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TITLE: GENOMIC AND ENVIRONMENTAL RISK FACTORS FOR CARDIOMETABOLIC DISEASE IN KENYA- AWIGEN-PHASE II

PRINCIPAL INVESTIGATOR: CATHERINE KYOBUTUNGI - APHRC

CONTACT DETAILS:
APHRC Campus
Manga Close, Off Kirawa Road
PO Box 10787-00100
Nairobi Kenya
Email: ckyobutungi@aphrc.org
Telephone: +254 (20) 400 1000

ACRONYMS

AWI-Gen – African Wits-INDEPTH Partnership for genetic studies on the role of the genome and environment in body composition, as a risk factor for cardiometabolic disease- AWIGEN-Phase II

BMI – Body Mass Index

CC – Collaborative Center

CMD – Cardiometabolic diseases

CNV – Copy Number Variation

DNA – Deoxyribonucleic acid

DHEA- Dehydroepiandrosterone

DHEAS- Dehydroepiandrosterone sulfate

FSH – Follicle Stimulating Hormone

GWAS – Genome-wide association studies

H3Africa – Human Heredity and Health in Africa

HIV – Human Immunodeficiency Virus

HDSS – Health and Demographic Surveillance Systems

INDEPTH – International Network for the Demographic Evaluation of Populations and Their Health in Low- and Middle – Income Countries

MC4R – Melanocortin 4 receptor

NUHDSS – Nairobi Urban Health and Demographic Surveillance System

SHBG – Sex Hormone Binding Globulin

SNP – Single Nucleotide Polymorphism

SSA – Sub-Saharan Africa

T2D- Type 2 diabetes

T2DM- Type 2 diabetes mellitus

Title of Project:

Genomic and Environmental Risk Factors for Cardiometabolic Disease in Africans (Kenya)

Investigators and Institutional Affiliations

African Population and Health Research Center (APHRC)

- Catherine Kyobutungi, PhD: Kenya Site PI
- Gershim Asiki, PhD: Co-Investigator (Project Manager)
- Shukri Mohamed, MPH: Kenya Site Project Coordinator
- Isaac Kisiangani MPH: Kenya Site Research Officer

University of the Witwatersrand – South Africa

- Prof Michèle Ramsay, PhD (Overall Project PI)
- Furahini Tluway, MPH (Overall Project Manager)

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Abstract

The *Genomic and environmental risk factors for cardiometabolic disease in Africans* (AWI-Gen) project is a collaborative study between the University of the Witwatersrand (Wits) and the INDEPTH Network funded under the Human Heredity and Health in Africa (H3Africa) initiative. The H3Africa is a ground-breaking initiative to build institutional and individual capacity to undertake genetic and genomic studies in the African region. This collaboration, involves five INDEPTH sites i.e. 1) Navrongo – Ghana; 2) Nanoro – Burkina Faso; 3&4) Agincourt and Digkale - South Africa; and 5) Nairobi – Kenya) plus the Soweto-based birth-to-twenty cohort. AWI-Gen phase I was a population based cross-sectional study with a research platform of over 12,045 participants aged 40-60 years from Burkina Faso, Ghana, Kenya and South Africa. It aimed to understand the interplay between genetic, epigenetic and environmental risk factors for obesity and related cardiometabolic diseases (CMD) in sub-Saharan Africa and it generated epi-demographic, environmental, health history, behavioral, anthropometric, physiological and genetic data across a range of rapidly transitioning African settings. This provided a unique resource to examine genetic associations and gene-environment interactions that will contribute to Afrocentric risk prediction models and African-appropriate Mendelian Randomization instruments, and exploit their potential to improve personal and population health – while strengthening regional research capacity. We plan to continue this work in AWIGEN-phase II among the same participants recruited in AWIGen-I offering an opportunity to examine data in a longitudinal manner.

The AWI-Gen phase II project aims to establish the genomic contribution to CMD and risk at a time when multiple interacting transitions, in the presence of high background HIV or malaria prevalence, are driving a rapid escalation in CMD across the African continent. The project capitalizes on the unique strengths of existing longitudinal cohorts and well-established health and demographic surveillance systems(HDSS) run by the partner institutions. The six study sites

represent geographic and social variability of African populations which are also at different stages of the demographic and epidemiological transitions. The work in Kenya will be undertaken in the Nairobi Urban Health and Demographic Surveillance System (NUHDSS) run by African Population and Health Research Center (APHRC) following participants who were recruited in AWIGEN-Phase I.

AWI-Gen II consists of five main aims: i) AIM-1 (Sub-study 1): Genetic associations studies to elucidate functional pathways involved in determining body composition and risk for CMD by detecting pivotal genomic and environmental contributors; ii) AIM 2 (Sub-study 2): Genomics and bioinformatics-impact of genomic diversity on disease risk and precision public health; iii) AIM 3 (Sub-study 3): Examine changes over the menopausal transition in body composition and CMD risk; iv) AIM 4 (Sub-study 4): Examine gut microbiome in older adults and its relationship to obesity, diabetes and glucose tolerance and ageing; and v) AIM 5 (Sub-study 5): Explore respiratory disease in context of multi-morbidity.

In this application, we seek ethical approval for the Kenya study only. The other partners will seek approval from their appropriate ethics review authorities in their countries. The study budget is $248,613 and is funded by National Institute of Health (NIH)-USA under H3Africa. Data collection will be undertaken for approximately 12 months but sample processing, data analysis, manuscript writing, capacity building and policy engagement will be continued up to three years after field work (up to 2022).

I. Introduction/Background

The wealth of genetic information collected in non-African populations has given us insights into the genetic determinants of conditions such as obesity, hypertension and diabetes. However, contextual differences - in socioeconomic conditions, nutritional status, obesogenic environments, or exposure to environmental pollutants – experienced from infancy through adulthood, may shape physiologic responses to genetic risks [1]. Environmental differences between western countries, where most genetic studies have been conducted, and sub-Saharan Africa (SSA) countries may attenuate or exacerbate genetic effects. The increasing burden of disease due to cardiometabolic diseases in SSA necessitates the need to understand genetic influences on complex traits and modifiable risk factors since current knowledge is based on data from western populations. For example, as the obesity epidemic increasingly affects African populations, it is especially useful to examine whether the genetic determinants of obesity differ in communities where obesity is rare compared to communities where obesity is common. It is increasingly recognized that the accumulation of risk factors across the life course shapes how those risk factors influence long-term health outcomes.

Longitudinal studies have been the foundation of observational epidemiology, clinical research and therapeutic evaluations and have identified important risk factors for CMD [2, 3]. Genome technologies are now providing opportunities to study the influence of genomic variation on diseases in large-scale population based studies. Establishing a series of well characterized adult

cohorts in SSA will provide valuable information to enhance an understanding of the interplay between genetic variation and environmental factors in the evolution of CMD and risks on the continent.

Aging is associated with an increased prevalence of obesity and associated diseases including hypertension, type 2 diabetes, heart disease and dyslipidaemia [4]. There is some evidence to suggest that hormonal alterations may be involved. Thus, in females the menopause transition is associated with a fall of estradiol levels and an increase in FSH [5]. Studies largely conducted in the developed world have shown that CMD risk factors and endpoints increase during the menopause transition and that this may be related to hormonal changes [6]. In males it is known that testosterone levels fall with age and that this is associated with an increase in CMD risk [7, 8].

Microbiome has evolved with humans and has particularly rapidly changed very recently at the same time as lifestyles have changed world-wide [9]. Diet and levels of physical activity both affect the microbiome [10, 11] and the role of the microbiome in epidemiological transition is known to be important but not fully understood [12]. Dugas et al, identify the importance of cohort studies to understand how microbiome and environment affects cardio-metabolic status and particularly obesity.

Reduced lung function is a significant predictor of cardiovascular mortality [13][14]. Chronic obstructive pulmonary disease (COPD) which is primarily caused by tobacco smoking has predictive capacity for cardiovascular disease (CVD) incidence and mortality [15][16][17]. Reduced forced expired volume in 1 second (FEV1) and forced capacity volume have shown to predict cardiovascular morbidity and mortality [14][18].

II. Problem Statement/Justification

There are a number of reasons why it would be important to use African populations for the determination of the genetic etiology of obesity and body fat distribution. African genomes harbor more genetic diversity than their European counterparts [1] and Single Nucleotide Polymorphisms (SNPs) common to populations in both regions often have different allele frequencies. It is therefore possible that rare genetic determinants of body fat mass are present at higher frequencies in African populations and thus easier to identify. Furthermore, polymorphisms that confer obesity risk in European populations may be different from those that confer risk in African populations. Thus, one should not simply infer the genetic cause of obesity in Africa from the data derived from European population studies. Also, the African genome has smaller linkage disequilibrium (LD)[1] blocks than other genomes[1] and can therefore be used to narrow large LD blocks that have been shown to harbor possible disease-associated variants in European populations. Thus, by performing genetic analyses in indigenous African populations it

[1]If two genes are in linkage disequilibrium, it means that certain alleles of each gene are inherited together more often than would be expected by chance

may be possible to discover new obesity-risk alleles and hence uncover some of the so-called missing heritability of obesity.

The long-term aim of studying the genetic contribution to body fat mass would be to be able to identify people with the highest risk of becoming obese, thus allowing for early interventions. The present study will contribute to this aim by developing the infrastructure and the scientific expertise in African countries to be able to screen for obesity-causing polymorphisms across large population groups. The infrastructure that will be developed through this project will also allow us to perform future genome-wide association studies (GWAS) for other metabolic disorders as well as many non-metabolic diseases. The collection of phenotypic data is integral to this aim and the centers involved in this study have already developed systems for collecting such data. We hope to build on this infrastructure to allow for the future collection and sharing of more in depth phenotypic data across all sites.

Early detection of CMD is crucial in curbing the epidemic of CVD in most African countries [19]. Given the ethnic disparities in CVD [20] some researchers argue that use of European-derived risk prediction models in Africans may underestimate the CVD risk and may lead to exclusion of some individuals who will benefit from more aggressive CVD interventions [19]. The development of Afrocentric risk prediction strategies/algorithms that combine genomic, physiological and behavioural markers will be novel thereby be contributing to developing prevention strategies.

Aging is associated with an increased prevalence of obesity and associated diseases including hypertension, type 2 diabetes, heart disease and dyslipidaemia [4]. The physiological reasons for these age-related metabolic changes are not fully understood. This study will provide valuable and novel information on the influence of hormonal and epigenetic changes during the menopause transition on CMD risk factors. Given the high prevalence of obesity, hypertension and diabetes in older SSA subjects, these data may uncover new interventions to alleviate this epidemic of CMD particularly in urban African populations.

There is a complex relationship between health, microbiome, food intake, other environmental factors and the human genome. Many studies have shown that dysbiosis of the microbiome is associated with a range of ill health, and particularly cardio-metabolic disorders: obesity, T2D and hypertension. In some cases, there is powerful evidence that this association is causative-modification of the microbiome changes health status[21], [22][23][24]–[26] [15–20] . There are relatively few studies of the microbiome in Africa, and even fewer examining association with cardio-metabolic health. Many African countries going through transition of lifestyle (food, physical activity), now find cardio-metabolic disorders (obesity, type-2 diabetes) a serious health challenge, and it is important to understand how the microbiome is associated with these disorders.

Respiratory health is under-studied in low and middle income countries particularly in Africa. The WHO reports that smoking is increasing in Africa, and indoor and outdoor air quality is of concern especially in urban informal settlements. Understanding the causes and consequences of

impaired respiratory health in the urban slums of Kenya is important to design ways of reducing this burden on the individual, as well as the health care systems that are already strained. Respiratory disease diseases often co-exist with CMD such as type 2 diabetes (T2D) and obesity, which are increasing in low and middle income countries. This will result in an increase in the proportion of the population with more than one chronic disease (multimorbidity). Exploration of key gene environment interactions that may be pivotal in specific end points, including obesity, hypertension, stroke, diabetes and respiratory failure. With the measure of respiratory health, we will be able to study the causes (genetic and environmental) and consequences of such multimorbidity.

III. Review of Literature

Obesity burden in SSA and associated CMD

Obesity is common in SSA with the highest prevalence documented in South Africa, where 27.4% of the female population is obese [27]. Furthermore, the prevalence of overweight and obesity in urban areas of SSA has been estimated to be between 20-50%[28][29][30]. An analysis of longitudinal data derived from HDSSs in 7 countries in SSA demonstrated that over a decade, the prevalence of overweight/obesity in urban African females increased by nearly 35% [31], whilst a report from the WHO suggested that by 2025, 75% of obese subjects worldwide will be in developing countries [32].

The rising prevalence of obesity across SSA [31] is mirrored by increasing levels of obesity-related CMDs including type 2 diabetes [33], hypertension [34] and coronary artery disease [35]. This rise in the prevalence of non-communicable diseases on the African continent is further highlighted by Lopez et al's study [36] which demonstrated that nearly half of the disease burden of low- and middle-income countries arises from lifestyle diseases. The increasing prevalence of obesity in SSA has largely been attributed to changes in diet and reduced energy expenditure as former rural populations become more urbanized and growing prosperity allows increased access to a more Westernized diet[29] [37]–[39] . However**,** studies conducted in populations of European ancestry have clearly shown that there is a strong genetic component to body fat mass [40] and body fat distribution [41] with a degree of heritability of between 40 to 70% for both. Thus, obesity is the result of an interaction between environmental and genetic factors, with the phenotype only being expressed when the individual is exposed to an "obesogenic" environment.

In Kenya, the national prevalence of overweight or obese is at 33% among women and Nairobi has the highest proportion at 48% of women who are overweight or obese. The risk of being overweight or obese increases with age and urban women are more likely to be overweight or obese (43%) than rural women (26%) [42].

The role of genetics in obesity

Despite the evidence of a strong genetic etiology for obesity, the gene polymorphisms involved have been hard to find. Recent advances in high-throughput techniques for genotyping large numbers of single nucleotide polymorphisms (SNPs) in high sample numbers have led to a

plethora of genome-wide association studies (GWAS) of obesity. These studies have discovered 36 new obesity-associated loci. However, these SNPs explain only 1.45% of the heritability of body fat mass[43], [44] . Only one GWAS for the discovery of obesity-associated SNPs has been performed in an indigenous African population. This study was carried out in a cohort of 1188 Nigerian subjects and replicated the association of the Melanocortin 4 receptor (*MC4R)* gene with body mass index (BMI), but no other significant associations were detected [45]. It is possible that this study was underpowered and the authors did suggest that sample sizes similar to those used in populations of European descent would be required to detect significant obesity-associated SNPs in African populations using the current GWAS techniques.

The prevalence of obesity in nearly all African countries is significantly higher in females than males [46], [47] . This pattern is not observed in high income countries, where obesity is present at a very similar level across genders or is slightly more prevalent in females [48]. The present study will therefore provide an excellent opportunity to assess the relative roles of genetic and environmental factors in light of stark gender differences in obesity.

It has been suggested that epigenetic mechanisms, which include deoxyribonucleic acid (DNA) methylation, may play a role in the etiology of CMD and obesity [49]. Methylation patterns also change with age and a recent study using DNA isolated from peripheral blood cells has shown age related changes in methylation levels at disease- associated loci [50], [51] . It is therefore possible that CMD may increase with age due to methylation changes at specific loci.

The heritability of body composition as measured by BMI is estimated to be between 40-70%. To date, GWAS have identified 32 loci associated with BMI and other measures of body adiposity. Current GWAS have primarily focused on populations of European origin, with an explicit deficit of African-centric research. Genetic association studies in African populations have the significant advantage that linkage disequilibrium (LD) generally exists over a shorter genomic distance, increasing the efficiency of the identification of causal variants. Although replication studies of the GWAS findings for obesity risk have been performed in African Americans [52][53][54][55][56] [57] only a few are reported in well characterized African populations.

Menopause and CMD risk

During the menopause transition epigenetic changes may occur that increase the risk of CMD. The menopause transition is associated with dramatic changes in specific hormones including estradiol, follicle stimulating hormone (FSH) and sex hormone binding globulin (SHBG), changes that have been associated with increased CMD risk [5, 6]. It is possible that these hormonal changes may be initiated by age-related epigenetic modifications since the expression level of factors that alter serum levels of these hormones, and some of their receptors, can be altered by DNA methylation in the promoter region of their genes [58], [59]. Furthermore, the hormones themselves may cause epigenetic changes. Thus it is interesting to note that in post-menopausal females, hormone replacement does induce epigenetic changes and the total genome wide DNA methylation level is lower in postmenopausal females with higher Framingham General Cardiovascular Risk Scores [60][61] . The relationship between estradiol levels and CMD is

uncertain. Some studies show that estradiol levels are negatively related to blood pressure and that estradiol replacement reduces blood pressure, but this is not supported by all investigations [62]. With regard to diabetes, it is thought that estradiol preserves beta cell mass and protects the beta cell from insulin secretory failure in the face of insulin resistance [56]. With regards to lipid levels, the lipid profile becomes more atherogenic after menopause and hormone replacement does improve this [63].

Gut microbiome and CMD

There is a complex relationship between health, microbiome, food intake, other environmental factors, and the human genome. Many studies have shown that dysbiosis of the microbiome is associated with a range of ill health, and particularly cardio-metabolic disorders: obesity, T2D and hypertension. In some cases, there is powerful evidence that this association is causative — modification of the microbiome changes health status[21]–[26] . The fact that obesity and associated T2D are expected to affect more than half a billion people by 2030 [64] has prompted extensive research on the involvement of the gut microbiome in obesity, BMI and to a lesser extent T2D [65]. Alterations in the gut microbiota have been observed in obese humans [24], and the obesity phenotype has been transmitted from one individual to another by transplant of microbes harvested from either obese mice or obese humans to gnotobiotic lean mice[66], [67] . A recent study has demonstrated that obesity is due in part to a heritable cluster of microbes including the families Methanobacteriaceae (Archaea) and Dehalobacteriaceae (Firmicutes) and the orders SHA- 98 (Firmicutes), RF39 (Tenericutes), and ML615J-28 (Tenericutes) centered on the rare family Christensenellaceae [68]. Obese individuals may have a larger proportion of Firmicutes could explain their higher weight, despite consuming essentially the same calories as lower weight individuals. In other populations, different sets of microbes may carry out similar metabolic processes. Due to high levels of gut microbial redundancy, there are likely multiple ways to ″build″ a metabolically altered microbial state [66].

Respiratory disease in the context of multi-morbidity

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable lung disease, which is characterized by persistent airflow limitation resulting from inflammation and remodelling of the airways ([69][70]. Besides the respiratory impairment, extra-pulmonary manifestations and comorbidities influence disease burden and mortality [70]. Common comorbidities include cardiovascular disease and metabolic syndrome [71][72]. Systemic manifestations such as osteoporosis, depression, cardiovascular disease (CVD) and Type 2 Diabetes Mellitus (T2DM) are highly prevalent inmthese patients and significantly contribute to symptom burden and health status [73][69]. CVD and T2DM are present across all COPD disease stages [69] and increase the risk of hospitalization and mortality [74]. Cardiometabolic risk is not only increased in obese patients but also in normal weight COPD patients with low muscle mass and abdominal obesity [75][76]. Furthermore, patients with COPD have lower mechanical efficiency, i.e. the proportion of work accomplished to energy expended, compared to healthy

controls [77], [78], possibly due to an increased oxygen cost of breathing [77] and impaired muscle mitochondrial metabolism [78]–[80]. As a lower mechanical efficiency can contribute to impaired exercise performance and hamper efficacy of aerobic exercise training, patients with COPD might benefit from interventions targeting mechanical efficiency

Visceral fats and CMD

Visceral fat is of greater physiological relevance than other body fat depots in its contribution to the disease process of many obesity-associated disorders. Visceral adipocytes have distinct secretory and metabolic profiles that distinguish them from subcutaneous adipocytes and contribute to their disease-causing prowess [81]. The heritability of visceral fat mass has been estimated at between 50 – 55% [41]. Currently, only one GWAS has been performed using specific visceral fat measurement (via CT-scan) as one of the principal phenotypic variables [82]. This study was performed in a Hispanic American population and found strong evidence for association with visceral adiposity of SNPs in the gene, regulator of G-protein signaling 6 (*RGS6*). The use of computerized tomography (CT) for measuring visceral and subcutaneous abdominal adiposity is not possible in the current study due to lack of appropriate infrastructure as well as the high cost of the equipment. Furthermore, the infrastructure at some of the HDSS study centers participating in this investigation has been developed such that phenotypic data collection can occur in the field. Since access to infrastructure at a central point may be limited, it is important that equipment to measure body fat distribution is portable, thus precluding either CT or magnetic resonance imaging (MRI) assessment.

IV. Research Objectives

General objectives

The main objectives of the AWI-Gen phase II project are to: 1) To examine genomic and environmental factors that interact with individual physiology and behaviours that influence body composition, body fat distribution and CMD risk in African population; 2) To establish the genomic contribution to CMD and risk at a time when multiple interacting transitions, in the presence of high background HIV or malaria prevalence, are driving a rapid escalation in CMD across the African continent; 3) Establish a network to explore respiratory disease in context of multi-morbidity.

Specific objectives

1. To examine genetic associations and gene-environment interactions with measures of change in CMD and risk derived over 5 years in a population cohort aged 40-60 years at baseline.

2. To replicate and validate significant genetic association signals identified from population cohort in Kenya

3. To identify high impact rare genetic variants that influence CMD risk among African populations in Kenya.

4. To examine changes over the menopausal transition in body composition and CMD risk factors, and evaluate the resulting risk from physiological, genetic and epigenetic perspectives.

5. To examine the microbiome in older adults and its relationship to obesity, diabetes and glucose tolerance, and CMD risks arising from the menopausal transition.

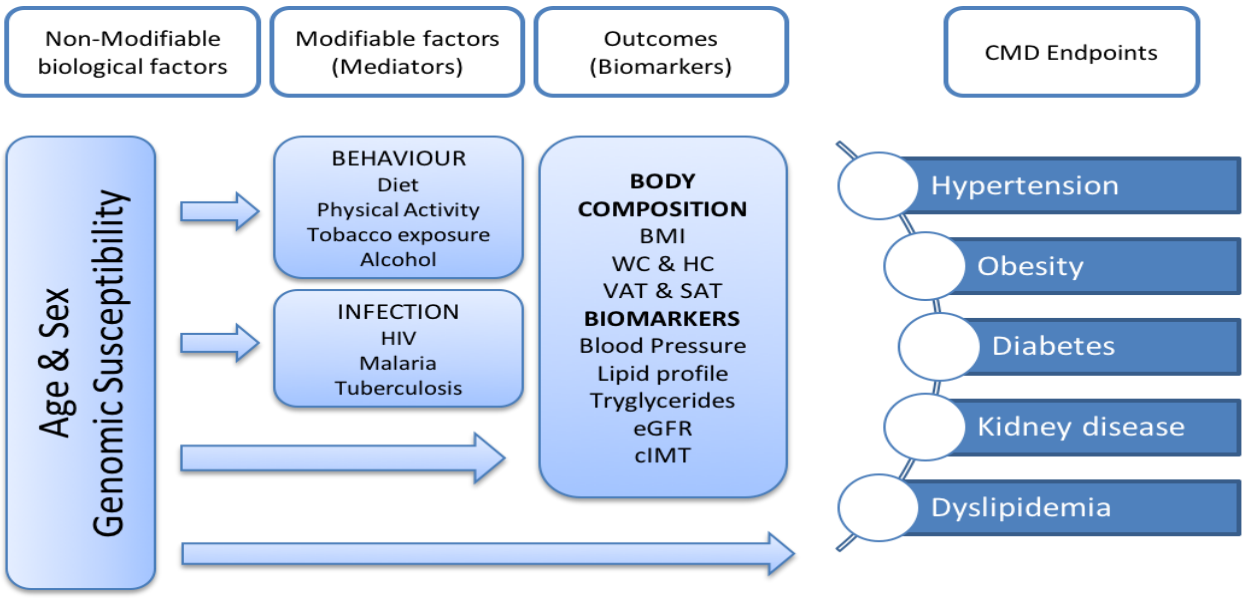
6. To explore respiratory disease in the context of multi-morbidity in Kenya.

V. Conceptual Framework and Operationalization

The major innovation of this study is the participation of indigenous African populations in south, west and east Africa for the study of the genetic etiology of obesity and body composition. The current study use subjects from diverse African populations to determine whether the genetic etiology of obesity and body fat distribution differs between these groups. This may allow us to identify multiple unique obesity-associated gene variants and will also provide valuable data on population substructure.

In Figure 1, we show the interplay between genetics, physiological and environmental risk factors for CMD. The current study will attempt to identify SNPs that are associated with total body fat, as ascertained using BMI and also investigate the genetic etiology of body fat distribution.

Figure 1- The interplay between genetics, physiological and environmental risk factors for CMD



VI. Hypotheses and research questions

Hypothesis

a) There are distinct gene-environment profiles that confer varying degrees of risk (greater or lesser) for CMD.
b) Hormonal and epigenetic changes during menopause are drivers of obesity and CMD risk.
c) Differences in microbiome status that are implicated in cardio-metabolic status are implicated in oestrogen metabolism which affect health progression.

Research questions

a) What is the relationship between gene-environment interaction in CMD and risk derived over time?
b) What is the impact of rare genetic variants that influence CMD risk on obese?
c) What is the link between CMD and cognitive decline and dementia?
d) How does changes in DNA methylation levels at CpG islands of specific candidate gene occur in women who transition through menopause?
e) What is the relationship between menopause transition in females and anthropometric measures over time?
f) What is the diversity of the microbiome in African populations at different stages of epidemiological transition?
g) What is the relationship between microbiome status and cardio-metabolic health?
h) How does the microbiome change over time and particularly for women going through hormonal transition?
i) What is the relationship between host genome and microbiome?
j) What is the relationship between respiratory diseases and CMD?

VII. Study Design and Sampling Strategy

a) Study design: A prospective cohort study to examine genetic associations and gene-environment interactions with measures of change in CMD and risk derived over 5 years (AWI-Gen I survey was in 2014/2015, and survey for phenotypic characteristics (under AWI-Gen II) among the same individuals will be repeated in 2019/2020). This will extend baseline (AWI-Gen I) to provide longitudinal data (AWI-Gen II).

b) Study site (geographical)

The study in Kenya will be conducted in Nairobi, specifically in Korogocho and Viwandani urban informal settlements which are covered by the NUHDSS.

c) Study populations

Sub-study 1 & 5: Adult (40-60 years at baseline) residents of Korogocho and Viwandani informal settlements registered in the NUHDSS.

Sub-study 3 & 4: Women (45-50 years) residents of Korogocho and Viwandani informal settlements registered in the NUHDSS.

d**) Sampling**

Sub-studies 1 and 2: For AWI-Gen II, we will revisit all the living and willing study participants from AWI-Gen I who remain residents in NUHDSS sites. The NUHDSS managed by the African Population and Health Research Center (APHRC) follows about 89,000 individuals living in approximately 33,000 households in Korogocho and Viwandani. We enrolled 2003 participants who were randomly selected from the NUHDSS dataset. We will track these participants for AWIGEN-II.

Sub-study 3 and 4: We will randomly select 250 women in a specified age bracket (45-50 years), from amongst the AWIGEN-I participants, who we were pre-menopausal during AWIGEN-I and postmenopausal at AWIGEN-II.
Sub-study 5: We will select 10-15% of all living and willing study participants from AWI-Gen I who remain resident in NUHDSS. This will translate to 200 to 300 participants.

e**) Sample size**

A sample size of 2000 per site (12000 in total) was used in AWIGEN-I based on power calculations and effect sizes. The power calculations show that we have power to detect realistic effect sizes, based on studies in other populations. Figure 2 illustrates the relationship between power and effect size for two different phenotypes, illustrating that the detectable effect size is realistic.

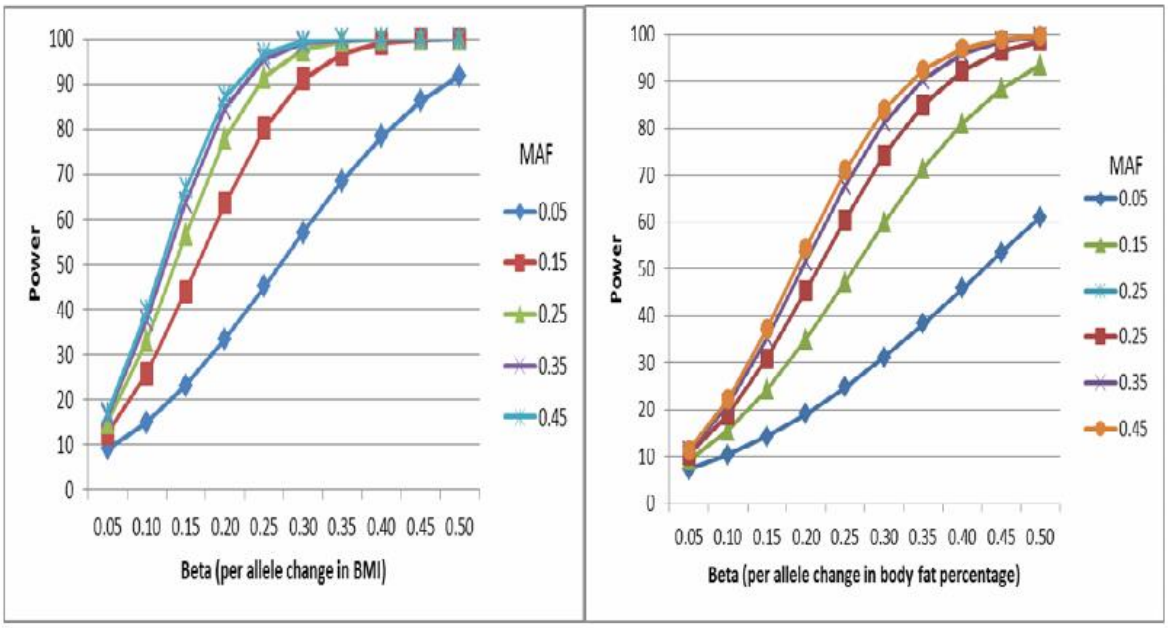
Power analysis for a sample size of 12000 individuals based on proposed candidate gene study for BMI (shown on the left) and for DXA (total body fat) (shown on the right). Given a sample size of 12000 in the AWI-Gen study, this graph shows effect size (x) which could be detected at a given power (y) for different minor allele frequencies (ranging from 0.05-045). For example, with a minor allele frequency of 0.25, we will have 80% power to detect an effect size (Beta) of 0.20 per allele change in BMI, and an effect size of 0.25 per allele change in body fat percentage.

For AWIGEN 2, we will follow the same participants. We anticipate a retention of 70% from the 2000 participants recruited in phase 1. Thus, our sample size for AWIGEN-11 will be approximately 1400 participants for the Kenyan site to for sub-studies 1 and 2.

For Sub-studies 3 & 4 we will randomly sample 250 individuals for each sub-study which is a large sample by most microbiome project standards.

For Sub-study 5 we will include all participants selected in Sub-study 1

Figure 2- Power analysis for a sample of 12000 individuals based on two candidate gene studies.



VIII. Data Collection

Participants from the AWI-Gen phase I study will be invited to participate in the study virtually by phone for the questionnaire section of the study. They will then be invited to a central place for sample collection.

a) Variables

AWI-Gen II data collection will include all relevant questions used in AWI-Gen I including age, gender, BMI, Visceral fat levels, T2 diabetes status, blood pressure, socio-economic status, lifestyle (diet, tobacco, alcohol, exercise etc.) and HIV infection status. In addition, for participants in microbiome study we will ask information on antibiotics use. We will repeat the anthropometric measurements including height, weight, waist and hip circumference and ultrasound measurements of visceral and subcutaneous fat, and cIMT.

Table 1 below shows the nature of data collection for AWI-Gen I and II. The majority of the participants will be between the ages of 45 and 65 during the Phase 2 data collection. For Sub-study 1, we will collect additional data on aging and cognition in order to examine genomic associations with cognitive function and dementias. Questions on childhood adversity and recent trauma has been added.

Table 1: Variables to be collected in AWI-Gen II

Category	Variable	AWI-Gen I	AWI-Gen II

Socio-demographic	Age, Sex, Country, Home language, Self-reported ethnicity/tribe, Family composition, Pregnancy status, Marital status, Employment, Level of education, Household attributes for social economic status (SES)	Yes	Yes
Health History (Cardiometabolic risk factors and general health)	Diabetes, stroke, hypertension, angina, heart attack, congestive heart failure, high cholesterol, thyroid disease, kidney diseases, breast/cervical/prostate/other cancers, asthma or reactive air diseases, weight problem/obesity	Yes	Yes
Anthropometry	Weight, Height, Blood pressure, Pulse, Waist circumference, Hip circumference	Yes	Yes
Ultrasonography	Visceral fat and Subcutaneous fat Carotid intima media thickness (cIMT)	Yes	Yes
Environmental	Tobacco use, Alcohol use, Drug use Diet, Exercise/general physical activity questionnaire (GPAQ), Exposure to pesticides	Yes	Yes
Infection history	Malaria, Tuberculosis, HIV	Yes	Yes
Aging and Cognition	Measures will be adapted from the Phase 1 HAALSI tool (based on the Mini Mental State Examination (Folstein MF et al)); and the just-published validation in Agincourt of a novel, well-performing tablet-based cognitive screen (Humphreys G et al., 2016).	No	Yes
Trauma/adversity	Childhood and Past five years	No	Yes
Category	Variable	Phase 1	Phase 2
Blood collection	Buffy for DNA Serum Plasma Dried blood spot (DBS) Point of care (lipid / glucose levels)	Yes Yes Yes No No	Yes Yes Yes Yes Yes
Urine collection	Biomarkers (total protein, albumin, creatinine)	Yes	Yes
Spirometry	Forced expiration volume (FEV), Forced capacity volume (FCV)	No	Yes

b) Procedures

The minimum phenotype data that will be obtained for each of the study participants is outlined in **Table 2** below. A phenotype questionnaire has been developed and is submitted together with

this proposal as **Appendix 2**. The primary tool for collecting demographic and phenotypic data will be a customized REDCap forms.

Blood and other sample collection and processing

A total of 30ml of venous blood (after overnight fasting) will be taken to extract analysis materials as outlined in Table 3. Overnight fasting blood samples will be collected from an antecubital vein with minimum stasis by trained phlebotomists. The collected samples will be temporarily stored in cool boxes in the field and then transported to the office laboratory within one hour of collection.

The plasma and serum samples will be obtained by centrifuging blood samples at 200xg for 20 minutes at 4°C. Plasma, serum and buffy coat extracts will be immediately aliquoted for storage. Plasma and serum aliquots will be stored at -80°C until assayed. Buffy coat aliquots will be stored at -80°C until DNA extraction. Date of sample collection will be noted and the research team will be cognisant of timeframes governing optimal biochemical analyses for different measures.

For DBS, whole blood tube will be inverted 2-4 times and subsequently stopper opened carefully. Using a micropipette, 50µl will be aspirated and transferred to the center of one circle without touching the DBS card directly. This procedure will be repeated to fill all required circles of the card and then air dried. The filter paper card will then be placed in a single gas impermeable Ziploc bag containing 1 to 2 desiccant sachets to protect specimens from moisture. The bag will be transferred to -20^{o}C or lower temp freezer as soon as possible.

Table 2- Phenotype measures to be collected from each participating individual

Indicators	**Measures**
(1) BMI	(1) Continuous variable; categorical overweight & obese classifications
(2) Waist & hip circumference	(2) Waist/hip ratio; waist/height ratio
(3) Body fat composition	(3) Ultrasound scan measures of subcutaneous abdominal fat and Visceral abdominal fat
(4) Blood pressure	(4) Systolic and diastolic
(5) Blood Glucose	(5) Fasting Blood glucose; HbA1c
(6) Lipid profile	(6) Fasting total cholesterol, LDL, HDL, Triglycerides
(7) Carotid artery thickness	(7) Carotid Inter-Medial Thickness (cIMT)
(8) HIV status	(8) HIV serostatus – dried blood spots to be tested at a later stage
(9) Kidney function	(9) Albumin to total protein ratio and Creatinine levels
(10) Lung function	(10) Spirometry measurements for lung function (forced expiration volume (FEV_1), Forced capacity volume (FCV) and FEV_1/FCV

A 20ml spot urine sample will be collected from each participant in order to test albumin, total protein ratio and Creatinine levels. The samples will also be transported from the field to the laboratory within an hour of collection. The urine will be centrifuged and aliquoted immediately for storage. Urine aliquots will be stored at -80°C until assayed. Date of sample collection will be noted and the research team will be cognisant of timeframes governing optimal biochemical analyses.

A fresh small stool/faecal/poo sample will be collected in a sterile 50mL polypropylene conical tubes for bacterial DNA. It will then be stirred by a sterile spatula in the absence of liquid nitrogen immediately post-defecation. The samples will be transported from the field to the laboratory within an hour of collection. Five 18-22-mg subsamples will be taken from the stool sample. The samples will be snap frozen and stored at -80^{0}C until DNA extraction. The samples will not be thawed until extraction.

Testing for HIV status will be voluntary. This test will only be performed by a fully trained registered counsellor or nurse, or trained staff member. Only participants who have consented to receive an HIV test and have been counselled will be tested for HIV using the rapid test. Before they are tested, the participants will be asked whether or not they wish to receive the results. Disclosure of test results will be done according to HIV testing protocols in Kenya. If the test report states negative it means that there are no antibodies to HIV however, important information about the window period will be explained to the participants. If the report states positive, the participant will be referred to VCT for counselling and second test to check the result.

Table 3- Collection of blood samples to extract materials for analysis of different phenotype and genotype measures

Tube type	**Additive**	**Quantity**	**Material for analysis**	**Measure**	**Aliquots**
Purple top	EDTA	6 ml	Buffy coat ,whole blood, plasma	HbA1c	1X 1 ml
				DNA	1X0.4 ml
				Biobank	1X1 ml
				Centre Backup	1X1 ml
Red top	None	20 ml	Serum	Hormones(Sex Hormones*)	1X0.5 ml
				Hormones (Inhibin B, FSH, SHBG)	4X0.5 ml
				Lipids	2X0.5 ml
				Creatinine	
				Insulin	
				Biobank	2X0.5 ml

				Centre Backup	2X0.5 ml
Grey top	NaOX (Sodium fluoride-Glycolytic inhibitor)	4ml	Plasma	Glucose	1X1 ml

*****Sex hormones tested: Aldosterone, androsterone, cortisol, 11-deoxycortisol, cortisone, corticosterone, dehyroepiandrosterone (DHEA), Dehyroepiandrosterone sulfate (DHEAS), dihyrotestosterone, estradiol, 17-hydroxyprogesterone, progesterone and testosterone

Most of the testing will be performed in South Africa at the University of the Witwatersrand. Testing of DNA often requires complex machines and experts to run them, and this is not available at the APHRC. In this case, we will a send small amount of our DNA out of the country for testing. All the results will be reported directly back to us, and no other copies of the results will be stored.

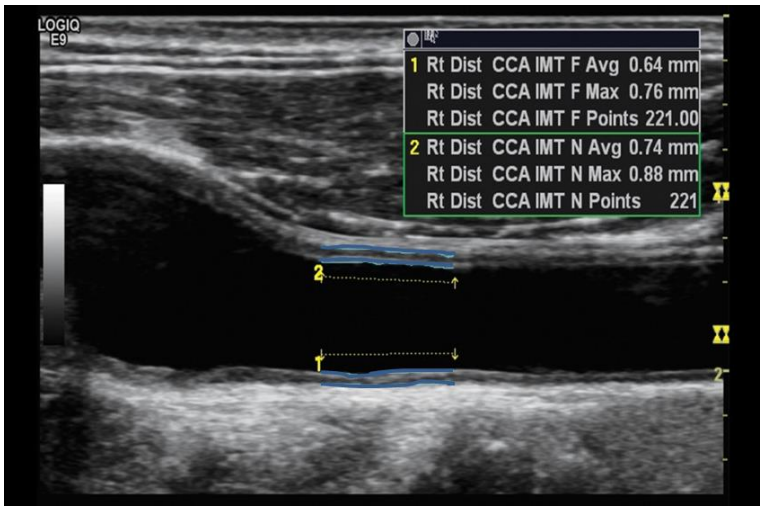
Collection of data for other Phenotype Measures

(1) Body weight and height, in light clothing and without shoes, will be measured using an electronic scale and a fixed or mobile stadiometer (Holtain, UK). The waist circumference will be measured with a soft measuring tape to the nearest 0.5cm at the level of the smallest girth above the umbilicus in the standing position. The hip circumference will be measured over the widest part of the gluteal region. From these measures we will be able to determine BMI, waist/hip ratio, waist/height ratio, and prevalence of underweight, normal weight, overweight and obesity using the WHO cut offs.

(2) Ultrasound will be used to determine abdominal adipose depths as proxies for visceral (VAT) and subcutaneous (SCAT) adipose tissue. A LOGIQ e ultrasound system (USS) (GE Healthcare, CT, USA) with a 2-5 MHz 3C-RS curved array transducer will be used to determine VAT and SCAT thicknesses. USS VAT thickness will be defined as the distance (cm) from the peritoneum to the vertebral bodies, and USS SCAT thickness will be defined as the depth (cm) from the skin to the linea alba [83]. The scan depth will be set at 15 cm for the visceral fat measure and 9 cm for the subcutaneous fat measure so as to visualise the relevant anatomical structures. Both measurements will be obtained where the xyphoid line and the waist circumference meet. All USS measurements will be taken by trained operators. Relative intra-observer technical error of measurement (TEM) will be assessed regularly to ensure that the TEM remains below 2% at each site in comparison with the central trainer. TEM will be calculated on repeated measurements in at least 15 individuals. All USS images will be centrally re-analysed.

(3) The carotid inter-medial thickness will be determined first by scanning the neck area in a longitudinal plane to find the common carotid artery (CCA) and scanning the area immediately after for a length of about 2cm. The top line of the posterior intima is identified and fixed and the cursor is then moved along the anterior aspect of the intima and the line fixed as shown in the figure below. Readings for min, max and average

thickness will be given in mm. The right carotid will be scanned first followed by the left carotid.



(4) Blood pressure will be measured three times using a digital device (Omron M6; Omron, Kyoto, Japan). Appropriate cuff sizes will be used, and participants will be measured seated and resting with a three-minute break between measurements. The first blood pressure measurement will be discarded and the second and third measurements averaged.

(5) Spirometry tests to measure lung function will be measured using a spirometer by a study Professional-qualified nurse- where the participants breathe into it. It will be necessary to repeat the test up to 8 times to ensure three similar results are obtained. The whole procedure will take about 15 minutes to complete. Those with decreased function, will be invite to participate in a test that will examine whether their decreased lung function can be reversed. This will involve them taking 4 puffs of a drug called salbutamol and then after a wait of 15 minutes repeating the spirometry test. Salbutamol is often used to treat asthma and commonly used in these types of reversibility tests. Those with allergic reaction to any inhaled drugs will not take part in this reversibility test.

(6) Socio-demographic data will be collected using telephone interviews (for those with active phone numbers) and face to face interviews (for those missing phone numbers) that will include questions on:

a) Home language, self-reported ethnicity (for primary respondent, parents and grandparents), medical and health histories (in particular, self-reported information on HIV serostatus, (if willing), TB, other non-communicable disease), health service access, and menstrual history for females.
b) Current living conditions: Household SES (banded income, assets, and housing) and social support.

Training of research assistants and piloting

We will select field workers based on the type of samples and data to be collected. They will include clinical officers/nurse/laboratory personnel and other experienced and qualified non-clinical data collectors.

- Collection of blood samples and data for other phenotype measures will be undertaken by field workers trained over a five-day period, preferably with prior experience taking the same kind of measures or with a clinical/nursing background.
- Ultrasound imaging will be done by trained and licensed ultra-sonographers who will undergo additional 2-week long training in South Africa at University of Wits to ensure consistency in taking and reading the measurements at all the participating sites.
- Spirometer test will be done by a nurse who will undergo 4 days training in South Africa at University of Wits to ensure consistency.
- The socio-demographic data will be collected by experienced interviewers trained for five-days.

Training of the field team will cover the study rationale, objectives, study approach and the data collection procedures. The team will be trained together to ensure that they all understand each other's roles as well as their own and what others are doing. In addition, the training will cover ethical issues, specifically confidentiality, privacy and voluntary participation.

The team will also be taken through every page of the information brief to be used for informed consent, to explain the key elements and clarify any issues that may not be clear. They will also be taken through every question to understand the purpose, the data it is intended to collect, and the objective it answers. The training will involve lectures, open discussions, demonstrations and role plays. A two-day pilot will be undertaken outside the study area with every member of the team expected to collect data on at least 6 participants. A one-day debriefing session will be held to discuss any questions that are unclear, wrong instructions, questions respondents struggled with etc. Thereafter the tools will be revised and printed.

c) Ethical considerations

This study will collect information that is critical for understanding the pathways to the development of CMD. The information will include genetic, phenotypic, environmental and social factors associated with obesity in adults living in informal urban and rural African environments. The overall AWI-Gen study protocol has been approved by the University of the Wits Ethics Committee. In addition, the research team in Kenya has undergone the NIH training on protecting human research participants (copies of certificates attached at the end of the application). Ethical review and approval will be sought from AMREF ESRC.

Virtual consent process

For telephone /virtual interviews, participants will be contacted in advance and briefed on the study. An informed consent will be discussed and the interviewer will administer the consent in an audio-recorded telephone conversation and allow the participants to give an audio recorded

consent. Study participants who prefer to sign on the form will be given the information sheet and consent form to sign during clinic procedures.

Face-to-face consenting process

Given the envisaged data use, sharing and storage arrangements, **broad consent** will be sought from the participants. Broad consent provides for answering the specific research questions in the AWI-Gen project as well as any additional future research questions that will contribute to the knowledge of genetics in Africans. As the field of genetics grows globally and in Africa, and with advancements in techniques and technologies for genetic studies, the current study offers an unprecedented opportunity to collect and store materials that may be used in future studies.

Given the complexity of the study, participants will be requested to consent separately to different components of the study. For instance, a participant may consent to having their socio-demographic data being collected, phenotype measures taken, testing for the HIV serostatus, testing for kidney function, genetic testing and broad consent for future studies. Data and samples from participants that do not give broad consent will be sent to the H3A Bio-repository or EGA, but access will not be granted to scientists outside the AWI-Gen project or to AWI-Gen scientists who wish to answer research questions outside what is defined in the AWI-Gen protocol. All participants will have the right to withdraw consent at any time. In that case their data will be withdrawn from the database and their samples will be destroyed wherever they are.

Approach to informed consent

A harmonized informed consent process has been developed for implementation across all the AWI-Gen study sites and adapted to the local context in each country. Informed consent will be preceded by community engagement and information sessions and an opportunity to ask questions about the project. IEC materials will be produced to be used in these sessions. Since data and sample collection will take place at a centralized place, participants will be initially contacted by a community mobiliser who will seek preliminary consent. Only those who accept to participate in principle will be given an appointment. At the data collection center, a group session will be organized for all participants mobilized for that day explaining the study rationale, the procedures, benefits and potential harms, rights and conditions of participation. After that each individual will be taken through the process again to clarify any concerns and to obtain individual consent for the various study components.

Benefits:

The discoveries that come from the genetic studies will not be of direct benefit to the study participants and will not be communicated back to them. The discoveries may lead to new knowledge that may in the future be helpful in diagnosing and managing CMD conditions in African populations. However, in assessing the phenotype, participants will receive some of their cardiometabolic risk measures such as weight, height, BMI, blood pressure, blood glucose and cholesterol levels. Awareness of their risk may spur some of them to take action and seek care

or change their lifestyles. Those with moderate-high risk will be referred for further management at the various clinics established with support from APHRC through previous projects in the study communities. Such clinics exist at Kariobangi health centre, Lunga Lunga health centre, Provide International and Korogocho community clinic. In addition, participants who wish to know their HIV serostatus will be provided with a voucher to undergo HIV prevention counselling before getting tested at accredited VCT centres.

Risks:

Taking a blood sample from a vein may cause a little discomfort and a little pain. This discomfort will be reduced because the procedure will be done by a qualified nurse or phlebotomist. The DNA study will enable us to pick up cases of non-paternity (this is when the stated father is not the biological father of the child). Should this be detected, this information will not be conveyed back to the respondents and the samples will then be treated as independent (unrelated) samples in the case of family trios. There is a remote risk of the participants' genetic and socio-demographic information being used to identify individuals. This will be mitigated by ensuring that all shared data and samples are de-identified and that linkage back to individual identifiers is through a series of steps that are only possible with the involvement of the restricted number of study team members in Kenya.

Other measures to minimize risks: No participant will be interviewed without informed consent (see informed consent forms - Appendix 4). Prior to the data collection, there will be a community meeting in which the study will be introduced and questions will be answered. Also, potential participants will be read a consent script containing the following:

- A statement that they are being asked to participate in a research study
- A statement explaining the purpose of the research, the expected duration of the subject's participation and the procedures to be followed
- A description of how the research will benefit the target group and the potential risks of participation
- An explanation of how the privacy of the respondent will be protected and how confidentiality will be maintained
- The name and the telephone contact of the Principal Investigator and contacts of the AMREF ethical review board who the subject may contact with any pertinent questions about the research, or to whom the subject may register a complaint.

Voluntary Participation:

Participants will be informed during the consent process that they may refuse to participate or may refuse to answer any question which they do not want to answer, and no harm will occur to them or anyone in their family regardless of their participation decisions. Participants will also be free to withdraw from the study at any point in time. In case this happens once the data and samples are already in the bio-repositories, information will be rapidly transferred from the

Kenya site principal investigator (PI), to the AWI-Gen overall PI, to H3A Bio-repository and the EGA for the deletion of any stored data and destruction of any stored specimens.

Confidentiality:

Interviews will occur in private and will be conducted in a place and environment that allows the respondent to freely express their views without fear of victimization. All personnel involved in data/sample collection, supervision, editing, and analysis will be trained on research ethics, especially the importance of protecting privacy and confidentiality. No individual respondents will be identified in any publications.

IX. Data Processing and Analysis

a) Data management, storage and sharing

Individuals will be assigned barcodes that will be placed on all the samples collected, questionnaires, ultrasound images and sample aliquots. Data will be captured in a secure online data capture system (RedCap®). Data transmitted to university of Wits for pooled analyses will not have any personal identifiers other than the barcodes.

The following key principles will guide the data management, storage and sharing:

The long term storage of the DNA samples from this project will be done in two locations, one in the country of origin (in this case Kenya) and one in the laboratory that will coordinate the genetic and epigenetic analyses. Since data collected from the Kenya site will be analysed with those from five other sites, there is a need for harmonization and standardization in the collection and analysis of samples for phenotyping and DNA extraction. The same applies for genomic and genetic analyses. For these reasons, the samples from this study and all those from the five other sites will be shipped to (a yet-to-be determined) central place for DNA extraction and analysis. The choice of the central analysis laboratory will depend on capacity to conduct the required analyses, quality standards and certifications, and cost. All sites will retain samples in storage that can be used for future analyses and genetic studies.

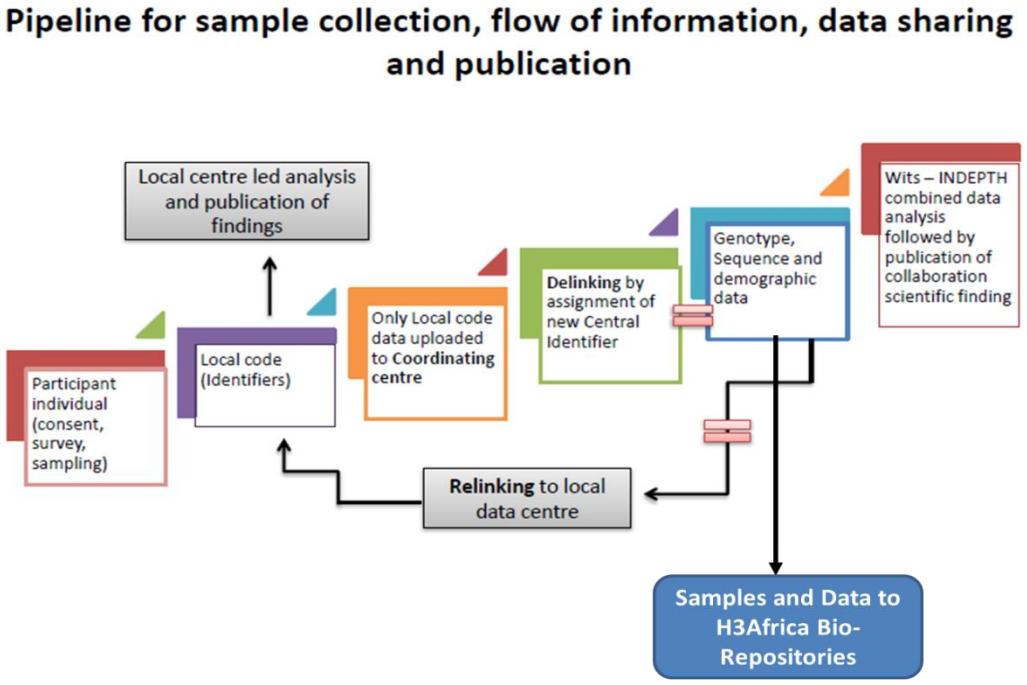
Second, as part of the data sharing and access policy of the whole H3Africa consortium, all participating sites (not just those in the AWI-Gen project) are required to avail their data and a DNA sample in a publicly accessible repository after an appropriate period of time during which the data generators will exploit the data. These repositories include the H3A Bio-repository, funded through the same H3Africa initiative and the European Genome Phenome Archive (EGA). A draft H3Africa Data Access and Release Policy is provided in Appendix 5. Underpinning the H3Africa data access and sharing policy is the need to maximise the returns on investments in this pioneering initiative and to assure the availability of samples and data for future genetic studies, discoveries and innovations that are likely to benefit Africans as this field of research grows. It is therefore a distributed model which ensures that DNA is safeguarded against accident or disaster. This is important for capacity development in the different African countries and to give the Centres autonomy in the future use of the DNA samples. The access to the samples will

be governed by a set of policies developed to ensure controlled, but wide access in an ethical manner with minimal risk to the research participants in terms of confidentiality and potential stigmatisation.

In Figure 3, we show the flow of data and samples from the sites of collection to the central processing laboratory, the H3Africa Bio-repositories and back to the sites. The opportunities for site-specific data analyses and publications as well as project-wide analyses and publications are also shown.

For analyses of samples from the AWI-Gen project, provisions will be made for staff from the collecting centres to accompany the samples to the central laboratory, participate in the analyses and undergo training in specific laboratory techniques for genetic studies. This is part of the capacity building strategy.

Figure 3 – Sample and Data collection, flow and sharing



b) Data sharing

This project will generate a lot of genetic data from samples collected from participants as well as other population data (e.g. anthropometric data, demographic data). We have an obligation to release these data to the wider scientific community and also to protect the study participants. In this regard, we are bound to accept the H3Africa's consensus Data Sharing, Access and Release policy (Appendix 5). The policy, as indicated above, aims to maximize the impact our data could have in driving medical research forward, while protecting those who contributed to this valuable resource. A set of guidelines for using the project data has been developed, specifying who will be granted access for which purposes. Furthermore, a data use

agreement form will be developed including the terms and conditions of accessing the data (see below). The following documents must accompany all requests to use the data: 1) A clear and concise description of the intended purpose and method of analysis of the data and 2) A list of the names and organizational affiliations of all those who will engage in this analysis. Applications will be considered by the H3Africa Sample and Data access committee in consultation with the overall AWI-Gen PI. All datasets to be released will not contain any personal identifiers or links to personal identifiers.

c) Data Analysis

1) Analytical approach – population epidemiology study

Population characteristics will be expressed as means (SDs) or medians (interquartile ranges) for continuous variables (depending on whether these are normally distributed) e.g. BMI, waist/hip and waist/height ratios, blood pressure and visceral and subcutaneous adipose tissue. For categorical variables, frequencies will be expressed as percentages e.g. underweight/normal weight/overweight/obesity, demographic data (home language, self-reported ethnicity, medical and health histories, health service access, menstrual cycle) as well as current living conditions (household SES, social support).

2) Analytical approach – genetic association study

Genotype and allele frequencies will be calculated by simple allele counting. The association of phenotype with the genetic variables will be done using a t-test or Mann-Whitney U test for continuous variables and a chi-square test for categorical variables. A linear regression model will be used to analyse the association between genetic variables and those variables that were statistically significant in the bi-variable analysis. All statistical analyses will be performed using R and other statistical packages (i.e. Stata), and appropriate significance levels will be used. Programs such as STRUCTUE and ADMIXTURE will be used to assess population sub-structure.

X. Plan for Communicating Findings of the Study

The long-term aim of studying the genetic contribution to body fat mass would be to be able to identify those subjects with the highest risk of becoming obese, thus allowing for early interventions. The findings from the phenotype and socio-demographic components will be shared with the study communities through open dissemination forums (Barazas). There will be two dissemination meetings, one at the community and another one with individual participants.

The study findings will also be first shared with Community Advisory Committee(CAC)-Nairobi County and national policy makers in Kenya. In addition, the aggregated findings from the genetic analyses will be widely shared through available public platforms such as the HapMap as well as academic forums such as scientific conferences and peer-reviewed publications.

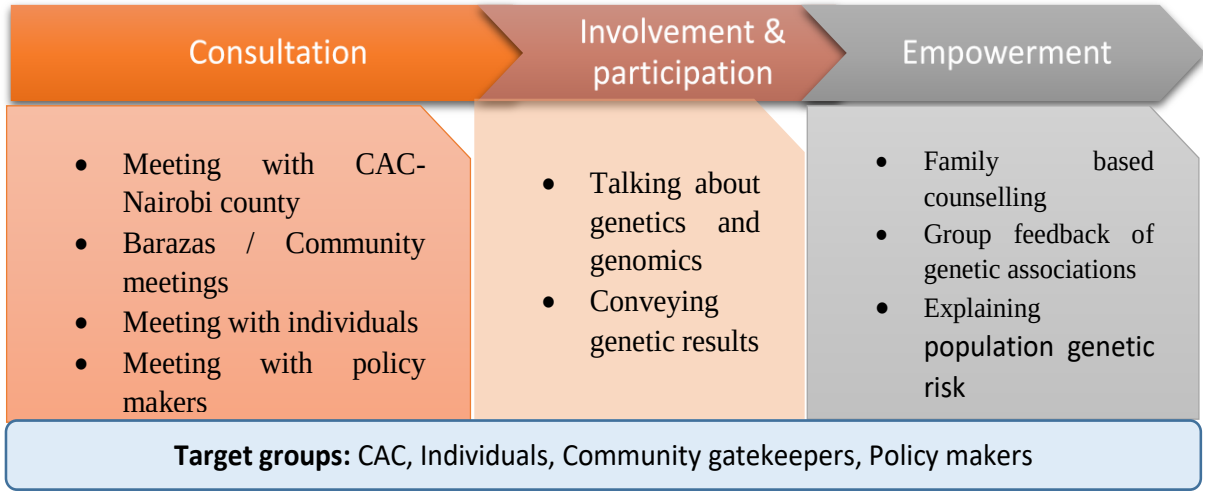


Figure 4: Dissemination plan

XI. Study Limitations and Risks

During the long term DNA storage, there is a possibility of DNA denaturation despite all the safety guidelines due to unprecedented storage systems malfunction, accident or disasters. In order to mitigate the risk and associated loss, there will be a distributed model in the long term storage of the DNA samples from this project in two locations, one in the country of origin (in this case Kenya) and one in the laboratory that will coordinate the genetic and epigenetic analyses.

XII. Management and Organization of the Study

a) Role of each Investigator

Catherine Kyobutungi, the Kenya site PI is the executive director at APHRC. Her role is to provide overall intellectual guidance and coordination of the project, supervise the research officers' activities, and provide the external reporting needed by the funder. She will participate in data analyses and will lead the site specific scientific publications

Gershim Asiki is a research scientist at APHRC. His role will be to manage the project hence will be in charge of overall coordination of the project including overseeing the research activities, dissemination, policy engagement and reporting. He will be leading the quantitative and qualitative aspect of the study. He will participate in analyzing the data and writing scientific outputs.

Shukri Mohamed is a research officer at APHRC. Her role will be to coordinate the activities for the study. She will manage the day to day project management and will be primarily responsible for the quality of the data and samples collected in Kenya. She will participate in data analysis and scientific writing.

Isaac Kisiangani is a research officer at APHRC. He will also coordinate the study activities. He will manage the day to day project activities and will be primarily responsible for the quality of samples collected in Kenya. He will supervise the research assistant and participate in data analysis and scientific writing.

Field coordinator will also coordinate the day to day data collection activities, organize field logistics and oversee the work of the laboratory technologist. This person will participate in data analysis and scientific writing.

Michèle Ramsay, the AWI-Gen overall PI is a Professor in the Division of Human Genetics at the National Health Laboratory Service and University of the Wits in Johannesburg. Given her wide experience in genetic basis and molecular epidemiology of single gene disorders; will also provide overall guidance on the research study, designing tools, oversee the sample quality control processes, manage the data sharing process through the H3Africa Data and Sample Access Committee, lead the data analysis and interpretation and build the capacity of the research teams in Kenya and the other participating sites, reporting to the NIH.

b) Time Frame/Duration of the Project

The baseline data collection and analysis for this study lasted to 2.5 years. The same individuals recruited in the first wave will be followed for five years. An inception meeting with other study partners will be held in October 2019 after ethical approval process is done. Recruitment and training of the data collectors will be done in November/December. Data collection will begin in January/February 2020 and is expected to last 12months. Sample processing will be done in parallel to the data/sample collection. Data quality control will take between 4-6 months in a central place and will be immediately followed by genotyping for component 2 – which will last for about 6 months. Data management and curation for the genetic association component will take about 2-3 months, before the analytical data files are available for analysis to all the participating sites. The whole genome sequencing for the population structure component will start after. Joint analyses will be undertaken by all the sites during workshops held in various venues in early 2021. Scientific publications will be submitted within a few weeks of the analysis workshops. A detailed timeline with the different project activities is provided in Appendix 6 of this submission.

c) Budget

1) Summary Budget

Item	Sub-total ($)	Subtotal (KES)
Personnel costs	90,096	9,009,600
Materials and Office Consumables	2,400	240,000
Data Collection and Entry	101,351	10,135,100
Meetings, Community mobilization, Dissemination	4,706	470,600
Equipment and Study Consumables	31,081	3,108,100
Indirect costs	18,979	1,897,900

Total	**$248613**	**KES 24,861,300**

2) Detailed Budget

Detailed budget is presented in Appendix 7

3) Justification of the budget

The budget is based on the current estimates of prices and wages and includes, competitive field allowances, and estimated institutional administrative overheads. The personnel salaries and benefits costs cover the facilitative fee for the proportion of time that the Principal Investigators, Co-Investigators, data systems manager, program assistant and community relations office will devote to the activity. Community meetings to sensitize the community on the study and disseminate findings have also been budgeted for. Data collection costs include; training costs for the field team, fieldwork costs, consumables costs, HIV testing costs, point of care phenotype costs, urine collection costs and sample processing costs. The budget also includes materials, office consumables costs and equipment to facilitate data collection. The institutional administrative overheads (indirect costs) are calculated at 8% of the total costs.

XIII. Appendices and References

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b) Appendices

Appendix 1: Curriculum Vitae of Investigators

CV of (Dr. Kyobutungi Catherine)

Proposed Position in Research:	Kenya Site Principal Investigator
Proposed role in the study:	Technical oversight
Organisation:	African Population & Health Research Center
Name of Staff:	Dr. Kyobutungi Catherine
Profession:	Epidemiologist, Executive Director
Date of Birth:	January 7th 1972
Years with Organisation:	Twelve
Nationality:	Ugandan
Membership in Professional Societies:	International Epidemiology Association Global Health Systems
Detailed Tasks Assigned in Project:	She is will be the PI and will offer overall technical direction to the study and be the main contact person for any correspondence.
Education & Qualifications:	

Qualification	Awarding Institution	Country	Year
PhD – Epidemiology	Medical faculty of the Ruprecht-Karls-University, Heidelberg	Germany	Jan 2006
MSc – Community Health and Health Management (CHHM)	Ruprecht-Karls-University, Heidelberg,	Germany	Sept 2002
MBChB	Makerere University Kampala,	Uganda	1995

Employment Record:

From (year)	To (Year)	Position	Employer
October 2017	To-date	Executive director	African Population and Health Research Center
20th Nov 2014	October 2017	Director of Research	African Population and Health Research Center
Jan 2013	2014	Senior Research Scientist: Head, Health Challenges and Systems Research Program and Head of Policy Engagement and Communications	African Population and Health Research Center
Jan 2010	Dec 2012	Research Scientist	African Population & Health Research Center, in Nairobi Kenya
Nov 2007	Dec 2009	Associate research Scientist	African Population & Health Research Center, in Nairobi Kenya
May 2006	Oct 2007	Post-doctoral fellow	African Population & Health Research Center, in Nairobi Kenya

Summary of research experience:

I have been involved in research since 2002 when I embarked on my PhD studies. Soon after my PhD studies, I joined APHRC in 2006 as a post-doctoral fellow where I have been involved in research on a full time basis. Since 2006, I

have been a research project manager of more than 14 projects and a principal investigator on more than 10 projects. I have published more than 60 peer-reviewed papers.

Selected Peer-Reviewed Publications:

1. Haregu TN, Oti S, Ngomi N, Khayeka-Wandabwa C, Egondi T, **Kyobutungi C.** Interlinkage among cardio-metabolic disease markers in an urban poor setting in Nairobi, Kenya. Glob Health Action. 2016 Feb 9;9:30626. doi: 10.3402/gha.v9.30626. eCollection 2016. PubMed PMID: 26864740.
2. Atela M, Bakibinga P, Ettarh R, **Kyobutungi C**, Cohn S. Strengthening health system governance using health facility service charters: a mixed methods assessment of community experiences and perceptions in a district in Kenya. BMC Health Serv Res. 2015 Dec 4;15(1):539. doi: 10.1186/s12913-015-1204-6. PubMed PMID: 26637186; PubMed Central PMCID: PMC4670501.
3. Werner ME, van de Vijver S, Adhiambo M, Egondi T, Oti SO, **Kyobutungi C**. Results of a hypertension and diabetes treatment program in the slums of Nairobi: a retrospective cohort study. BMC Health Serv Res. 2015 Nov 17;15(1):512. doi: 10.1186/s12913-015-1167-7. PubMed PMID: 26577953; PubMed Central PMCID: PMC4650397.
4. van de Vijver S, Oti S, Oduor C, Ezeh A, Lange J, Agyemang C, **Kyobutungi C**. Challenges of health programmes in slums. Lancet. 2015 Nov 21;386(10008):2114-6. doi: 10.1016/S0140-6736(15)00385-2. Epub 2015 Oct 6. PubMed PMID: 26452707.
5. Oti, S., van de Vijver, S., **Kyobutungi, C**., Gomez, G.B., Agyemang, C., Eric P. Moll van Charante, E.P., Brewster, L.M., Hendriks, M.E., Schultsz, C., Ettarh, R., Ezeh, A., and Lange, J (2013). A community-based intervention for primary prevention of cardiovascular diseases in the slums of Nairobi: The SCALE UP Study protocol. *Trials* Dec 1; 14:409.
6. Ettarh, R., van de Vijver, S., Oti, S., and **Kyobutungi, C** (*2013*). Overweight, obesity and perception of body image among slum residents in Nairobi, Kenya. *Preventing Chronic Disease* Dec 19; 10:
7. **Oti, S.O., van de Vijver, S.,** Agyemang, C., & **Kyobutungi, C** (2013). The magnitude of diabetes and its association with obesity in the slums of Nairobi, Kenya: results from a cross-sectional survey. *Tropical Medicine and International Health* Dec;18(12):1520-30
8. Egondi, T., **Kyobutungi, C**., Ng, N., Muindi, K., Oti, S., van de Vijver, S., Remare, E. and J. Rocklöv, (2013). "Community Perception of Air Pollution and Related Health Risks in Nairobi Slums" International Journal of Environment Research and Public Health, Vol. 10 4851-4868.
9. **Van de Vijver, S., Oti, S.O.,** Cohen, T., Hankins, C., **Kyobutungi, C**., Gomez, G. B., Brewster, L., Agyemang, C., and Lange, J (2013). Introducing a model of cardiovascular prevention in Nairobi's slums by integrating a public health and private sector approach: the SCALE UP study. *Global Health Action* Oct 21;6:
10. Van de Vijver, S., & Oti, S.O., Agyemang, C., Gomez, G., & **Kyobutungi, C (2013)**. Prevalence, awareness, treatment and control of hypertension among slum dwellers in Nairobi Kenya. *Journal of Hypertension.* May; 31(5): 1018-24

11. Di Cesare, M., Khang, Y., Asaria, P., Blakely, T., Cowan, M.J., Farzadfar, F., Guerrero, R., Ikeda, N., Kyobutungi, C. Msyamboza, K.P., Oum, S., Lynch, J.W., Marmot, M.G., & Ezzati, M on behalf of the Lancet NCD Action (2013). Group Inequalities in non-communicable diseases: challenges and opportunities for action. *The Lancet.* February; 381 (9866): 585-597

12. Ye Y, **Kyobutungi C**, Ogutu B et al (2013) Malaria mortality estimates: need for agreeable approach - Editorial- *Tropical Medicine and International Health*, DOI: http://dx.doi.org/10.1111/tmi.12020. February; 18(2): 219-221

13. Egondi, T., **Kyobutungi**, **C.,** Kovats, S., Muindi, K., Ettarh, R., Rocklöv, J (2012). Time-series analysis of weather and mortality patterns in Nairobi's informal settlements. *Global Health Action 5: 19065*

14. Ekirapa A, Mgomella GS, **Kyobutungi C** (2012). Civil society organizations: Capacity to address the needs of the urban poor in Nairobi**.** *J Public Health Policy*. Nov;33(4):404-22

15. Ettarh, R., Mutua, M.K., **Kyobutungi, C.** (2012). Ethnicity and delay in measles vaccination in a Nairobi slum. *Tropical Medicine and Health*, *40*(2): 59-62

16. Ettarh R. Kimani, J.K., & **Kyobutungi, C.** Correlates of HIV status awareness among adults in Nairobi slums. *African Journal of AIDS Research. 11(4): 337-342*

17. Ettarh, R., & **Kyobutungi, C** (2012). Physical access to health facilities and family planning in Kenya. *Journal of Family Planning and Reproductive Health Care, 16[3]: 47-55*

18. Bellows B, **Kyobutungi C**, Mutua MK, Warren C, Ezeh A (2012). Increase in facility-based deliveries associated with a maternal health voucher programme in informal settlements in Nairobi, Kenya*. Health Policy and Planning*. 27(4),1-9

19. Kimani JK, Ettarh R, **Kyobutungi C**, Mberu B, Muindi K (2012).. Determinants for participation in a public health insurance program among residents of urban slums in Nairobi, Kenya: results from a cross-sectional survey. *BMC Health Service Research*. 19; 12 :66.

20. Karanja S, Mbuagbaw L, Ritvo P, Law J, **Kyobutungi C**, Reid G. Ram R, Estambale B. and Lester R. (2011). A workshop report on HIV mHealth synergy and strategy meeting to review emerging evidence-based mHealth interventions and develop a framework for scale-up of these interventions. *The Pan African Medical Journal, 10*, 37.

21. Ziraba, A.K., **Kyobutungi, C.,** & Zulu, E.M. (2011). Fatal injuries in the slums of Nairobi and their risk factors: results from a matched case-control study. *Journal of Urban Health, 88* (Suppl 2), 256-265.

22. Kimani-Murage EW, Madise NJ, Fotso JC, **Kyobutungi C**, Mutua MK, Gitau TM, Yatich N (2011). Patterns and determinants of breastfeeding and complementary feeding practices in urban informal settlements, Nairobi Kenya, *BMC Public Health* May 26; 11: 396

23. Falkingham JC, Chepngeno-Langat G, **Kyobutungi C**, Ezeh A, and Evandrou M (2011). Does Socioeconomic Inequality in Health Persist among Older People Living in Resource-Poor Urban Slums? *Journal of Urban Health 88* (Suppl 2), 381-400

24. Ng N., Kowal, P., Kahn, K., Naidoo, N., Abdullah, S., Bawah, A., Binka, F., Chuc, N.T., Debpuur, C., Egondi, T., Xavier Gómez-Olivé, F., Hakimi, M., Hirve, S., Hodgson, A., Juvekar, S., **Kyobutungi, C.,** Van Minh, H., Mwanyangala, M.A., Nathan, R., Razzaque, A., Sankoh, O., Kim Streatfield, P., Thorogood, M., Wall, S., Wilopo, S., Byass, P., Tollman, S.M., & Chatterji, S. (2010) Health inequalities among older men and women in Africa and Asia: evidence from eight Health and Demographic Surveillance System sites in the INDEPTH WHO-SAGE Study. *Global Health Action.* 27: 3

Selected Successful Grant Applications

1. IDRC: **Principal Investigator**; *Building Research Capacity and the evidence base for Multi-Sectoral Action for NCD prevention in SSA*; Jan 2013-Dec 2016. (**Grant amount: USD 1,726,534**)

2. Comic Relief: **Principal Investigator**; *Partnerships for Maternal, newborn and child health in Nairobi's slum settlements;* Jul 2012-Dec 2015. **(Grant amount: GBP £1,525,191)**

3. NIH**: Co-applicant;** *Genomic and environmental risk factors for cardiometabolic disease in Africans (H3Africa)*; Aug 2012-Jul 2015. **(Grant amount: USD 240,000)**

4. ESRC: **Co-applicant**; *Understanding resilience in later life in a low resource setting*; Jan 2013-Dec 2014. (Grant amount: ~GBP 84,500)

5. MRC/ESEI: **Co-PI**; *Epidemiology, Ecology and Socio-Economics of Disease Emergence in Nairobi*; Aug 2012 – Jul 2017. **(Grant amount: USD 404,000)**

6. Wellcome Trust: **Supervisor**; *Assessing the impact of personalized home-based counselling on MIYCN in Nairobi's slum settlements*; Mar 2012 – Feb 2015. **(Grant amount: USD 684,111)**

7. GlaxoSmithKline Oncology Ethnic Research Initiative (GSK ERI): **Co-PI**; *Triple Negative Breast Cancer (TNBC) in Kenya – A centrally coordinated approach to determine prevalence and clinico-pathologic characteristics of high risk breast cancer in distinct ethnic groupings*; Mar 2012-Feb 2014; **(Grant amount: ~USD 57,000)**

8. Amsterdam Medical Center (AMC) Foundation; **Co-PI** *Scalable models for primordial and primary prevention of CVD in slum populations in Nairobi; Kenya*; Aug 2011 – Jul 2014. **(Grant amount: 1m Euros)**

9. Office of U.S. Foreign Disaster Assistance (OFDA): **Co-PI**; Sep 2010 to Sep 2013; *Development of Indicators for Urban Humanitarian Emergencies*. **(Grant amount: USD 812,000)**

10. World Diabetes Foundation: **Principal Investigator**; Mar 2009 – Feb 2012; *Improving the lives of diabetics in Nairobi's slums through access to quality health care*. **(Grant amount: USD 200,000)**

11. Doris Duke Charitable Foundation; **Core team member**; Oct 2008-Mar 2009; *The partnership for a healthy Nairobi – improving the quality of health services for residents in three Nairobi slums Planning grant*. (**Grant amount: USD 149,923**)

12. Wellcome Trust; **Principal Investigator**; Jan 2008 to Dec 2010; *Assessing the linkages between socioeconomic status, perceived personal risk, and risk factors for cardiovascular and related non-communicable diseases in a population of slum dwellers in Nairobi, Kenya*. (**Grant amount: GBP 307,949**)

Language proficiency:

Language	**Speaking**	**Reading**	**Writing**
English	✓	✓	✓
Swahili		✓	

I, (Kyobutungi Catherine), certify that the information provided here in is correct to the best of my knowledge as of **(13/08/2018).**

CV of (Gershim Asiki)

Proposed Position in Research:	Project Manager
Proposed role in the study:	Kenya team lead
Organisation:	African Population & Health Research Center (APHRC)
Name of Staff:	Gershim Asiki
Profession:	Research Scientist
Date of Birth:	18 August 1975
Years with Organisation:	2 years
Nationality:	Ugandan
Membership in Professional Societies:	International Society of Social Paediatrics (ISSOP)
Detailed Tasks Assigned in Project:	Supports a cohesive team to ensure that the project is efficiently implemented and contributes to dissemination of the results through publications and policy engagement Also participates in proposal writing to fundraise for further research in the same theme. Also mentors junior researchers and represents the Centre at high – level national, regional and international forums, including relevant technical working groups and expert committees

Education & Qualifications:

Qualification	**Awarding Institution**	**Country**	**Year**
PhD	Karolinska Institutet	Sweden	2016
M.Sc. International Health	University College London	UK	2007
Medicine and Surgery (MBChB)	Makerere University	Uganda	2000

Employment Record:

From (year)	**To (Year)**	**Position**	**Employer**
July 2019	To date	Research Scientist	African Population and Health Research Center, Nairobi
2017	June 2019	Associate Research Scientist	African Population and Health Research Center, Nairobi
2015	2017	Technical Advisor	ICAP at Columbia University
2008	2015	Senior Scientist	Medical Research Council/Uganda Virus Research Institute

2007	2008	Project Medical Officer	Infectious Diseases Institute, Uganda
2001	2006	Medical Officer	Nyapea Hospital, Uganda
2000	2001	Internship	Mulago National Referral Hospital

Summary of research experience:

Asiki has a research experience of 10 years, first worked with the British Medical Research Council (MRC) Unit in Uganda (2008-2015), leading research projects (population based studies and clinical trials) on HIV and non-communicable diseases in vulnerable rural farming and fishing populations in Uganda. He later joined ICAP at Columbia University (2015-2017) as a Technical advisor and provided technical support to country-wide Population based HIV Impact Assessments (PHIAs) in Uganda, Namibia and Cameroon. He currently works at APHRC as an Associate Research Scientist in the Health and Systems for Health Unit focusing on generating evidence to drive stronger and more resilient systems for improved health of vulnerable populations. He provides scientific leadership to programs and projects, supports a cohesive team and ensures projects in thematic area of NCDs are efficiently implemented and , contributes to policy engagement and strategic planning as may be needed, Leads and contributes to proposal development and fundraising for research projects in the unit, mentors junior researchers and facilitates in the Centre's training programs as needed, represents the Centre at high – level national, regional and international forums, including relevant technical working groups and expert committees, contributes to institutional publications

Publications:

1. Stockdale L, Nash S, Nalwoga A, ….**Asiki G,** et al. Human cytomegalovirus epidemiology and relationship to tuberculosis and cardiovascular disease risk factors in a rural Ugandan cohort. *PLoS One.* 2018;13(2):e0192086.
2. Newton R, Labo N, Wakeham K, …..**Asiki G,** et al. Kaposi Sarcoma-Associated Herpesvirus in a Rural Ugandan Cohort, 1992-2008. *J Infect Dis.* 2018;217(2):263-269.
3. Rawstron AC, Ssemaganda A, de Tute R, …..**Asiki G,** et al. Monoclonal B-cell lymphocytosis in a hospital-based UK population and a rural Ugandan population: a cross-sectional study. *The Lancet. Haematology.* 2017;4(7):e334-e340.
4. Murphy GA, **Asiki G,** Young EH, et al. Erratum. Cardiometabolic Risk in a Rural Ugandan Population. Diabetes Care 2013;36;e143. *Diabetes Care.* 2017;40(4):625.
5. Murphy GA, **Asiki G**, Nsubuga RN, et al. Erratum. The Use of Anthropometric Measures for Cardiometabolic Risk Identification in a Rural African Population. Diabetes Care 2013;37:e64-e65. *Diabetes Care.* 2017;40(4):625.
6. **Asiki G**, Murphy GA, Baisley K, et al. Correction: Prevalence of Dyslipidaemia and Associated Risk Factors in a Rural Population in South-Western Uganda: A Community Based Survey. *PLoS One.* 2017;12(2):e0173133.
7. Wekesa C, **Asiki G**, Kasamba I, et al. Atherogenic Risk Assessment among Persons Living in Rural Uganda. *J Trop Med.* 2016;2016:7073894.
8. Reniers G, Wamukoya M, Urassa M, …**Asiki G**, et al. Data Resource Profile: Network for Analysing Longitudinal Population-based HIV/AIDS data on Africa (ALPHA Network). *Int J Epidemiol.* 2016;45(1):83-93.
9. Obuku AE, **Asiki G**, Abaasa A, et al. Effect of Schistosoma mansoni Infection on Innate and HIV-1-Specific T-Cell Immune Responses in HIV-1-Infected Ugandan Fisher Folk. *AIDS Res Hum Retroviruses.* 2016;32(7):668-675.

10. Kamali A, Nsubuga RN, Ruzagira E, **Asiki G** et al. Heterogeneity of HIV incidence: a comparative analysis between fishing communities and in a neighbouring rural general population, Uganda, and implications for HIV control. *Sex Transm Infect.* 2016;92(6):447-454.
11. **Asiki G,** Reniers G, Newton R, et al. Adult life expectancy trends in the era of antiretroviral treatment in rural Uganda (1991-2012). *Aids.* 2016;30(3):487-493.
12. **Asiki G**, Newton R, Marions L, Seeley J, Kamali A, Smedman L. The impact of maternal factors on mortality rates among children under the age of five years in a rural Ugandan population between 2002 and 2012. *Acta paediatrica (Oslo, Norway : 1992).* 2016;105(2):191-199.
13. Abaasa A, **Asiki G**, Price MA, et al. Comparison of HIV incidence estimated in clinical trial and observational cohort settings in a high risk fishing population in Uganda: Implications for sample size estimates. *Vaccine.* 2016;34(15):1778-1785.
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22. Abaasa A, **Asiki G,** Mpendo J, et al. Factors associated with dropout in a long term observational cohort of fishing communities around lake Victoria, Uganda. *BMC Res Notes.* 2015;8:815.
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Language proficiency:

Language	Speaking	Reading	Writing
English	✓	✓	✓
Swahili	✓	✓	✓

I, **(Gershim Asiki),** certify that the information provided here in is correct to the best of my knowledge as of **(13/08/2019).**

CV of (Shukri F Mohamed)

Proposed Position in Research:	Project Officer
Proposed role in the study:	Coordination oversight
Organization:	African Population & Health Research Center (APHRC)
Name of Staff:	Shukri F Mohamed
Profession:	Research officer
Date of Birth:	June 15th 1975
Years with Organization:	9
Nationality:	Kenya
Membership in Professional Societies:	International Epidemiology Association (IEA) International Union for the Scientific Study of Population (IUSSP)
Detailed Tasks Assigned in Project:	Coordinate the activities for the study.

Education & Qualifications:

Qualification	Awarding Institution	Country	Year
Doctor of Philosophy (PhD)	Warwick University	UK	Ongoing
Master of Public Health (MPH)	Johns Hopkins Bloomberg School of Public Health	USA	2006
Doctor of Pharmacy Degree (PharmD)	University of Maryland, School of Pharmacy	USA	2004
Associate Degree in Science (AS)	Northern Virginia Community College, Alexandria	USA	2000

Employment Record:

From (year)	To (Year)	Position	Employer
September 2010	present	Research officer	African Population & Health Research Center (APHRC)
Mid-March 2010	September 2010	Research intern	APHRC
August 09	mid-October 09	Internship	APHRC
April 08	- -July 2009	Intern	National AIDS/STDS Control Programme Kenya (NASCOP)
2004	March 2008	Pharmacist	Giant Pharmacy, USA

Summary of research experience:

Dr Shukri Mohamed is a public health specialist with over 8 years' experience in research, project planning and management, and also has four years of clinical pharmacy practice experience. She also has strong skills in proposal writing, project management, project implementation, data quality assurance, data analysis and scientific writing. Dr Mohamed has authored 20 peer reviewed publications. She attained a Masters in Public Health from the Johns Hopkins Bloomberg School of Public Health and a Doctor of Pharmacy Degree from the University of Maryland School of Pharmacy. Her areas of interest include include non-communicable disease prevention and control with an emphasis on cardiovascular disease, health systems research and translating research to policy and action. Dr Mohamed has served on a number of expert/technical working group such as the technical working group on non-communicable diseases prevention policies and the Kenya Cancer Research track group. Dr. Mohamed is also successfully coordinated the first ever special issue on data from WHO STEPS survey for Kenya.

Publications:

1. **Mohamed, S. F**., Mutua, M. K., Wamai, R., Wekesah, F., Haregu, T., Juma, P., Nyanjau, L., Kyobutungi, C., … Ogola, E. (2018). Prevalence, awareness, treatment and control of hypertension and their determinants: results from a national survey in Kenya. BMC public health, 18(Suppl 3), 1219. doi:10.1186/s12889-018-6052-y
2. **Mohamed SF**, Mwangi M, Mutua MK, Kibachio J, Hussein A, Ndegwa Z, Owondo S, Asiki G, Kyobutungi C. Prevalence and factors associated with pre-diabetes and diabetes mellitus in Kenya: results from a national survey. BMC public health. 2018 Nov;18(3):1215.
3. Wekesah FM, Nyanjau L, Kibachio J, Mutua MK, **Mohamed SF**, Grobbee DE, Klipstein-Grobusch K, Ngaruiya C, Haregu TN, Asiki G, Kyobutungi CK. Individual and household level factors associated with presence of multiple non-communicable disease risk factors in Kenyan adults. BMC public health. 2018 Nov;18(3):1220.
4. Haregu TN, Wekesah FM, **Mohamed SF**, Mutua MK, Asiki G, Kyobutungi C. Patterns of non-communicable disease and injury risk factors in Kenyan adult population: a cluster analysis. BMC public health. 2018 Nov;18(3):1225.
5. Ali, S. A., Soo, C., Agongo, G., Alberts, M., Amenga-Etego, L., Boua, R. P., Choudhury, A., Crowther, N. J., Depuur, C., Gómez-Olivé, F. X., Guiraud, I., Haregu, T. N., Hazelhurst, S., Kahn, K., Khayeka-Wandabwa, C., Kyobutungi, C., Lombard, Z., Mashinya, F., Micklesfield, L., Mohamed, S. F., Mukomana, F., Nakanabo-Diallo, S., Natama, H. M., Ngomi, N., Nonterah, E. A., Norris, S. A., Oduro, A. R., Somé, A. M., Sorgho, H., Tindana, P., Tinto, H., Tollman, S., Twine, R., Wade, A., Sankoh, O., **Mohamed SF**, … Ramsay, M. (2018). Genomic and environmental risk factors for cardiometabolic diseases in Africa: methods used for Phase 1 of the AWI-Gen population cross-sectional study. Global health action, 11(sup2), 1507133.
6. **Mohamed SF**, Juma P, Asiki G, Kyobutungi C. Facilitators and barriers in the formulation and implementation of tobacco control policies in Kenya: a qualitative study. BMC public health. 2018;18(1):960. https://doi.org/10.1186/s12889-018-5830-x.
7. Juma PA, Mapa-tassou C, **Mohamed SF**, Matanje Mwagomba BL, Ndinda C, Oluwasanu M, et al. Multi-sectoral action in non-communicable disease prevention policy development in five African countries. BMC public health. 2018; 18(1):953. https://doi.org/10.1186/s12889-018-5826-6.
8. Juma PA, **Mohamed SF**, Matanje Mwagomba BL, Ndinda C, Mapa-tassou C, Oluwasanu M, et al. Non-communicable disease prevention policy process in five African countries authors. BMC public health. 2018; 18(1):961. https://doi.org/10.1186/s12889-018-5825-7.
9. Wisdom JP, Juma P, Mwagomba B, Ndinda C, Mapa-Tassou C, Assah F,… **Mohamed SF**, et al. Influence of the WHO framework convention on tobacco control on tobacco legislation and policies in sub-Saharan Africa. BMC public health. 2018; 18(1):954. https://doi.org/10.1186/s12889-018-5827-5.
10. Asiki, G., Shao, S., Wainana, C., Khayeka–Wandabwa, C., Haregu, T. N., Juma, P. A., **Shukri Mohamed**,…. Kyobutungi, C. (2018). Policy environment for prevention, control and management of cardiovascular diseases

in primary health care in Kenya. BMC Health Services Research, 18, 344. http://doi.org/10.1186/s12913-018-3152-4
11. Haregu, T., **Mohamed, S**., Muthuri, S., Khayeka-Wandabwa, C., & Kyobutungi, C. (2018). Body mass index and wealth index: Positively correlated indicators of health and wealth inequalities in Nairobi slums. Global Health, Epidemiology and Genomics, 3, E11. doi:10.1017/gheg.2018.10
12. Asiki, G., **Mohamed, S. F**., Wambui, D., Wainana, C., Muthuri, S., & Ramsay, M. (2018). Sociodemographic and behavioural factors associated with body mass index among men and women in Nairobi slums: AWI-Gen Project. Global Health Action, 11(Suppl 2), 1470738. http://doi.org/10.1080/16549716.2018.1470738Sayed, Shahin, Molo, Zahir …….Catherine Kyobutungi, **Shukri Mohamed**, Tilahun Haregu….2017. Ethnicity and Breast Cancer Characteristics in Kenya. *Breast Cancer Research Treatment*.
13. Sayed, Shahin, Molo, Zahir …….Catherine Kyobutungi, Shukri Mohamed, Tilahun Haregu….2017. Ethnicity and Breast Cancer Characteristics in Kenya. Breast Cancer Research Treatment.
14. Juma, P. A., **Mohamed, S. F**., Wisdom, J., Kyobutungi, C., & Oti, S. (**2016)**. Analysis of Non-communicable disease prevention policies in five Sub-Saharan African countries: Study protocol. *Archives of Public Health*, *74*(1), 25.
15. **Shukri F Mohamed**, Blessing Uchenna Mberu, Djesika Amendah et.al (**2016**). Rapid Urbanization, Urban Food Deserts and Food Security in Africa, 978-3-319-43566-4, 369699_1_En (8)".
16. **Shukri F Mohamed**, Chima Izugbara, Ann Moore et.al. Estimated Incidence of Induced abortion in Kenya. BMC Pregnancy and Child Health **2015**, **15**:185 doi:10.1186/s12884-015-0621-1.
17. Abdhalah Ziraba, Chimaraoke Izugbara, Brooke A. Levandowski, Hailemichael Gebreselassie, Michael Mutua, **Shukri F Mohamed**, Carol Egesa, Elizabeth W. Kimani-Murage. Unsafe abortion in Kenya: a cross-sectional study of abortion complication severity and associated factors. BMC Pregnancy and Child Health **2015**.
18. Kimani-Murage EW., Schofield, L., Wekesah, F., **Mohamed, S**., Mberu, B., Ettarh, R., Kyobutungi, C, & Ezeh, A. Vulnerability to food insecurity in urban slums: Experiences from Nairobi, Kenya. Journal of Urban Health **2014**.
19. Lilly Schofield, **Shukri F Mohamed**, Elizabeth Wambui Kimani-Murage et.al. *Spotting the invisible crisis: early warning indicators in urban slums of Nairobi, Kenya.* Field exchange **2013**.
20. Djesika Amenda, Stephen Buigut, & **Shukri Mohamed**. *Coping Strategies among Urban Poor: Evidence from Nairobi, Kenya. Plos One **2013**.*

Language proficiency:

Language	Speaking	Reading	Writing
English	✓	✓	✓
Swahili	✓	✓	✓
Somali	√	√	√

I, **(Shukri F Mohamed),** certify that the information provided here in is correct to the best of my knowledge as of **(13/08/2019).**

CV of (Isaac Kisiangani)

Proposed Position in Research:	Project Officer
Proposed role in the study:	Project Coordinator and M & E officer

Organisation:	African Population & Health Research Center (APHRC)
Name of Staff:	Isaac Simiyu Kisiangani
Profession:	Research officer
Date of Birth:	
Years with Organisation:	11 months
Nationality:	Kenya
Membership in Professional Societies:	Member of African Organization for Research & Training in Cancer (AOTIC)
Detailed Tasks Assigned in Project:	Coordinate the activities for the study. He will manage the day to day project management. He will participate in data analysis and scientific writing.

Education & Qualifications:

Qualification	Awarding Institution	Country	Year
Bsc. Medical Laboratory Science	Jomo Kenyatta University of Agriculture & Technology	Kenya	July 2010
MSc in Public Health	Jomo Kenyatta University of Agriculture & Technology	Kenya	November 2016

Employment Record:

From (year)	To (Year)	Position	Employer
August 2018	Present	Research officer	African Population & Health Research Center (APHRC)
July 2011	July 2018	Assistant Research Officer	Kenya Medical Research Institute (KEMRI)

Summary of research experience:

Publications:

1. Lydia, K., Erastus, M., Anne, K., Jane, M., Chrispine, O. O., Judith, K., ... & **Isaac, K**. A. Stroke distribution patterns & characteristics in Kenya's leading public health tertiary institutions: Kenyatta National Hospital & Moi teaching & Referral Hospital: Cardiovascular Journal Of Africa; Vol. 29(2), Mar/April 2018, pg. 68-72.

2. **Kisiangani, I.**, Mbakaya, C., Makokha, A., & Magu, D. Prevalence of malnutrition among preschool children (6-59 months) in Western Province, Kenya: Journal of Public Health & epidemiology; Article Number - A80EE2047913 Vol.6(11), pp.398-406, Nov2014
3. **Kisiangani, I**., Mbakaya, C., Makokha, A., & Magu, D. Assessment of iron status among preschool children (6 to 59 months) with and without malaria in western province, Kenya: Pan African Medical Journal: Article Number: 68562014070553-4560: doi:10.11604/pamj.2015.21.62.4560
4. **Kisiangani, I**., Mbakaya, C., & Makokha, A. Prevalence of anaemia and associated factors among preschool children (6-59 months) in western province, Kenya: Public Health Journal vol.1. No.1, 2015, pp.28-32.
5. Lydia Kaduka, Zipporah Bukania, Moses Mwangi, **Isaac Kisiangani**, Yeri Kombe, Charles Mbakaya. Predictors of insulin resistance among urban population in kenya: 7th KEMRI Annual Scientific Health (KASH) conference (2017).
6. Coralie Marie-Audrey Ngbichi, Abdhalah Kasiira Ziraba, David Wainaina, Pauline Bakibinga, **Isaac Kisiangani**, Pauline Njoroge, Rumana Noor, Ngugi Njoroge, Raha Abdi Salah, Elmi Mohamed. "If there are no female nurses to attend to me, I will just go and deliver at home": results from a qualitative study in Garissa, North Eastern Kenya. BMC Pregnancy and Child-**19**, Article number: 332 (2019)

Language proficiency:

Language	**Speaking**	**Reading**	**Writing**
English	✓	✓	✓
Swahili	✓	✓	✓
Bukusu	√		

I, **(Isaac Kisiangani),** certify that the information provided here in is correct to the best of my knowledge as of **(13/08/2019).**

Appendix 2: Detailed timeline with activities

Activity	Y1 Q1/2	Y1 Q3/4	Y2 Q1/2	Y2 Q3/4	Y3 Q1/2	Y3 Q3/4	Y4 Q1/2	Y4 Q3/4	Y5 Q1/2	Y5 Q3/4
Develop questionnaire, instruments and submit ethics	X	X								
Epidemiological studies	X	X	X	X	X	X	X	X	X	X
Genomic and bioinformatics studies	X	X	X	X	X	X	X	X	X	X
Workshops	X	X		X		X		X	X	X
Microbiome recruitment					X	X				
Cohort recruitment			X	X	X	X	X	X	X	
Data QC	X	X	X	X	X	X	X	X	X	X
Publications	X	X	X	X	X	X	X	X	X	X

Appendix 3: Informed Consent Documents (Attached)

Appendix 4: Data collection tools (Attached)

Appendix 5: NIH training certificates