characterized as MHO. Many studies have shown that MHO often present less visceral fat and more superficial subcutaneous fat than their metabolically obese peers (26, 96, 106). Visceral fat and subcutaneous fat (deep and superficial) all have their own intrinsic activities (Table 8) (100). All these layers significantly differ in their way to store excessive

energy, which could explain the clinical differences found secondary to the expansion of one versus the other.

Table 8. Morphologic characteristics and functional features by adipose tissue compartment (102)

	SSAT	DSAT	VAT
Development sequence	Primary	Secondary	Secondary
Differentiation and demarcation of lobule	Best demarcated	Intermediate	Least demarcated
Stability of triglycerides stores	More stable	Unkwnown	Least Stable
Vascularity of lobules	Least vascular	Intermediate	More vascular
Cytokine Secretion and pro-inflammatory state	Less	Unknown	More
Physiology of excessive fat storage	Hyperplasia	Unknown	Hyperplasia Hypertrophy
Relative distribution	80%		20%

A certain gradient in the level of organization found in adipose tissue layers exists. Fat within the superficial subcutaneous layer appears as organized packed lobules and is less vascular. This layer contains the majority of adipocytes found in the gluteal region and presents the lowest transmembrane fluxes of fatty acids. Therefore it constitutes a stable storage of triglycerides in the body (105).

Fat within the deep subcutaneous layer is found in large lobules, more irregular and less organized (105). Deep subcutaneous fat is usually restricted to the upper body, and its implication in the pathogenesis of metabolic complications remains unclear. In 2001, Smith et al. published a study on the association between fat layers and the metabolic complications of obesity. They found that DSAT was significantly associated to a detrimental metabolic profile (107). Similar associations were found in other studies, and it has been suggested that deep subcutaneous tissue has detrimental metabolic activities, such as lipolysis and the release of inflammatory factors (108) .

Finally, visceral adipose tissue contains a developed vascularisation with undefined lobules, which can explain its strong association with metabolic diseases, even though it constitutes the smallest compartment. VAT, which generally represents 20% of the total body fat distribution, has been shown to secrete free fatty acids and various adipocyte factors directly into the portal vein, which provides around 80% of the abdominal blood supply (105).

Expansion of the three different layers increases the risk of metabolic and cardiovascular diseases. It is well documented that upper body obesity, particularly the expansion of VAT, is associated with a greater risk of dyslipidemia, hyperglycemia and vascular diseases (82, 100, 106, 109). On the other hand, the implication of SAT (DSAT and SSAT) in the release of systemic free fatty acids cannot be ignored. Although it has a limited vasculature, SAT accounts for the majority of systemic circulating free fatty acids. As it was highlighted in a previous study by Smith et al. on the relation between total body fat and cardiometabolic risk factors, SSAT and DSAT are both good predictors of cardiometabolic complications of obesity (107).

One's propensity to store fat in the second compartment (VAT) versus the primary (SSAT and DSAT) is also influenced by ethnic origin. For example, studies have shown that, for a similar body fat percentage, Asians tend to present a higher VAT, whereas Afro Americans rather store their fat in the lower limbs and are prone to SAT accumulation (5).

In summary, the pathogenesis of metabolic diseases is significantly influenced by the characteristics of fat storage. Adipogenesis or adipocyte hyperplasia allows, to a certain extent, a functional expansion and maintains an adequate level of circulating free fatty acids, while adipocyte hypertrophy seems to be associated with lipotoxicity. Both the primary (SSAT and DSAT) and the secondary (VAT) compartments can undergo cell hypertrophy. When located in the upper body, VAT have a pathogenic potential, whereas the exact impact and metabolic consequences of SAT expansion and particularly SSAT remains controversial. As it is explained by Smith et al., cardiometabolic risks associated with obesity have been largely attributed to increases in VAT. However, more and more investigators have cast doubt on the potential detrimental contribution of SAT to the metabolic syndrome (107).

Visceral Adipose Tissue

VAT is generally assessed using a single CT or MRI slices at a predefined lumber level. Recent studies have shown the validity and the reproducibility of ultrasonography to assess abdominal fat. Using ultrasound, VAT can be measured from the median line between the *linea alba* and one of the lumbar vertebral corpus, L3 or L4 (101, 104, 110) (Figure 9, Figure 10). Other investigators quantify VAT by measuring the distance between the *linea alba* and the anterior wall of the abdominal aorta (101). So far, no specific ranges of VAT measured by ultrasonography has been established by the international scientific community.

Subcutaneous adipose tissue

Various imaging techniques such as CT scan, DEXA scan or ultrasonography offer direct and valid measures of total SAT, usually from the skin to the *linea alba*. The *fascia superficialis*, the anatomical component dividing SSAT and DSAT, is clearly recognized on CT or MRI (100) (Figure 9). A large-scale study by Gradmark et. al has shown a weak potential for ultrasounds to differentiate the deep layer of sat (DSAT) from its superficial layer (SSAT), however the authors recommend its use for SAT and VAT measures (103).

Visceral-to-Subcutaneous adipose tissue ratio

Some studies suggest that beyond the absolute quantity of fat accumulation, the predisposition to stock fat viscerally rather than subcutaneously is more strongly associated with cardiometabolic risk (94). Absolute values of VAT or SAT do not assess the relative distribution of fat layers in the body. A number of studies have proposed that VAT/SAT is an independent predictor of cardiometabolic risk. Most of them have reported a positive association between VAT/SAT and cardiometabolic risk factors (94, 111, 112). However, the relevance of this ratio is still discussed and its accuracy remains uncertain (91).

Chapter 3

3.1 Urban migration

Since 2008 and for the first time in history, more than half of the worldwide population lives in urban areas. In 2005, it was estimated that 35.0% of sub-Saharan Africans were living in urban areas, a rate expected to increase to 62.0% by 2050 (113). In 2009, 32.3% of the Kenyan population were living in urban areas, whereas 67.7% were still living in rural regions (114).

In 2008, a United Nation expert group published a report on urbanization, internal migration and world population distribution (113). According to this group, urban migration in SSA is principally driven by economic reasons. Indeed, there seems to be considerable benefits to live in cities, where are concentrated employment and investment opportunities, and where the average income tends to be higher. Cities also offer a variety of services, including water sanitation, waste management, transport, education and communication. However, as it is highlighted in the report, urban areas and particularly large cities growing in developing countries do not guarantee a better life quality. Urban dwellers are prone to suffer from air pollution, soil contamination or inadequate waste disposal system. Actual disparities among urban dwellers also imply that the poorest generally suffer from the negative aspects of urbanization. Because of housing cost, most of the less fortunate are forced to live in overpopulated slums with deficient sanitation facilities (113).

In 1990, Poulter et. al published one of the first longitudinal observational studies of migrants, following a group of Kenyans from a rural village to the capital, Nairobi. They found that migrants had a significantly higher blood pressure than the control group and, surprisingly, the initial increase of blood pressure occurred very early after the migrants' arrival in the urban area. In average, differences in blood pressure were apparent within a month (44). Another longitudinal observational study of Tanzanian migrants from rural areas moving to Dar es

Salam, the ex-capital, identified significant increases in BMI and fasting lipids in men and women after one year of urban life. The authors also reported a significant decline in vigorous physical activity and an increase in red meat consumption (113, 115).

As it is now generally accepted, SSA populations living in urban areas are at an increased risk of certain non communicable diseases, including obesity, diabetes, dyslipidemia and hypertension, compared to rural dwellers (115). The main determinants thought to underlie these rural-urban differences regarding the mentioned diseases are changes in diet and physical activity (27).

Caloric intake excess and poor diet quality have been associated with urbanization and migration in developing countries, especially among the poorest populations who tend to buy highly refined products (116). In 2008, Unwin et al. evaluated the health of 123 Tanzanian urban migrants after one year of living in the capital, and compared it to their initial rural health baseline. They reported that Tanzanian urban migants were consuming bigger portions per week and had a higher saturated fat intake compared to their initial rural diet. According to the authors, this can be explained by an easier access to fried food, red meat and potatoes in city centers of SSA countries (115). The Kenyan Luo migration study also reported a higher dietary sodium and a lower dietary potassium intake in urban migrant populations of Nairobi (44). Ebrahim et al., who studied urban migration in Indian populations, also found significant changes in diet of newly arrived urban migrants, which included increased fat intake in men and women compared to their rural counterparts (117).

Rural populations in SSA are known to be physically active because of their traditional lifestyle associated with hunting, gathering or farming (116). For example, in Kenya, most rural populations have an agriculture-based economy, with few ethnic groups also living from fishing and pastoralism (118). In 2012, Christensen et al. published a cross-sectionnal study about cardiorespiratory fitness and physical activity level in rural Kenya. They showed that rural East Africans presented a 50% higher level of physical activity compared to a similar European population (119). Other migration studies in Eastern African populations have shown an

important decline in physical activity level following urban migration (44, 115). Urban migration leads to a more sedentary lifestyle; as services become more accessible daily, physical activity declines. Moreover, as it is pointed out by C. Fall in *"Non-industrialised countries and affluence"*: "Exercise as a healthy leisure activity is a recent Western concept; there are often strong climatic, economic and cultural factors discouraging exercise among urban populations in non-industrialised countries as well as migrants from these countries" (116).

Other significant environmental factors might be associated to SSA urban lifestyle, such as tobacco and alcohol consumption. Smoking has been extensively associated with cardiovascular diseases. However, it remains unclear if urban migration in SSA is associated with a higher proportion of smokers. Migration studies have shown divergent results. Unwin et. al found a non-significant increase in tobacco consumption with urban migration in Tanzania in men (7.6% increase), while no woman reported smoking before or after migration (115). On their side, in an extensive cross-sectional household survey comparing rural regions of Nigeria and Kenya to urban areas in Tanzania and Namibia, Hendricks et. al reported a higher prevalence of smokers in rural areas compared to the urban ones (120). Concerning alcohol, urban migration tends to be associated with a rise in alcohol consumption, however to a much smaller extent for women compared to men. Migration studies in Tanzania and India have shown an increased consumption of alcohol in urban migrant men compared to rural men, but drinking remained very rare in urban and rural women (115, 117).

Finally, the migration process in itself is often presented as a risk factor for chronic diseases, mainly because of the severe stress it can induce. Language disparities, loss of social network, and new environmental, social and economic conditions are usual challenges faced by urban migrants. Studies have shown that workers from rural areas settling in foreign cities tend to have low income and to suffer from poverty. They commonly experience social inequality, have a reduced access to health care and lack of social network and family support (121). Social inequality and poor access to health care have been extensively associated with cardiovascular diseases, type 2 diabetes and MS (122).

Chapter 4

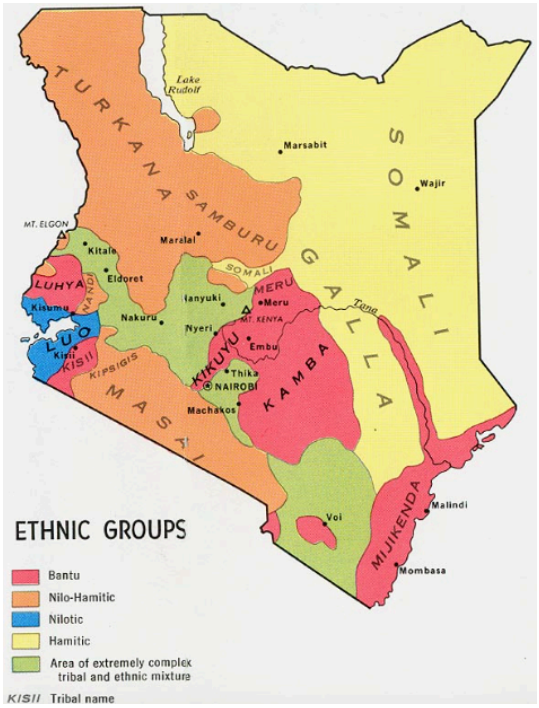
Research Project: The Kenya Diabetes Study

4.1 Population of Kenya

Kenya is a sub-Saharan country and one of the founding members of the East African Community. In 2014, 45 million people were living in its territory (123).

The Kenyan population has always been multiethnic. The country counts more than 70 different tribes, mostly from 3 distinct ethnic origins: Bantu (Kikuyus, Luhyas, Merus, Embus), Nilotic (Masaais, Luo, Kalenjins, Samburu, Pukot) and Cushitic (Ormas, Somali, Boranas). Kambas, Taitas, Gyramias and Swahili are populations of mixed origins (124). Figure 11 shows the distribution of these ethnic groups accross the country.

Figure 11. Ethnic groups distribution in Kenya (41)



In this project, three ethnic groups were specifically chosen for their major lifestyle differences: Luo, Kamba and Maasai. Luo are known to consume mainly maize and fish from their activities on Lake Victoria (118). In 2009, their population was estimated at around 4 million, and most of them were living around Lake Victoria (123). The Kamba population, on the other side, was estimated at 3 million (123) and is known to live of agriculture and to consume mainly grain food (118). The Kamba live in the eastern province of Kenya. The Maasai, with a population estimated at 841 000 in 2009 (123) and mostly living around the Kenyan-Tanzanian border, are known for their alimentation based on milk, blood and meat from their cattle (118). However, these lifestyles are about to change drastically following the rapid urbanization and the demographic transition the country is currently facing.

4.2 The Kenya Diabetes Study

The Kenya Diabetes Study was initiated in August 2004 and data were collected in the country from August 2005 to January 2006. The initial objective was to estimate the prevalence of obesity and the differences in body composition in rural and urban populations in Kenya among the Luo, the Kamba and the Maasai. A paper adressing the prevalence of obesity between all three ethnic groups was published in 2008 (125). Another paper, published in 2012, evaluated the association between anthropometric measures and metabolic profile in a sub-population of overweight Kenyan adults (126).

The second objective of the initial project was to measure daily energy expenditure, cardio-respiratory fitness level, and physical activity patterns, and to assess whether there were differences between rural and urban populations and between the Luo, the Kamba and the Maasai ehtnic groups. In 2012, Christensen et al. published a study describing physical activity energy expenditure and cardio-respiratory fitness in rural Luo, Kamba and Maasai (119).

Finally, the third objective was to estimate the prevalence of diabetes and impaired glucose tolerance between rural and urban populations among the Luo, the Kamba, and the

Maasai, and to determine the risk factors for glucose intolerance. In 2009, a paper describing the prevalence of glucose intolerance in rural and urban Kenyan populations, as well as risk factors for glucose intolerance in Kenya, was published (54). A study specifically looking at the dietary patterns and food intake between the Luo, the Kamba and the Maasai was also written in 2011 (118). Finally, Christensen et al. recently published a study addressing the relationship between cardiometabolic diseases in rural Kenya and non-modifiable risk factors such as sex, age and ethnicity (73).

Objectives

In 2008, Christensen et al. published a relevant study, assessing the prevalence of obesity and differences in body composition between rural and urban Kenyan. They found that the Kenyan cohort presented a relatively high prevalence of obesity and overweight, and that urban residency was associated with higher BMI, VAT and SAT in men and women (125).

In 2012, using the same Kenyan population, Handlos et al. also studied the association between anthropometric parameters and cardio-metabolic profile in a sub-group of 245 overweight Kenyan adults (126). They found a positive and significant association between abdominal obesity (WC and VAT) and a detrimental metabolic profile (plasma lipids, blood pressure, serum insulin and blood glucose). However, it remained unclear if this association would be maintained in a healthy population of Kenyan men and women. Also, the authors did not included VAT/SAT in their study, a parameter that has been recently introduced as a potential anthropometric indicator of CMD in scientific literature. Finally, the authors used a newly created Metabolic Z-score to assess CMD risk factor. This score was defined as follows:

Metabolic Z-score = (plasma lipids + blood pressure + blood glucose + serum insulin) / 4.

Plasma lipids were referring as:

(Fasting plasma LDL-C + plasma triglycerides + plasma total cholesterol – plasma HDL-C) /4

Blood pressure was defined as follows:

(Systolic blood pressure + diastolic blood pressure) / 2

However, MS has rather been extensively used in the scientific literature and it is an eloquent and well accepted reference for CMD global risk.

Thus, this study aimed to assess the association between anthropometric measures of fat accumulation and CMD risk factors in a large, healthy population of rural and urban Kenyan.

Another objective was to evaluate the association between anthropometric measures and MS, and to determine the best parameters to predict MS in a Kenyan population.

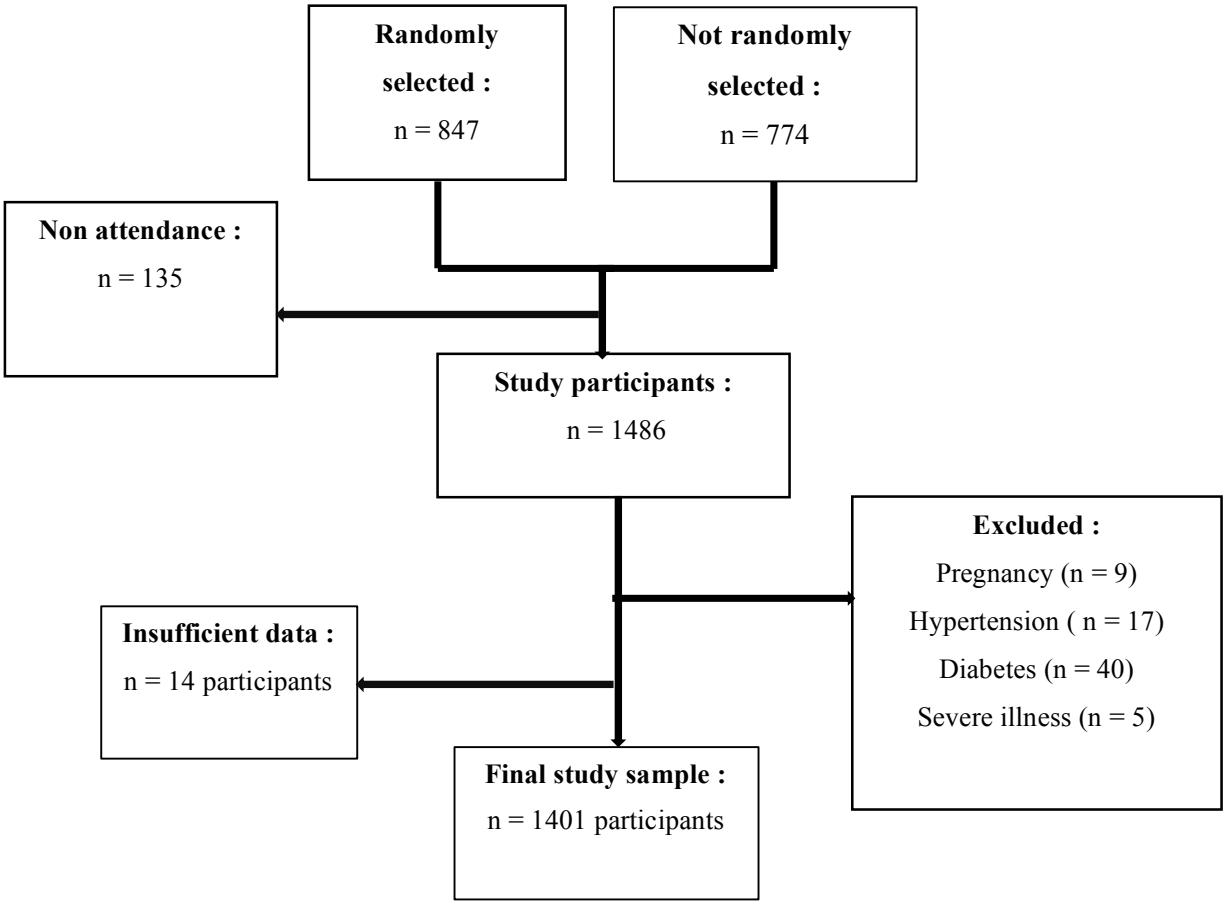
Methodology

Participants

Inclusion criteria were to be ≥17 years old, to be a Luo, a Maasai or a Kamba or being biologically and culturally related to one of these three communities. Ethnicity was self reported, and was defined as having at least one parent being from one of those specific ethnic group. To be considered as an urban subject, a participant had to be living permanently in the urban area for at least two years prior the beginning of the study. Exclusion criteria for this study were pregnancy (9 participants), severe illness, severe mental illness or inability to walk (5 participants). Subjects diagnosed and treated for hypertension (17 participants) or diabetes (40 participants) were excluded of the analysis. A total of 14 participants were also excluded for insufficient data.

A socially associated local coordinator met potential participants from the three atudied geographical areas with a statement describing the project. All interested participants were registered and assigned a specific day to attend at one of the study sites. If a pre-selected participants did not show up, they were substituted by volunteer who showed up at the study site for the purpose of enrollment in the study. In Nairobi, it appeared difficult to include participants who worked, as they needed a letter of invitation and their employer's acceptance to show up at the study site. It was decided to approach participants at their work or at church services. Therefore, they were not randomly selected. In total, 450 rural men, 704 rural women, 131 urban men and 116 urban women were included in the study (a total of 1,401 participants). A flow charts of the sampling procedure is shown in Figure 12.

Figure 12 : Flow chart of registration and participation in rural and urban area



All participants gave written or oral informed consent. The study was given official permission by the National Ethical Review Committee in Kenya and approval by the Danish National Committee on Biomedical Research Ethics in Denmark.

Anthropometry and body composition

Weight was measured with participants only wearing underwear, using a portable high precision scale (Tanita, type BWB-800S MA, Tokyo, Japan). Height was measured twice to the nearest 0.1cm with a portable stadiometer (Meterex II, D97, UNICEF, Copenhagen, Denmark).

Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Waist circumference (WC) was obtained with a body tape, placed between the costal margin and the iliac crest, following a quiet expiration.

Abdominal visceral and subcutaneous fat thickness (cm) was measured by ultrasonography (Aquila Basic Unit, Esaote, Pie Medical Equipment, Masstricht, the Netherlands) with a 3.5/5.0 MHz transducer (Probe Article no. 410638 Curved Array HiD probe R40 Pie Medical Equipment, Maastricht, the Netherlands). A straight line was drawn between the iliac crest and the costal margin. The mid-point of this line on both sides was marked with the subject standing. A straight line was drawn between the left and right midpoint. Three new marks were drawn on this line marking the point for the visceral, i.e. intra-abdominal measurements (centrally just above the navel and 10 cm distally in a straight line to both sides) with the transducer. Measurements of VAT were made from the spine to the *linea alba*, while SAT was measured from the *linea alba* to the skin. Using ultrasonography for measurement of abdominal visceral and subcutaneous fat thickness has been shown to be a reliable method when validated against the gold standard method computed tomography (103, 127). VAT/SAT was calculated from the measure of VAT divided by SAT. Measurements to determine inter or intra-observer variations were not carried out.

Socio-economic level, smoking and alcohol consumption

After informal consent had been obtained, all subjects were interviewed on socio-economic and demographic facts, food intake, nutritional status, physical activity, cardiovascular and metabolic risk factors. Age was taken from their personal ID card, or by their account. If a participant did not know his age, an estimate was made according to personal events. Socio-economic data were collected using a standardized questionnaire [see Annex]. Medical history, including smoking status (yes or no), alcohol and drug intake was obtained and a general clinical examination was also performed. Interviewees were made in

Kishwahili, English or in the local language by a team of investigators and trained local assistants.

Dietary intake

Daily nutrient intake was evaluated using a *24-hour recall* and was assessed by locally trained staff members. Each participant was evaluated twice; first recall was conduced from monday to saturday and the second four days later and always on two different week days. Evaluations used in this project were developed specifically to collect dietary information in rural and urban populations from developing countries (128). As much as possible, recipes were recorded for calculation of nutrient intakes.

Data were entered into the *General Intake Estimation System* (GIES) (National Food Institute, Søborg, Denmark), which helps investigators in the field to detect obvious errors or misunderstanding, allowing them to immediately make corrections. Data from the GIES program were then linked to an *ad-hoc* food composition database, based on the composition of foods Commonly Eaten in East Africa (129), the UK Nutrient Databank (130) and the National Food Composition Tables and The Planning of Satisfactory Diets in Kenya (131).

To evaluate the validity of the dietary intake obtained from the 24-hour recall evaluations, the Goldberg method was used (132). This method is based on tabulated cut-off limit identifying minimum plausible energy intake (EI) below which one could not live a normal life-style, depending on age, sex and body weight. The EI estimated from food databases was divided by age-specific and sex-specific BMI. If the ratio obtained was below a certain cut-off point, it was regarded as physiologically implausible. Based on a methodology proposed by Goldberg et al. (132) (n=1000 to 1400 and 1-4 days of observation), a group level cut-off of 1.53 was applied for this study. Meals were defined in terms of quantity and frequency. Energy contribution was calculated and expressed as EI in calories.

Physical activity energy expenditure and cardio-respiratory fitness

Level of physical activity energy expenditure and cardio-respiratory fitness were obtained from the combination of a uni-axial accelerometer and heart rate sensor (Actiheart, Cambridge Neurotechnology, Cambridge, UK). The participants were asked to perform an 8-minutes step test on a 21.5 cm high step and two minutes of post-step recovery. The stepping frequency was 15 step cycles (body lifts) per minute in the first minute, after which it increased up to 33 steps per minute at the end. Heart rate was measured for at least 90 seconds of recovery. Individual heart rate in response to the step test was used to estimate the cardio-respiratory fitness level (mlO2 · min-1· kg-1), by extrapolating age-predicted maximal heart rate (133) and adding an estimate of metabolic rate, using Oxford equation for basal metabolic rate (BMR) (134). Participants had to perform at least 4 minutes of step test to be included in this analysis.

Subsequently, each participant was asked to wear an Actiheart monitor continuously over the five days; the recorded data were included in the analysis if their monitors contributed for at least 24-hours of valid activity data. Mean heart rate (HR) above sleep and physical activity energy expenditure were measured. Resting metabolite rate (RMR) was estimated from a formula using weight, age, sex and height (134). Torso accelerations were caught by the means of the uni-axial accelerometer and combined with calibrated HR into activities intensity "time series". Time distribution of activity intensity was converted to units of metabolic equivalent of task (MET) (kcal . kg^{-1}. h^{-1}) by using the mean of RMR (135). Sedentary behavior was then established at an intensity of less than 1.5 MET. Due to the extremely low percentage of time when participants were recording high intensity activity (>6 METS), it was decided to combine moderate (3 to 6 METS) and vigorous activities and defined them as intensity higher than 3 METS.

Hemodynamics

Systolic and diastolic blood pressure was obtained twice in sitting position from a full-automatic device (Omron M6, HEM-7001-E, Kyoto, Japan) while heart rate (HR) was measured

twice in the upper arm of the participant (cubital fossa). If systolic or diastolic blood pressure had a difference bigger than 5 mmHg, a third measurement was made. Mean values of all measures were used in our statistical analysis.

Blood samples

Trained lab technicians collected blood samples between 7:30 and 11:00 am from participants following an overnight fast ≥8 hours. On the same day they were collected, samples were sent at the nearest facility center in Kenya. Blood was centrifuged and stocked in cryotubes at -20.0 degree Celsius . Later on, they were sent to Centre for Public Health Research, KEMRI (Nairobi, Kenya) and kept at -80° Celsius, before being shipped to Steno Diabetes Center in Copenhagen (Denmark) for further analyses.

Lipid profile analysis

Using an enzymatic colorimetric, plasma triglyceride (TG) was measured by the GPO-PAP method (enzymatic test for the qualitative detection of triglycerides in human plasma) (136) while total cholesterol (TC) was established using a CHOD-PAP method (enzymatic test for the qualitative detection of total cholesterol in human plasma) (137) with a Hitachi 912 System (Roche Diagnostics GmbH, Mannheim, Germany). A homogeny enzymatic colorimetric test was used to measure plasma HDL-C isolated by precipitation of apo B containing lipoproteins with dextran sulfate. Very low-density-lipoprotein was calculated from the following equation: VLDL-C = TG/2.2 (138) from which low-density lipoprotein cholesterol (LDL-C) was also calculated (LDL-C = TC - VLDL-C -HDL-C).

Oral glucose tolerance test

Following an overnight fast a venous blood sample was collected in between 7:30 and 11.00 am and immediately analyzed. All participants were asked to undergo a standard 75g oral glucose tolerance test (OGTT) except those with known diabetes and a fasting venous glucose level higher than 11.1 mmol/l equivalent to diabetes diagnosis at 2-h (WHO 2006 criteria) (50).

Glucose levels in fasting and 2-hours samples were determined using the Glucose dehydrogenase method, by haemolysation and deproteinisation on a HemoCue B-Glucose 201+ device (HemoCue AB, Ängelholm, Sweden) with 5 µl of blood. Participants known to have diabetes were not excluded from the initial Kenya Diabetes Study. However, following the specific objectives of the present research project (to assess the association between anthropometric measures and CMD risk factors in a healthy population of rural and urban Kenyan), it was decided to exclude subjects known to have diabetes or to take antidiabetic medication prior to the study.

The remaining blood samples were kept on ice in local field facilities; serum was centrifuged and then sent to KEMRI in Nairobi for subsequent analysis. Fasting serum insulin was measured by a 1235 AutoDELFIA automatic immunoassay system, using a time-resolved fluoro-immunoassay technique (kit no. BO80-101, PerkinElmer Life and Analytical Sciences, Wallac Oy, Turku, Finland). Insulin resistance was calculated with the homoeostasis model assessment of insulin resistance (HOMA-IR), following the equation given by Mattews and al.: fasting serum insulin (µU/ml) × fasting plasma glucose (mmol l-1)/22.5 (139). HOMA-IR has been shown to be a robust tool to assess insulin resistance (140, 141).

Metabolic syndrome

Various expert groups have developed clinical criteria to define the MS. A widely accepted definition was published in 2009 by the IDF, based on a consensus. Central obesity, hyperglycemia , dyslipidaemia and hypertension were accepted as the principal components of the MS (1).

Due to the paucity of data, IDF criteria use identical cut-off for women of all ethnic origins. WC has been adapted for men of Asian origin, however few data are available from other non-Caucasoid populations. European male recommendations are applied for men from sub-Saharan Africa, the Middle East and the Eastern Mediteraneen region.

In this study, MS was diagnosed if one presented at least 3 out of those 5 following criteria :

1.Fasting triglycerides ≥1.70 mmol/L

2.SBP ≥130 mmHg and/or DBP ≥85 mmHg

3.Fasting plasma glucose ≥5.6 mmol/L,

4.HDL-Cholesterol ≤1.03 mmol/L for men and ≤ 1.29 mmol/L for women

5. WC ≥ 94 cm for men and ≥ 80 cm for women

Statistical analysis

Sample size

All statistical analyses were done with Stata 12.0 Intercooled version (Stata Corp, College Station, USA). Analyses were stratified for sex (male and female) and urbanity (rural and urban). Continuous variables were tested for normality using a graphic method, displaying distribution of variable. To consider a variable normally distributed, 95% of the values had to lie within 1.96 standard deviation of its mean. Skewed data were log transformed prior to analysis. In this study, SAT, VAT/SAT ratio, triglycerides level, fasting serum insulin, HOMA-IR and 2-houres glucose were log transformed, while all other continuous variables were normally distributed.

T-test was used to compare means of continuous variable in between rural and urban groups, stratified for men and women. Chi-Square test was used to test for differences in proportion of smoking, alcohol consumption, hypertriglyceridemia, hypertension, abdominal obesity, elevated plasma glucose and reduced HDL-C. P-value ≤ 0.05 were considered statistically significant.

Associations between anthropometric variables and lipid profile, glycaemic profile and blood pressure were assessed through multivariate linear analysis, stratified by sex. The established model was adjusted for cofounders: age, smoking status, alcohol consumption, daily total energy intake, fitness level and urban residence. Associations between anthropometric variables and MS were assessed through multivariate logistic analysis, stratified by sex. The established model was also adjusted for cofounders: age, smoking status, alcohol consumption, daily total energy intake, fitness level and urban residence. All results are presented as β-coefficient and P-value. In both models, homoscedasticity was tested using a graphical method, plotting residuals versus predicted values. Multicollinearity was also checked using a particular command in Stata 12.0, the “Variance inflation factor”.

Manuscript

ANTHROPOMETRIC MEASURES AND THEIR ASSOCIATION WITH CARDIO-METABOLIC RISK FACTORS AND THE METABOLIC SYNDROME IN SUB-SAHARAN RURAL AND URBAN POPULATIONS

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INTRODUCTION

According to the World Health Organization (WHO), 2.8 millions of people across the globe die each year due to overweight or obesity (WHO, 2010). Cardio-metabolic disorders (CMD) such as type 2 diabetes, dyslipidemia, hyperuricemia and cardiovascular diseases have been extensively associated with obesity (Stern, 1995). In sub-Saharan Africa (SSA), these diseases are rising rapidly and are projected to become the leading cause of death by 2030, exceeding maternal, perinatal, infectious and nutritional deaths combined (WHO, 2010). Indeed, the data suggests that by this time, more than 27% of SSA adults would have a body mass index (BMI) $\geq$25 kg/m^2 (WHO, 2010). Already, an estimated 34.9% of adult Kenyans residing in urban areas present with the metabolic syndrome (MS), a unique cluster of closely related cardiovascular risk factors (Kaduka et al., 2012).

The association between anthropometric indicators of fat accumulation and cardio-metabolic risk factors as well as the diagnosis of MS is understudied and still poorly understood in SSA rural and urban populations. In 2015, 13.2% of Kenyan males and 24.9% of Kenyan females were considered as overweight (WHO STEPS non communicable disease risk factors surveillance, 2015). The rising number of Kenyans affected by fat accumulation and obesity might have a detrimental impact on this population's cardio-metabolic health. It becomes essential to understand the relation linking fat accumulation and CMD in black African population, in order to develop practical screening tools. However, it remains unclear which of the available anthropometric indices of fat accumulation has the strongest association with CMD and MS. Recent studies suggest that fat accumulation might differ between ethnic groups, which is reflected in their cardio-metabolic risk profile (Després et al., 2000; Goedecke et al., 2010; Jørgensen & Christensen, 2008). For example, Goedecke et al. reported significant ethnic differences between black and white South African women in fat storage around the gluteal region or in the subcutaneous layer of the abdomen, as well as in the visceral adipose tissue (Goedecke et al., 2010). Environmental factors such as physical activity, energy intake or level of urbanization could partly explain these differences (Faurholt-Jepsen et al., 2014; Goedecke et al., 2010; Jørgensen & Christensen, 2008). A recent cross-sectional study of rural and urban communities from Cameroon reported a strong association

between abdominal obesity and MS components (Fezeu et al., 2010). However, the authors only included waist circumference (WC) as a surrogate of abdominal obesity. When it comes to the use of anthropometric measurements to evaluate obesity in SSA countries, very few studies have included quantitative measurements of abdominal fat distribution, such as visceral and subcutaneous adipose tissue (VAT and SAT) or visceral to subcutaneous adipose tissue ratio (VAT/SAT). These measures have been described as strong predictors of CMD, even above and beyond other anthropometric measurements (Kaess et al., 2012). The anatomic location of excess body fat has an impact of the risk of CMD. VAT, which is located more deeply in the abdomen, seems to be more pathogenic than SAT (Kaess et al., 2012). As VAT and SAT have been shown to be differentially associated to CMD risk factors, to elucidate their respective correlation with CMD in different ethnic groups, such as black SSA populations is of clinical interest.

The objective of this study was to compare the association between anthropometric features of body composition (including VAT, SAT and VAT/SAT) and risk factors of CMD, as well as components of MS in a large sample of Kenyan rural and urban individuals.

MATERIALS AND METHOD

Study population

A cross-sectional rural-urban study was carried out comparing three distinct populations, i.e. the Luo, Kamba, and Maasai in rural areas from Kenya, as well as an ethnically mixed population in Nairobi, the capital of Kenya.

Inclusion criteria were: ≥17 years old, being from Luo, Kamba, or Maasai origin or being biologically and culturally related to one of these three communities. To be considered as an urban subject, a participant had to be living permanently in the urban area for at least two years prior to beginning of the study. Exclusion criteria were pregnancy (9 participants), severe illness such as malaria, hepatitis, and severe mental illness or inability to walk

unassisted (5 participants in total). Participants diagnosed and treated for hypertension or diabetes were also excluded from the analysis (57 participants). In total, 1,401 participants (450 rural men, 704 rural women, 131 urban men and 116 urban women) were included in the study. All participants gave written or oral informed consent. The study was approved by the National Ethical Review Committee in Kenya and by the Danish National Committee on Biomedical Research Ethics in Denmark.

Anthropometric measures

Anthropometric measures (height, weight and waist circumference (WC) were measured by trained assistants, as described elsewhere (Christensen et al., 2008). Body mass index (BMI, kg/m^2) was calculated. VAT and SAT (cm) were measured by ultrasonography (Aquila Basic Unit, Esaote, Pie Medical Equipment, Masstricht, the Netherlands) with a 3.5/5.0 MHz transducer (Probe Article no. 410638 Curved Array HiD probe R40 Pie Medical Equipment, Maastricht, the Netherlands). VAT measurements were made from the spine to the *linea alba,* whereas SAT was measured from the abdominal muscles to the skin, with no pressure on the skin. Using ultrasonography for measurement of VAT and SAT thickness has been shown to be a reliable method when validated against the gold standard method of computed tomography (Gradmark et al., 2010; Soo et al., 2004; Stolk et al., 2001). VAT/SAT was calculated from VAT divided by SAT. Measurements to determine inter or intra-observer variations were not carried out.

Lifestyle, diet and fitness

All subjects were interviewed on socio-economic and demographic facts and food intake. Dietary patterns were assessed from number of meals and snacks per day, and their contribution to energy intake (EI) was calculated. The method has been described elsewhere (Hansen et al., 2011). Physical activity and cardio-respiratory fitness measurements were carried out using a combined uniaxial accelerometer and heart rate sensor (Actiheart, CamNtech Ltd, Cambridge, UK). Further methodological details can be found elsewhere (Christensen et al.,

2012). Medical history including smoking status, alcohol consumption and drug intake was obtained by a medical officer. A general clinical examination was performed. All interviews were done in Kiswahili, English or in the local language.

Blood pressure

For each participant, systolic and diastolic blood pressure (SBP and DBP) (mmHg) were measured twice in the right upper arm, after being seated at least 15 minutes, using a full-automatic device (Omron M6, HEM-7001-E, Kyoto, Japan).

Blood sample

Following an overnight fast, a venous blood sample was collected and analyzed to determine fasting blood glucose (FBG), fasting serum insulin and serum lipids (triglycerides, total cholesterol, LDL-C, HDL-C). All participants were asked to undergo a standard 75 g oral glucose tolerance test (OGTT) (WHO 1999 criteria) (WHO, 1999). Homoeostasis model assessment of insulin resistance (HOMA-IR) was calculated as described by Matthews and co-workers: fasting serum insulin (μU/ml) × fasting glucose (mmol/L)/22.5 (Matthews et al., 1985) .

Metabolic syndrome (MS)

MS was defined according to the 2009 International Diabetes Federation consensus statement criteria, e.g. the presence of three out of the five following risk factors: WC ≥94 cm for men or ≥80 cm for women, fasting triglycerides ≥1.70 mmol/L, SBP ≥130 mmHg and/or DBP ≥85 mmHg, fasting plasma glucose ≥5.6 mmol/L, or HDL cholesterol ≤1.03 mmol/L for men and ≤1.29 mmol/L for women (Alberti et al., 2009).

Statistical Analysis

All statistical analyses were done with Stata 12.0 Intercooled version (Stata Corp, College Station, USA). Analyses were stratified for sex and residency and P ≤0.05 was regarded as statistically significant. Categorical variables are summarized as frequency (n (%)). Continuous normally distributed variables are expressed as mean and $IC_{95\%}$, whereas continuous variables with a skewed distribution are expressed as geometric mean and $IC_{95\%}$. These variables were logarithmically transformed prior to analysis.

Student's t-test was used to compare differences in means, and the Chi-square test was used to test for differences in proportion.

In order to measure the strength of association between anthropometric variables and cardio-metabolic parameters, β-coefficients were assessed using a model of multiple linear regression analysis, stratified by sex and adjusted for age, smoking status, alcohol consumption, daily total energy intake (kJ), cardio-respiratory fitness level (mL O_2 $kg^{-1}min^{-1}$) and urban residence, with a significance level of P ≤ 0.05. To compare the association between anthropometric measures of fat distribution and MS, β-coefficients were computed using a multivariate logistic regression analysis model, diagnosis of MS being the dichotomous dependant variable. This model was also stratified for sex and adjusted for smoking status, alcohol consumption, daily total energy intake (kJ), cardio-respiratory fitness level (mL O_2 kg^{-1} min^{-1}) and urban residence.

RESULTS

Characteristics of the population

Characteristics of the study population, stratified by sex and residency are presented in **Table 1**. Mean values in both rural and urban participants were normal in all anthropometric measures, except for urban women who had mean BMI superior to normal (26.9 kg/m^2) and a mean WC higher than MS cut-off (83.1 cm) (Alberti et al., 2009). Compared with rural, urban men and women had higher mean values of weight, BMI, WC, SAT and

VAT/SAT. Despite a greater daily caloric intake, rural men had a higher cardiorespiratory fitness level compared to urban. Rural women also had a greater daily caloric intake, but there was no significant difference between rural and urban women's cardiorespiratory fitness level.

Cardio-metabolic risk factors are presented in **Table 2**. Mean values of lipid levels, glycemic profile and blood pressure were normal in all subgroups, except for rural women who had a mean HDL-C level lower than MS cut-off. Urban participants for both men and women presented higher triglycerides, total and LDL-C levels ($P<0.05$) compared to rural. Urbans in both men and women had a higher level of FPG, glucose at 120-min, fasting plasma insulin and HOMA-IR ($P<0.05$). They also had a significantly higher mean value of SBP ($P<0.05$ in men and women).

There was a significant rural-urban difference in prevalence of MS and all its components. A total of 6.6% of rural men presented with MS, compared to 15.0% of urban men ($P<0.05$), whereas 9.9% of rural women presented with MS compared to 30.1% in the urban group ($P<0.05$). Abdominal obesity was identified in 8.2% and 31.0% of rural men and women, respectively, but this prevalence was twice as high in the urban group for both men and women. Hypertriglyceridemia, hypertension and hyperglycemia was found in a significantly higher proportion of urban participants in men and women ($P<0.05$ for both). On the other hand, HDL-C levels were lower in the rural groups for men and women and a significantly higher proportion of rural participants met the HDL-C abnormality criteria compared to urban.

Association between CMD risk factors and anthropometric measures

Associations between anthropometric features and cardio-metabolic risk parameters are shown in **Table 3** and **Table 4**. In both men and women, anthropometric variables remained strong indicators of cardio-metabolic risk factors.

In men and women, triglycerides, LDL-C and total cholesterol significantly increased with all anthropometric features ($P<0.05$). In men, HDL-C significantly decreased with weight (-0.0035 mmol/L per kg), BMI (-0.019 mmol/L per kg/m^2), WC (-0.0037 mmol/L per cm) and VAT (-0.033 mmol/L per cm), but was not associated with either SAT or VAT/SAT. Except for WC (-0.0034 mmol/l per cm) and VAT (-0.020 mmol/L per cm), HDL-C was not associated with any anthropometric features in women.

Fasting serum insulin and HOMA-IR significantly increased with all anthropometric measures in both men and women. For each unit of VAT (cm), HOMA-IR increased by 15.0% in men (β-coefficient = 0.14, $P<0.05$) and of 13.8% in women (β-coefficient = 0.13, $P<0.05$) (**Appendix** 1.2). HOMA-IR was also significantly associated with SAT in men and women (β-coefficient = 0.36 in men and 0.32 in women, $P<0.05$ respectively). Systolic and diastolic blood pressure also increased with all anthropometric parameters. For each unit of VAT, systolic blood pressure increased by 1.33 mmHg in men and 1.87 mmHg in women.

Association between MS and anthropometric measures

The β-coefficients from the multivariate logistic regression analysis between anthropometric measures and MS are presented in **Table 5** and **Table 6**. All anthropometrics features of fat accumulation in both men and women were significantly associated with an elevated risk of presenting the MS (at least three criteria). According to our analysis, the β-coefficients between VAT and MS were 1.00 ± 0.19 in men and 0.56 ± 0.11 in women. The β-coefficients between SAT and MS were the highest for both men (1.45 ± 0.32) and women (0.88 ± 0.14).

DISCUSSION

This is one of few studies addressing the association between features of fat accumulation, cardio-metabolic risk factors and MS characterizing abdominal fat by using ultrasound scanning technique in a sub-Saharan population from Kenya.

We showed that both urban men and women had greater weight, BMI, WC, SAT and VAT/SAT, but similar mean values of VAT when compared with rural populations. Among all three ethnic groups included in this study, Maasai participants have been previously described as individuals with greater VAT, both in absolute and relative terms (Christensen et al., 2008). The higher proportion of Maasai with higher VAT levels in rural men and women could explain the relatively high overall values of VAT found in rural populations, and the absence of differences between rural and urban populations.

As expected, rural men and women had lower triglycerides and LDL-C levels compared with urban, while HDL-C levels was significantly lower in rural populations. Rather than being an indicator of increasing CMD risk, these results might reflect the low total cholesterol in our rural populations, a phenomenon which has been reported in previous studies (Goedecke et al., 2010). On the other hand, total cholesterol levels measured in our rural and urban populations were higher than those reported in comparable studies made in SSA (Adediran, Adebayo, & Akintunde, 2013; Ntandou, Delisle, Agueh, & Fayomi, 2009). Other factors such as diet, physical activity level and ethnic polymorphism could partly explain this rural-urban variance.

In both men and women, triglycerides, total cholesterol and LDL-C levels were all positively associated with anthropometric features. Dyslipidemia being one of the most common metabolic consequences of fat accumulation, similar results had been pointed out by other studies made in SSA populations (Adediran et al., 2013; Fezeu et al., 2010). Our analysis did not show any association between HDL-C and SAT or VAT/SAT,

neither in men nor in women. Moreover, in women there was no significant association between HDL-C and weight or BMI. Similar lack of associations has been reported in studies made in black African populations (Delisle, Ntandou, Sodjinou, Couillard, & Després, 2013; Goedecke et al., 2010), but a causality remains to be elucidated. The coexistence of undernutrition along with overweight or obesity found in SSA populations could partly explain the phenomenon, as both normal weight and overweight states have been associated with a low level of HDL-C (Delisle et al., 2013). As it has been suggested in previous studies, hypocaloric diets, micronutrient deficiency (Delisle et al., 2013) and low protein intake (Goedecke et al., 2010) usually found in underweight individuals could be associated with low HDL-C levels and partly explain the general lack of association found between HDL-C and anthropometric measures of body composition.

In men and women, an increase in VAT was positively associated with the lipid profile, HOMA-IR, fasting plasma insulin and blood pressures. Several studies have previously described the strong association between VAT and CMD risk factors, especially with triglycerides and HOMA-IR (Christensen et al., 2014; Després et al., 1989). As VAT has been shown to have higher lipolytic activity compared to SAT (Ostman J., 1979), it would increase free fatty acid levels in the portal region and induce VLDL-TG synthesis and gluconeogenesis (Matsuzawa et al., 1995), which decreases insulin extraction by the liver and can lead to a state of hyperinsulinemia. Hyperinsulinemia would impair insulin-stimulated glucose utilization and glycogen synthesis in the peripheral skeletal muscles, contributing to insulin resistance, known to be a central element in MS (Després et al., 1989). On the other hand, we were also able to show significant associations between SAT and CMD risk factors. As previously suggested, SAT may also play a role in the pathophysiology of MS (Smith et al., 2001). Its deep layer, which is usually included in the measurement of SAT, has been correlated to insulin resistance (Misra et al., 1997) and MS (Jennings, Lambert, Collins, Levitt, & Goedecke, 2009).

MS prevalence in rural men and women was found to be 6.6% and 9.9%, respectively. In comparison, 15.0% in urban men and 30.1% of urban women were identified with MS, which is lower than the prevalence rates previously reported in studies from SSA populations (Kaduka et al., 2012; Kelliny, William, Riesen, Paccaud, & Bovet, 2008), but not in all (Jennings et al., 2009). In rural men and women and urban men, the low level of HDL-C was the most prevalent component of MS, whereas WC was the most frequent feature of MS to be found in urban women (66.4%). Our analysis showed positive associations between all anthropometric features of fat accumulation and the diagnosis of MS, except for VAT/SAT. These results suggest the potential contribution of fat accumulation in MS pathogenesis. Measures of abdominal fat, especially VAT and SAT, showed the strongest association with MS, which is consistent with previous studies made on MS in SSA (Fezeu et al., 2010; Jennings et al., 2009; Ntandou et al., 2009). This result was not concordant with previous studies, which have demonstrated that VAT is usually a stronger independent predictor of CMD (Bays et al., 2008; Christensen et al., 2008; Despres et al., 1989; Miyazaki & DeFronzo, 2009) . However, few studies have been carried out in SSA populations, but rather in Caucasian populations. This result could also be explained by our methodology, as we did not anatomically separate SAT in its deep SAT and superficial SAT. While superficial SAT adipocytes are known to be organized, small and ovoid, the deep SAT layer contains larger lobules, is less organized and widely spaced (Marinou et al., 2014). Several studies have shown that deep SAT has an important role in the pathophysiology of obesity complications, and especially in insulin resistance (Abate et al., 1995; Misra et al., 1997; Smith et al., 2001). Other studies have suggested that because SAT is a larger compartment than VAT, it might have a significant impact on the development of insulin resistance (Patel & Abate, 2013). Nevertheless, further research is needed to better understand the role of SAT and VAT in the pathophysiology of obesity CMD in black African populations.

The major strength of this study relies on the fact that our cohort consists of urban as well as rural populations of adult Kenyans, with presumably very few participants having concomitant diseases and none taking medication for cardiovascular or metabolic disorders. However, some limitations should be acknowledged. This study had a cross-sectional design, which does not enable us to conclude on the causality between fat accumulation and CMD. Also, the study population was based on a convenience sample as the intended random selection from village meetings in the rural areas and the inclusion of biological urban family members was only partly successful.

CONCLUSION

In conclusion, this study showed a higher prevalence of MS and other cardio-metabolic risk factors in urban Kenyans compared to rural Kenyan populations. Anthropometric measures of fat accumulation were all associated with MS and its components, except for low HDL-C level. VAT appeared as the best predictor of lipid levels, serum insulin, HOMA-IR and blood pressure, whereas SAT had the highest association with MS diagnosis. In epidemiological studies, ultrasound scanning of VAT and SAT should be considered as a valid tool to estimate abdominal fat distribution in SSA populations, as it appears as a good indicator of cardio-metabolic health as well as having high cost-benefit value. Considering the growing epidemic of obesity and cardio-metabolic disorders in SSA countries, it is of clinical interest to better understand the relationship between these conditions and fat distribution, in order to improve monitoring of CMD risk factors in these vulnerable populations.

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The authors' contributions were as follows: D.L.C. participated in data collection. F.L.T. drafted the first version of the manuscript and performed statistical analysis. All authors contributed to the discussion and data interpretation and reviewed the article for the intellectual content. All authors have read and approved the final version of the manuscript.

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TABLES

Table 1. Clinical and biological characteristics of 1,401 adult Kenyans, by place of residence and sex

	Men			Women		
	Rural	**Urban**	**P-value[2]**	**Rural**	**Urban**	**P-value[2]**
Participants (n%)	450 (32.4)	131 (9.4)		704 (50.6)	116 (8.4)	
Ethnic groups						
Luo (n (%))	175 (38.8)	51 (38.9)	**0.40**	219 (30.9)	19 (16.4)	**<0.05**
Kamba (n (%))	104 (23.1)	73 (55.7)	**<0.05**	297 (42.0)	97 (83.6)	**<0.05**
Masaai (n(%))	171 (38.0)	7 (5.34)	**<0.05**	192 (27.2)	0	**<0.05**
Age (years)	39.6 (38.5 ; 40.6)	33.7 (32.0 ; 35.6)	**<0.05**	37.9 (37.2 ; 38.7)	40.0 (38.0 ; 42.1)	**<0.05**
Smoking (n (%))	90 (20.6)	15 (11.0)	**<0.05**	38 (5.6)	3 (2.6)	**0.18**
Alcohol (n (%))	105 (24.1)	39 (28.7)	**0.30**	0	0	
Anthropometric measures						
Weight (kg)	62.0 (60.8 ; 63.2)	66.2(64.1 ; 68.2)	**<0.05**	56.9 (56.0 ; 57.7)	66.8 (63.7 ; 70.0)	**<0.05**
BMI (kg/m^2)	20.8 (20.4 ; 21.2)	23.0 (22.0 ; 23.9)	**<0.05**	22.2 (21.9 ; 22.5)	26.9 (25.9 ; 27.9)	**<0.05**
WC (cm)	78.67 (77.6 ; 79.8)	83.4 (80.6 ; 86.1)	**<0.05**	77.6 (76.8 ; 78.3)	83.1 (79.4 ; 86.8)	**<0.05**
VAT (cm)	6.2 (6.0 ; 6.4)	6.1 (5.8 ; 6.4)	**0.57**	5.6 (5.4 ; 5.7)	5.4 (5.1 ; 5.8)	**0.10**
SAT[1](cm)	0.7 (0.7 ; 0.7)	1.1 (1.0 ; 1.2)	**<0.05**	1.7 (1.6 ; 1.8)	2.5 (2.1 ; 2.7)	**<0.05**
VAT/SAT[1]	8.6 (8.1 ; 9.1)	5.6 (5.1 ; 6.2)	**<0.05**	4.1 (3.9 ; 4.3)	2.2 (2.0 ; 2.4)	**<0.05**
Nutrition						
Daily energy intake (kj)	8404.2 (8150.5 ; 8657.9)	7256.0 (6837.7 ; 7674.9)	**<0.05**	6661.3 (6099.6 ; 6897.7)	6498.7(6099.6 ; 6897.8)	**0.5**
Protein intake (g)	67.7 (65.1 ; 70.3)	53.8 (49.7 ; 57.9)	**<0.05**	50.1 (48.9 ; 52.01)	45.0 (41.6 ; 48.5)	**<0.05**
Carbonhydrate intake (g)	332.1 (320.8 ; 343.2)	297.8 (279.7 ; 316.1)	**<0.05**	287.2 (253.2 ; 290.3)	271.4 (253.2 ; 290.3)	**0.15**
Fat intake (g)	51.8 (28.9 ; 54.7)	43.6 (29.3 ; 47.8)	**<0.05**	33.6 (32.09 ; 35.1)	38.0 (34.3 ; 41.6)	**<0.05**
Fitness						
Cardio-respiratory fitness [1] ($ml\ O2\ kg^{-1}min^{-1}$)	42.5 (41.6 ; 43.3)	39.5 (37.7 ; 41.3)	**<0.05**	39.8 (39.2 ; 40.5)	40.1 (38.3 ; 41.9)	**0.74**
Time spent <1.5 MET (%)	58.5 (57.6 ; 59.5)	60.6 (57.5 ; 63.5)	**0.15**	58.3 (57.5 ; 59.1)	60.1 (55.4 ; 64.5)	**0.49**
Time spent >3 METs (%)	12.6 (11.9 ; 13.2)	3.4(2.4 ; 4.3)	**<0.05**	10.5 (10.0 ; 11.0)	1.8 (0.7 ; 2.9)	**<0.05**

Data as mean ($IC_{95\%}$)

[1] Geometric means ($IC_{95\%}$) [2] P-value for rural-urban differences

Smoking: Smoking status, Alcohol: Alcohol intake status, BMI: Body mass index, WC: Waist circumference, VAT: visceral adipose tissue, SAT: subcutaneous adipose visceral tissue, VAT/SAT: Visceral-to-subcutaneous adipose tissue ratio

Table 2. Cardio-metabolic profile of 1,401 adult Kenyans, by place of residence and gender

	Men			Women		
	Rural	**Urban**	**P value[2]**	**Rural**	**Urban**	**P value[2]**
Lipids						
Total cholesterol (mmol/l)	3.8 (3.7 ; 3.9)	4.4 (4.2 ; 4.5)	**<0.05**	3.7 (3.6 ; 3.8)	4.6 (4.4 ; 4.8)	**<0.05**
LDL-Cholesterol (mmol/l)	2.3 (2.2 ; 2.4)	2.7 (2.5 ; 2.8)	**<0.05**	2.2 (2.2 ; 2.3)	2.9 (2.7 ; 3.0)	**<0.05**
HDL-Cholesterol (mmol/l)	1.1 (1.0 ; 1.1)	1.2 (1.1 ; 1.3)	**<0.05**	1.1 (1.1 ; 1.1)	1.2 (1.2 ; 1.3)	**<0.05**
Triglycerides[1] (mmol/l)	0.9 (0.9; 1.0)	1.0 (0.9 ; 1.1)	**0.06**	0.9 (0.8 ; 0.9)	1.0 (1.0 ; 1.1)	**<0.05**
Glucose Metabolism						
Fasting venous glucose (mmol/l)	4.4 (4.3 ; 4.5)	5.0 (4.6 ; 5.4)	**<0.05**	4.5 (4.4 ; 4.6)	5.1 (4.7 ; 5.5)	**<0.05**
Glucose 120 min [1] (mmol/l)	4.9 (4.7 ; 5.2)	5.8 (5.3 ; 6.2)	**<0.05**	5.5 (5.3 ; 5.7)	6.0 (5.5 ; 6.5)	**<0.05**
Fasting plasma insulin[1] (pmol/l)	18.4 (21.8 ; 26.4)	25.2 (22.6 ; 28.2)	**<0.05**	24.0 (22.8 ; 25.1)	36.0 (32.2 ; 40.3)	**<0.05**
HOMA-IR[1] (mmol/l)	0.51(0.47 ; 0.55)	0.76 (0.67 ; 0.86)	**<0.05**	0.7(0.7 ; 0.7)	1.1 (0.9 ; 1.3)	**<0.05**
Blood pressure						
SBP (mmHg)	121.7 (120.2 ; 123. 6)	127.1 (124.4 ; 129.8)	**<0.05**	116.7 (115.4 ; 117. 7)	122.0 (119.2 ; 124.8)	**<0.05**
DBP (mmHg)	74.6 (73.7 ; 75.5)	75.3 (73.2 ; 77.4)	**0.50**	73.0 (72.3 ; 73.7)	74.9 (73.0 ; 76.8)	**0.06**
Metabolic Syndrome components [3]						
MS (n (%))	29 (6.6)	20 (15.0)	**<0.05**	70 (9.9)	35 (30.1)	**<0.05**
Hypertriglyceridemia (n (%))	35 (8.01)	22 (15.94)	**<0.05**	31 (4.60)	16 (13.22)	**<0.05**
Abdominal obesity (n (%))	37 (8.22)	23 (19.18)	**<0.05**	219 (30.98)	83 (66.4)	**<0.05**
Hypertension (n (%))	55 (12.30)	34 (23.61)	**<0.05**	44 (6.23)	15 (12.71)	**<0.05**
Elevated fasting glucose (n (%))	15 (3.33)	18 (12.33)	**<0.05**	20 (2.82)	14 (11.20)	**<0.05**
Reduced HDL-C (n (%))	220 (50.34)	46 (33.33)	**<0.05**	516 (76.56)	73 (60.33)	**<0.05**

Data as mean (IC95%)

[1] Geometric means [2] P-value for rural-ruban differences [3] Metabolic syndrome components according to IDF 2009 definition : Hypertriglyceridemia : fasting triglycerides ≥ 1.70 mmol/L , Abdominal obesity: WC ≥ 94 cm for men or ≥ 80 cm for women

Hypertension : SBP ≥ 130 mmHg and/or DBP ≥85 mmHg, Elevated fasting glucose : fasting glucose ≥5.6 mmol/L, Reduced HDL-C : reduced HDL cholesterol ≤ 1.0 mmol/L for men and ≤ 1.3 mmol/L for women, HOMA-IR : Homeostatic model assessment for insulin resistance, SBP : systolic blood pressure, DBP : diastolic blood pressure, MS : metabolic syndrome

Table 3. Cardio-metabolic parameters prediction by anthropometric features in 581 rural and urban Kenyan men

	Weight (kg)		BMI (kg/m^2)		WC (cm)		VAT (cm)		SAT [1] (cm)		VAT/SAT[1]	
	β-coeff	P-value	**β-coeff**	P-value	**β-coeff**	P-value	**β-coeff**	P-value	**β-coeff**	P-value	**β-coeff**	P-value
Lipids												
Triglycerides [1] (mmol/l)	0.010	<0.05	0.044	<0.05	0.0085	<0.05	0.057	<0.05	0.21	<0.05	-0.15	<0.05
LDL-Cholesterol (mmol/l)	0.018	<0.05	0.072	<0.05	0.018	<0.05	0.10	<0.05	0.39	<0.05	-0.29	<0.05
HDL-Cholesterol (mmol/l)	-0.0035	<0.05	-0.019	<0.05	-0.0037	<0.05	-0.033	<0.05	-0.011	0.70	-0.044	0.15
Total Cholesterol (mmol/l)	0.021	<0.05	0.080	<0.05	0.019	<0.05	0.11	<0.05	0.50	<0.05	-0.45	<0.05
Glucose metabolism												
Fasting glucose (mmol/l)	0.011	<0.05	0.048	<0.05	0.011	<0.05	0.062	0.11	0.23	<0.05	-0.14	0.21
Fasting plasma insulin [1] (pmol/l)	0.012	<0.05	0.058	<0.05	0.010	<0.05	0.090	<0.05	0.28	<0.05	-0.18	<0.05
Glucose 120 min [1] (mmol/l)	0.03	<0.01	0.019	<0.05	0.004	<0.05	0.016	<0.05	0.085	<0.05	-0.072	<0.05
HOMA-IR [1] (mmol/l)	0.021	<0.05	0.091	<0.05	0.019	<0.05	0.14	<0.05	0.36	<0.05	-0.17	<0.05
Blood pressure												
SBP (mmHg)	0.30	<0.05	1.35	<0.05	0.27	<0.05	1.33	<0.05	5.05	<0.05	-3.27	<0.05
DBP (mmHg)	0.14	<0.05	0.77	<0.05	0.13	<0.05	0.90	<0.05	3.60	<0.05	-2.59	<0.05

Data adjusted for age, smoking status, alcohol consumption, fitness, total daily energy intake and urban residence. Results are presented as β-coefficient and P-value

[1] Data logarithmically transformed prior to analysis

BMI: Body mass index, WC: Waist circumference, VAT: visceral abdominal adipose tissue, SAT: subcutaneous abdominal adipose tissue, VAT/SAT: Visceral-to-subcutaneous abdominal adipose tissue ratio, HOMA-IR: Homeostatic model assessment for insulin resistance, SBP : systolic blood pressure, DBP : diastolic blood pressure

Table 4. Cardio-metabolic parameters prediction by anthropometric features in 820 rural and urban Kenyan women

	Weight (kg)		BMI (kg/m^2)		WC (cm)		VAT (cm)		SAT [1] (cm)		VAT/SAT[1]	
	β-coeff	P-value	**β-coeff**	P-value	**β-coeff**	P-value	**β-coeff**	P-value	**β-coeff**	P-value	**β-coeff**	P-value
Lipids												
Triglycerides [1] (mmol/l)	0.0044	<0.05	0.015	<0.05	0.0073	<0.05	0.048	<0.05	0.067	<0.05	-0.019	<0.05
LDL-Cholesterol (mmol/l)	0.011	<0.05	0.038	<0.05	0.013	<0.05	0.083	<0.05	0.26	<0.05	-0.21	<0.05
HDL-Cholesterol (mmol/l)	-0.0019	0.10	-0.0041	0.22	-0.0034	<0.05	-0.020	<0.05	0.004	0.86	-0.03	0.18
Total Cholesterol (mmol/l)	0.012	<0.05	0.044	<0.05	0.013	<0.05	0.089	<0.05	0.30	<0.05	-0.33	<0.05
Glucose metabolism												
Fasting glucose (mmol/l)	0.0042	0.18	0.0070	0.45	0.0055	0.11	0.055	<0.05	0.077	0.90	0.05	0.41
Fasting plasma insulin [1] (pmol/l)	0.012	<0.05	0.045	<0.05	0.013	<0.05	0.09	<0.05	0.27	<0.05	-0.22	<0.05
Glucose 120 min [1] (mmol/l)	0.0009	0.30	0.0036	0.18	0.017	0.09	0.010	0.16	0.031	0.08	-0.019	0.31
HOMA-IR [1] (mmol/l)	0.016	<0.05	0.055	<0.05	0.018	<0.05	0.13	<0.05	0.32	<0.05	-0.22	<0.05
Blood pressure												
SBP (mmHg)	0.27	<0.05	0.97	<0.05	0.21	<0.05	1.87	<0.05	5.29	<0.05	-3.99	<0.05
DBP (mmHg)	0.17	<0.05	0.68	<0.05	0.15	<0.05	1.32	<0.05	3.31	<0.05	-2.42	<0.05

Data adjusted for age, smoking status, alcohol consumption, fitness, total daily energy intake and urban residence. Results are presented as β-coefficient and P-value,

[1] Data logarithmically transformed prior to analysis

BMI :Body mass index, WC :Waist circumference, VAT: visceral abdominal adipose tissue, SAT: subcutaneous abdominal adipose tissue, VAT/SAT: Visceral-to-subcutaneous abdominal adipose tissue ratio, HOMA-IR : Homeostatic model assessment for insulin resistance, SBP : systolic blood pressue, DBP : diastolic blood pressure

Table 5. Association between MS diagnosis and anthropometric features in 581 Kenyan men

	β-coefficient	SD	P-value
Anthropometric parameters			
Weight	0.12	0.022	<0.05
BMI	0.46	0.086	<0.05
WC	0.12	0.024	<0.05
VAT	1.00	0.19	<0.05
SAT	1.45	0.32	<0.05
VAT/SAT	-0.15	0.075	<0.05

Data adjusted for age, smoking status, alcohol consumption, fitness, total daily energy intake and urban residence.

Results are presented as β-coefficient, standard deviation (SD) and P-value, BMI: Body mass index, WC: Waist circumference, VAT: visceral adipose tissue, SAT: subcutaneous adipose tissue, VAT/SAT: Visceral-to-subcutaneous adipose tissue ratio

Table 6. Association between MS diagnosis and anthropometric measures in 817 Kenyan women

	β-coefficient	SD	P-value
Anthropometric parameters			
Weight	0.074	0.012	<0.55
BMI	0.22	0.033	<0.05
WC	0.12	0.016	<0.05
VAT	0.56	0.11	<0.05
SAT	0.88	0.14	<0.05
VAT/SAT	-1.59	0.33	<0.05

Data adjusted for age, smoking status, alcohol consumption, fitness, total daily energy intake and urban residence.

Results are presented as β-coefficient, standard deviation (SD) and P-value, BMI: Body mass index, WC: Waist circumference, VAT: visceral adipose tissue, SAT: subcutaneous adipose tissue, VAT/SAT: Visceral-to-subcutaneous adipose tissue ratio

Discussion

This study is one of the few addressing CMD risk factors, anthropometric measures of fat accumulation and MS in rural and urban populations from SSA. In regard of the actual epidemiological and nutritional transition SSA countries are currently facing, CMD' risk factors need to be addressed in the actual context, both in rural and urban populations. Although anthropometric measures of obesity have been positively associated to an increased risk of CMD in Caucasians, it is essential to evaluate this association in SSA populations and establish which of anthropometric values of fat accumulation should be used to monitor cardio-metabolic health. Ultrasounds scanning techniques have been established as a reliable method to estimate VAT and SAT (103, 127, 142). However, the use of VAT and SAT as health indicators still remain to be studied and used in populations from various ethnic origin, such as SSA Africans.

Rural-urban disparities in CMD risk

This study showed that both urban men and women presented higher anthropometric values (weight, BMI, WC, SAT and VAT/SAT) compared to rural participants. Abdominal obesity was present in a significantly higher proportion of urban men and women (19.2 vs 8.2% in men and 66.4 vs 30.2% in women, $P<0.05$), which is concordant with previous studies made in SSA populations (143, 144).

Urban participants from both sex presented greater levels of lipids (triglycerides, LDL-C, total cholesterol) and a significantly higher proportion of subjects with hypertriglyceridemia compared to rural participants (15.9 vs 8.0% in men and 13.2 vs 6.0% in women, $P<0.05$). Similar rural-urban differences have been previously found in a study from Tanzania (86). In a recent study from Benin, Adediran et al. also found a higher level of triglycerides in their urban participants (143), whereas Fezeu et al. reported a higher level of total cholesterol and triglycerides in their urban Cameroonian community, compared their rural counterparts (144).

Urban participants presented a higher level of fasting glycemia, 120-minutes glycemia , fasting insulin and HOMA-IR. These differences are concordant with similar studies from SSA countries (143, 144), but not with all (11).

In this study, urban men and women also showed higher systolic and diastolic blood pressure, a difference that has been reported in similar studies (143) and attributed to diet, particularly salt intake (44, 71) and other environmental factors associated to urbanity.

As it is suggested in most studies, these differences in CMD risk factors are likely to be caused by disparities between rural and urban's lifestyle, physical activity and diet. In our study, urban men had indeed a significantly lower level of cardio-respiratory fitness ($P<0.05$). Urban men and women also had lower amount of daily time spent in moderate-to-high intensity activity (>3 METS) ($P<0.05$). However, rural men had the highest mean of EI and the highest consumption of proteins, carbohydrates and fat, despite a leaner profile ($P<0.05$, respectively). This surprising finding can partly be explained by the higher proportion of time rural men spend in moderate-to-high intensity activity (>3 METs) compared to their urban counterpart (12.6% vs 3.4% in urban men, $P<0.05$). The effect of intense physical activity on fat accumulation has been studied before (24, 26). Results from a recent meta-analysis interested by the effect of exercise without hypocaloric diet in overweight and obese subjects have suggested that vigorous physical activities and aerobic fitness (>60% maximum heart rate), compared to low intensity activities, would have a greater potential to reduce fat accumulation, especially VAT (26). On the other hand, as it was explained in a previous study made by Hansen and Christensen (118), data from our cohort were collected immediately following harvest. Thus, our values might be overestimated and not reflect the all year long food intake consumed by rural Kenyan populations. Comparatively, rural Kenyan women presented a leaner profile than urban women. Both group had a similar level of cardio-respiratory fitness (39.8 vs 40.1 ml O_2 $kg^{-1}min^{-1}$, $P=0.74$) and spent a comparable amount of time in sedentary activities (58.3 % vs 60.1%, $P=0.49$). However, rural women spent 10.5% of their time in moderate-to-high intensity activities, which was significantly higher than urban women (1.8%, $P<0.05$). Rural women consumed significantly lower amount of fat (33.6 vs 38.0 g/daily, $P<0.05$), but a higher amount of proteins compared to their urban counterpart (50.1 vs 45.0 g/daily, $P<0.05$).

Association between anthropometric measures and CMD risk factors

In this study, triglycerides, LDL-C, and total cholesterol were positively associated with anthropometric measures of fat accumulation. These results are similar to Fezeu et al.'s study, which also reported a positive association between WC and triglycerides level in rural and urban populations of Cameroon (144). They are also concordant with the hypothesis that typical metabolic consequences of fat accumulation and adipocytes hypertrophy include an increased blood level of free-fatty acids, which lead to an elevation of fasting and post-prandial triglycerides, small dense LDL, total cholesterol levels and eventually leads to a lower HDL-C level (71, 105). However, in this study, HDL-C was not associated with either SAT or VAT/SAT in men and women, or BMI and weight in men. This lack of association, which could be partly explained by the particular diet of our participants and genetic factors, has been previously discussed in the manuscript. Hypocaloric diets, micronutrient deficiency (Delisle et al., 2013) and low protein intake (Goedecke et al., 2010) usually found in underweight and healthy individuals could be associated with low HDL-C levels and partly explain the general lack of association found between HDL-C and anthropometric measures of body composition. Another hypothesis states that for black Africans, HDL-C concentration would remain relatively low and not be affected by fat mass. In 2010, Goedecke et al. published an interesting study on ethnic differences in lipoproteins levels in black and white South-African women. They showed that black women had lower triglycerides and HDL-C level compared to white women and that body composition was the major determinant of serum lipids in white, but not in black women (145). On the other hand, these results are not concordant with a study published in 2000 by Deprès et al, who found a relatively high level of HDL-C in obese black individuals compared to obese white individuals. Deprès et al. suggested that differences in fat distribution and lipoprotein lipase activity among black and white would partly explain this variation (85, 146). Further studies are needed to better understand ethnic differences in lipoproteins level and particularly HDL-C level and its association with body composition.

Fasting insulin, blood glucose (fasting and 120 minutes) and HOMA-IR were positively associated with anthropometric measures in men. These results are concordant with the study made by Fezeu et al. in Cameroonian population (144). On the other hand, in our women group, except for VAT and fasting glucose, there were no association found between any anthropometric measures and blood glucose (fasting and 120 minutes) (Table 4). These surprising results were not concordant with another paper published by Christensen et al. in 2009 (54), which showed a significant association between anthropometric measures and glucose intolerance in rural and urban women from our cohort. Differences in selection procedure might partly explain this discordance. In this study, we excluded participants known to be diabetic or under anti-diabetic medications (40 participants, 27 men and 13 women), however those participants were included in Christensen's paper, which was specifically looking at the prevalence of glucose intolerance among ethnic groups of Kenya. Differences in statistical analysis (logistic and linear regression analysis) might also partly explain this difference. After running only age-adjusted multivariate linear analysis (data not shown), data showed that weight, BMI, WC and VAT were significantly associated with 120-minutes blood glucose in women. Thus, this lack of association might also be caused by cofounders such as diet, fitness, alcohol intake, smoking or urban residence.

Finally, systolic and diastolic blood pressure were both associated with anthropometric features in men and women. The strong association between hypertension and obesity have been extensively described and our results were indeed concordant with similar studies made in SSA populations (11, 143, 144).

Association between anthropometric measures and MS

This study showed a positive and significant association between weight, BMI, WC, VAT and SAT and the diagnosis of MS. Previous studies have shown similar associations in SSA populations. In 2009, Jenning et al. published a paper on the presentation of MS in black South African women, and concluded that VAT was the strongest anthropometric predictor of MS (12). Fezeu et al. found a strong association between WC and MS in Cameroonian men and

women (144), whereas Handlos et al. found a significant association between abdominal obesity (WC and VAT) and an adverse metabolic profile in an overweight population of Kenyan men and women . Fat accumulation can lead to adipose tissue dysfunction, or adipocyte hypertrophy, which is known to cause obesity-related metabolic disturbances such as insulin resistance and low-grade inflammation (14, 147). It would also contribute to the onset of dyslipidemia (71, 148), hypertension and non-alcoholic fatty liver diseases (149), pathological conditions which are all linked to the MS.

Surprisingly, VAT/SAT was negatively associated with MS, which goes against the results published by Kaess et al in 2012, looking at the correlation between VAT/SAT and CMD risk factors in a large sample from the Framingham Heart Study (94). The authors found positive and significant associations between VAT/SAT and LDL-C, triglycerides, SBP, DBP, HOMA-IR and fasting glucose and suggested that VAT/SAT was a strong correlate of CMD risk factors, even beyond BMI or WC. The disparity between our results and Kaess' study could be partly related to methodology. In Kaess' study, VAT/SAT was calculated from measures assessed by CT-scan. The abdominal wall was identified on CT-scan and traced manually to separate SAT from VAT and measure their thickness (94). In the present study, VAT and SAT were estimated with measurements from Ultrasonography. Ethnic differences between our two cohorts might also be part of the explanation. Indeed, several studies have shown that the propensity to stock fat in the visceral or the sub-cutaneous compartment is influenced by ethnicity. Individuals from black African origin would have a tendency to accumulate fat first in the sub-cutaneous layer (85, 150, 151) , thus would tend to present a lower VAT/SAT for a similar WC and BMI.

In this study, SAT showed the strongest positive association with MS diagnosis both in men (1.45 ±0.32) and women (0.88±0.14) ($P<0.05$). This is consistent with several studies that suggested that SAT plays a certain role in the pathophysiology of MS, and particularly in insulin resistance (106, 107). It is also concordant with other studies made in the late 90's in Caucasian populations, which found a stronger correlation between SAT and insulin resistance compared to VAT (108, 109). The pathophysiology explaining such results remain unclear. As it is explained in Goodpaster's study, the link between SAT and MS is a source of polemic. Because of technical limitations, our measures of SAT might have included DSAT, which have been

found to be highly correlated to insulin resistance and cardiovascular risk factors, independently of other anthropometric measures (107). Studies made in Caucasian population showed major functional and anatomical differences between subcutaneous layers and concluded that DSAT had a higher lipolytic activity compared to SSAT (152, 153). Also, as it is suggested by Patel and Abate in a scientific review published in 2013, SAT could be the major source of free fatty acid flux and might substantially contributes to the risk of developing CMD (106).

Limitations

As it was presented in the manuscript, this study had major strengths, including the relatively naïve population we studied, with very few participants having concomitant diseases or taking medication. It thus provided a unique opportunity to study the relationship between anthropometric measures and CMD in a non-obese, otherwise healthy, SSA population. The important number of participants included allowed a satisfying statistical power. Also, despite the fact we excluded men and women treated for hypertension or known to have diabetes prior to their enrollment, we diagnosed a relatively large number of participants with MS. This made us able to detect associations between anthropometric features of fat accumulation and CMD risk factors in our rural and urban populations.

Various limitations have been acknowledged in the manuscript of our study. However, some more can be recognized. First of all, we were not able to include data on socio-economic status, despite their initial collection from a questionnaire included in our protocol. Due to cultural and social disparities between participants, some might have misunderstood various questions which invalidated them. Second of all, we did not collected data on micro-nutrient diet, which might have an effect on lipid levels and other CMD risk factors (29), thus could act as a possible cofounder. Also, we were advised against the collection of data on HIV status and it was decided to avoid this question because of sociocultural reason and the risk of stigmatisation. HIV infections and HIV medication has been extensively linked to CMD risk factors and MS (154), thus also might have acted as a possible confounder in our study. Further studies should be done, including these important confounders, suspected to contribute to CMD epidemic in SSA countries.

Conclusion

In conclusion, this study showed a high prevalence of MS and other CMD risk factors in urban Kenyan men and women compared to their rural counterparts. This difference might be partly explained by significant disparities in their diet and fitness level.

Our results showed positive and significant associations between anthropometric measures of fat accumulation and CMD risk factors such as triglycerides level, LDL-C, total cholesterol, fasting insulin level, HOMA-IR, systolic and diastolic blood pressure in both men and women. Our results did not show a positive association between HDL-C and anthropometric parameters, despite a very high prevalence of our participants presenting low HDL-C. Future research projects should include a more extensive data collection on diet quality in rural and urban Kenyan population, in order to better evaluate the effect of nutrition on CMD risk, particularly lipid metabolism and HDL-C level.

This study also found positive and significant associations between anthropometric measures and MS diagnosis, except for VAT/SAT which was negatively associated with MS. SAT and VAT had both the strongest positive associations. In epidemiological studies, ultrasound scanning of VAT and SAT should be considered as a valid tool to estimate abdominal fat distribution in SSA populations, as it appears as a good indicator of cardio-metabolic health as well as having high cost-benefit value. Moreover, considering the strong relationship found between SAT and CMD risk factors, future analysis should include anthropometric measures which integrate SAT distribution, such as waist-to-hip ratio (WHR), and test their associations with CMD in Kenyan populations.

As previously presented, number of studies suggest it exists ethnic differences in the relationship between adiposity or anthropometric measures of body fat and CMD. European cut-points, which are currently recommended to assess CMD risk factors in SSA population, are likely to be inappropriate. Considering the growing epidemic of obesity, cardiovascular and metabolic disorders in SSA countries, it is of clinical interests to develop specific cut-off points of anthropometric measures in order to better monitor CMD in these vulnerable populations.

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Annexe 1

Calculations for log-transformed variables

Due to skewed distribution, some of our exposure variables where log-transformed prior to analysis. The effect on outcomes is then calculated from the log-transformed exposure (30). Some outcomes were also log-transformed prior to analysis, their associations with normally-distributed variables and log-transformed variables also have to be calculated. In this appendix, only significant β-coefficient are presented.

Calculations for men

1.1 Association between anthropometric measures and lipid profile markers

1.1.2 Association between anthropometrics and log-transformed triglycerides level

1 cm gained in W = $e^{\beta\text{-coefficient}}$ = 1.010 = 1.0 % of triglycerides level

1 kg/m^2 gained in BMI = $e^{\beta\text{-coefficient}}$ = 1.045 = 4.5 % of triglycerides level

1 cm gained in WC = $e^{\beta\text{-coefficient}}$ = 1.0085 = 0.85 % of triglycerides level

1 cm gained in VAT = $e^{\beta\text{-coefficient}}$ = 1.059 = 5.9 % of triglycerides level

10% gained in log-transformed SAT =1 $.10^{\beta\text{-coefficient}}$ = 1.020 = 2.0 % of triglycerides level

10% gained in log-transformed VAT/SAT = 1 $.10^{\beta\text{-coefficient}}$ = -1.014 = -1.4% of triglycerides level

1.1.2 Association between log-transformed SAT, VAT/SAT and LDL-C levels

10% gained in SAT = β-coefficient*log(1.10) = 0.016 mmol/l of LDL-C

10% gained in VS ratio = β-coefficient*log(1.10) = -0.012 mmol/l of LDL-C

1.1.4 Association between log-transformed SAT, VAT/SAT and total cholesterol

10% gained in SAT = β-coefficient*log(1.10) = 0.021 mmol/l of total cholesterol

10% gained in VS ratio = β-coefficient*log(1.10) = -0.019 mmol/l of total cholesterol

1.2 Association between anthropometric measures and glycemic homeostasis markers

1.2.1 Association between log-transformed SAT and fasting blood glucose

10% gained in SAT = β-coefficient*log(1.10) = 0.0095 mmol/l of LDL-C

1.2.2 Association between anthropometrics and log-transformed FPI

1 cm gained in W = $e^{\beta\text{-coefficient}}$ = 1.012 = 1.12% of FPI level

1 kg/m^2 gained in BMI = $e^{\beta\text{-coefficient}}$ = 1.060 = 6.0 % of FPI level

1 cm gained in WC = $e^{\beta\text{-coefficient}}$ = 1.010 = 1.0 % of FPI level

1 cm gained in VAT = $e^{\beta\text{-coefficient}}$ = 1.094 = 9.4 % of FPI level

10% gained in log-transformed SAT =1 $.10^{\beta\text{-coefficient}}$ = 1.027 = 2.7 % of FPI level

10% gained in log-transformed VAT/SAT ratio =1 $.10^{\beta\text{-coefficient}}$ = -1.017 = -1.7 % of FPI level

1.2.2. Association between anthropometrics and log-transformed glucose – 120 min

1 cm gained in W = $e^{\beta\text{-coefficient}}$ = 1.030= 3.0 % of glucose-120 min level

1 kg/m^2 gained in BMI = $e^{\beta\text{-coefficient}}$ = 1.019 = 1.9% of glucose-120 min level

1 cm gained in WC = $e^{\beta\text{-coefficient}}$ = 1.004 = 0.4 % of glucose 120-min level

1cm gained in VAT = $e^{\beta\text{-coefficient}}$ = 1.016 = 1.6% of glucose 120-min level

10% gained in log-transformed SAT =1 $.10^{\beta\text{-coefficient}}$ = 1.0081 = 0.81% of glucose 120-min level

10% gained in log-transformed VAT/SAT =1 $.10^{\beta\text{-coefficient}}$ = -1.0068 = -0.68% of glucose 120-min level

1.2.3 Association between anthropometrics log-transformed HOMA-IR

1 cm gained in W = $e^{\beta\text{-coefficient}}$ = 1.021 = 2.1% of HOMA-IR level

1 kg/m^2 gained in BMI = $e^{\beta\text{-coefficient}}$ = 1.095 = 9.5% of HOMA-IR level

1 cm gained in WC = $e^{\beta\text{-coefficient}}$ = 1.019 = 1.9% of HOMA-IR level

1 cm gained in VAT = $e^{\beta\text{-coefficient}}$ = 1.15 = 15.0 % of HOMA-IR level

10% gained in log-transformed SAT =1 $.10^{\beta\text{-coefficient}}$ = 1.034 = 3.4 % of HOMA-IR level

10% gained in log-transformed VS ratio =1 $.10^{\beta\text{-coefficient}}$ -1.016 = -1.6% of HOMA-IR level

1.3 Association between log-transformed SAT, VAT/SAT and blood pressures

1.3.1 Association between log-transformed SAT, VAT/SAT and SBP

10% gained in SAT = β-coefficient*log(1.10) = 0.21 mmHg of SBP

10% gained in VS ratio = β-coefficient*log(1.10) = -0.14 mmHg of SBP

1.3.2 Association between log-transformed SAT, VAT/SAT and SBP

10% gained in SAT = β-coefficient*log(1.10) = 0.15 mmHg of DBP

10% gained in VS ratio = β-coefficient*log(1.10) = -0.11 mmHg of DBP

Calculations for women

1.1 Association between anthropometric measures and lipid profile markers

1.1.1 Association between anthropometrics and log-transformed triglycerides level

1 cm gained in W = $e^{\beta\text{-coefficient}}$ = 1.0044 = 0.44 % of triglycerides level

1 kg/m^2 gained in BMI = $e^{\beta\text{-coefficient}}$ = 1.015 = 1.5 % of triglycerides level

1 cm gained in WC = $e^{\beta\text{-coefficient}}$ = 1.0073 = 0.73 % of triglycerides level

1 cm gained in VAT = $e^{\beta\text{-coefficient}}$ = 1.049 = 4.9 % of triglycerides level

10% gained in log-transformed SAT =1 $.10^{\beta\text{-coefficient}}$ = 1.0064 = 0.64 % of triglycerides level

10% gained in log-transformed VAT/SAT =1 $.10^{\beta\text{-coefficient}}$ = 1.0019 = 0.19 % of triglycerides level

1.1.2 Association between log-transformed SAT, VAT/SAT and LDL-C levels

10% gained in SAT = β-coefficient*log(1.10) = 0.011 mmol/l of LDL-C level

10% gained in VS ratio = β-coefficient*log(1.10) = -0.0087 mmol/l of LDL-C level

1.1.3 Association between log-transformed SAT, VAT/SAT and total cholesterol

10% gained in SAT = β-coefficient*log(1.10) = 0.012 mmol/l of total cholesterol

10% gained in VS ratio = β-coefficient*log(1.10) = -0.014 mmol/l of total cholesterol

1.2 Association between anthropometric measures and glycemic homeostasis markers

1.2.1 Association between anthropometrics and log-transformed FPI

1 cm gained in W = $e^{\beta\text{-coefficient}}$ = 1.012 = 1.2% of FPI level

1 kg/m^2 gained in BMI = $e^{\beta\text{-coefficient}}$ = 1.046 = 4.6 % of FPI level

1 cm gained in WC = $e^{\beta\text{-coefficient}}$ = 1.013 = 1.3 % of FPI level

1 cm gained in VAT = $e^{\beta\text{-coefficient}}$ = 1.094 = 9.4 % of FPI level

10% gained in log-transformed SAT =1 $.10^{\beta\text{-coefficient}}$ = 1.026 = 2.6% of FPI level

10% gained in log-transformed VS ratio =1 $.10^{\beta\text{-coefficient}}$ = -1.021 = -2.1 % of FPI level

1.2.2 Association between anthropometrics log-transformed HOMA-IR

1 cm gained in W = $e^{\beta\text{-coefficient}}$ = 1.016 = 1.6 % of HOMA-IR level

1 kg/m^2 gained in BMI = $e^{\beta\text{-coefficient}}$ = 1.057 = 5.7 % of HOMA-IR level

1 cm gained in WC = $e^{\beta\text{-coefficient}}$ = 1.018 = 1.8 % of HOMA-IR level

1 cm gained in VAT = $e^{\beta\text{-coefficient}}$ = 1.14 = 14.0 % of HOMA-IR level

10% gained in log-transformed SAT =1 $.10^{\beta\text{-coefficient}}$ = 1.031 = 3.1 % of HOMA-IR level

10% gained in log-transformed VAT/SAT =1 $.10^{\beta\text{-coefficient}}$ = -1.021 = -2.1 % of HOMA-IR level

1.3 Association between log-transformed SAT, VAT/SAT and blood pressures

1.3.1 Association between log-transformed SAT, VAT/SAT and SBP

10% gained in SAT = β-coefficient*log(1.10) = 0.22 mmHg of SBP

10% gained in VS ratio = β-coefficient*log(1.10) = -0.17 mmHg of SBP

1.3.2 Association between log-transformed SAT, VAT/SAT ratio and SBP

10% gained in SAT = β-coefficient*log(1.10) = 0.14 mmHg of DBP

10% gained in VS ratio = β-coefficient*log(1.10) = -0.10 mmHg of DBP

Annexe 2

Type 2-diabetes in a country in transition: A rural-urban migration study in Kenya on the role of diet, physical activity and other determinants.

SOCIAL ECONOMIC QUESTIONNAIRE

Recruitment Centre …… Date……Time .....

Subject Name. …… Subject No. …….. Sex……..

1. What is your date of birth?

   _____

2. What is your marital status?

   1. Single >>5
   2. Married
   3. Separated >>5
   4. Divorced >>5
   5. Widow/Widower. >>5

3. Is your partner working?

   1. Yes
   2. No >>5

4. If **yes to no. 3**, what is your partner's occupation?

5. What is the highest level of Education you have attained?

1 None
2 Primary
3 Secondary -'O' Level
4 Advanced Level -'A' Level
5 College / University
6 Other (Specify)…….

6. What mode of transport do you use to work?

1 Car – Privately owned / lift/Company
2 Public means – Matatu /Bus
3 Taxi
4 Bicycle
5 Walking

7. How would you describe your working status?

1. Employed
2. Self-employed
3. House wife/husband
4. Unemployed
5. Other (Specify)……

8 If employed, what is your Occupation/ job category?

1 Managerial
2 Support staff
3 Secretarial
4 Temporary/casual
5 Other (specify)…….

9 If self-employed, specify your occupation?

10 Do you have any other source of income?

1. Yes
2. No >>11

11 If **yes, to no. 9** which one(s)?

a)……..

b)……..

c)……..

12 Approximately how much money do you spend per month on the following items at home in Ksh?

Food	Clothes	General house hold commodities	Health-care	Water, electricity/cooking fuel	Transport to and from work	School Fees	Other

13 Who owns the house you live in?

1 Self / Spouse – built
2 Inherited
3 Rental
4 Other (Specify)…….

14 If self who owns the land you live in?

1. Self / Spouse – built
2. Inherited
3. Rental
4. Other (Specify)…….

15 What is the acreage of the land?

_____

15. What is your source of water for domestic use?

1 Piped Water (council)
2 Bore hole / Well
3 River / Stream
4 Trucked in water
5 Pool/Pond
6 Gutter water in tank
7 Other
(Specify)……

13. Approximately what is the distance from your house to the water source in meters?

1 Inside the house

2 Under 50 m

3 50 – 500m

4 500 – 1000m

5 Over 1000 m

14. Do you have any of the following in your house?

1 TV

2 Radio

3 Video/DVD/VCD

4 Refrigerator

5 Cooking Stove

6 Sofa Set

16. How many people live in your homestead?

17. How many dependants do you have?

_____

18. Do you own any domesticated animals?
    1. Yes
    2. No >>20

19. Which animals and how many of each?

20. In which area were you born?

_____

21. For how long have you lived in this area?

_____

22. Do you have any relatives in Nairobi?
    1. Yes
    2. No >>27

23. How many of them?

_____

24. How are you related to them?

25. Where do they work and live?

26. Approximately how old are the relative(s)?

27 Observe what the house is made up of, and record about the following….

Roof

Walls

Floor