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RELATIONSHIP OF DIET AND PHYSICAL ACTIVITY WITH GENETIC SUSCEPTIBILITY TO OBESITY: A LONGITUDINAL ANALYSIS IN ADULTS IN SOUTH AFRICA

By

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Original published work

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Doctor of Philosophy

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2024

Declaration

I, Monica Muti, declare that this thesis is my own original, unaided work. It is being submitted for the degree of Doctor of Philosophy at the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any degree or examination at any other University or institution.

Signed  on the 2nd day

of June 2024 in Harare

Dedication

I dedicate this thesis to my parents Never Tendayi and Virginia Komboni who have been the motivation for me to continue to scale greater heights.

Scientific outputs of this study

Included in this thesis are one published manuscript and two manuscripts in draft.

Published: Muti M, Ware LJ, Micklesfield LK, Ramsay M, Agongo G, Boua PR, Kisiangani I, Cook I, Gómez-Olivé FX, Crowther NJ, Kabudula C, Norris SA, Chikowore T. Physical activity and its association with body mass index: A cross-sectional analysis in middle-aged adults from 4 Sub-Saharan African countries. J Phys Act Health. 2023;20(3):217–225. https://doi.org/10.1123/jpah.2022-0539

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Draft manuscript: Muti M, Ware LJ, Ramsay M, Norris SA, Chikowore T. Gene-lifestyle interactions for BMI in black South Africans

Thesis Abstract

Background

Obesity-related disease conditions are a major public health concern in South Africa, exerting a healthcare cost of between ZAR 30 million and ZAR 36 million, the bulk of which is due to hypertension and type 2 diabetes. Moreover, evidence reveals that women in South Africa have higher BMI compared to men, yet men exhibit less insulin sensitivity and reduced beta cell function as well as stronger associations of adiposity with type 2 diabetes compared to women. The mechanisms underlying these sex differences are not known. BMI is highly polygenic in nature; however, genetic prediction of BMI has mostly been conducted using data from European ancestry populations that have poor predictive capacity in African ancestry populations. Moreover, the relationship of polygenic risks and proteomic profiles with regards to susceptibility to obesity and related cardiometabolic traits is yet to be explored in African populations. It has also been reported that using variants associated with the statistical variance of quantitative traits (vQTLs) like BMI aids in the depiction of components of BMI genetic susceptibility, which interacts with environmental factors such as diet and exercise. However, such studies are limited in continental Africans.

Aim

This thesis, sought to determine the interplay of diet and physical activity with BMI genetic susceptibility.

The specific objectives were:

1. To determine the association of physical activity with BMI in middle-aged black South African men and women.
2. To develop a highly predictive genetic risk score for BMI and test its longitudinal predictive ability in middle-aged black South African men and women.
3. To determine gene x lifestyle (GXE) interactions that influence BMI in Black South African adult men and women.

Methods

Data from 11853 adult men and women in the African-Wits-INDEPTH partnership for Genomic studies (AWI-Gen) Cohort was used to fulfil objective 1. To fulfil objectives 2 and 3, data from 5921 AWI-Gen cohort participants in the three South African (SA)

sites and a sub-study of AWI-Gen focusing on the factors influencing the risk of type 2 diabetes mellitus among middle-aged black South African men and women (GSK) was used. For objective 1, a sex-stratified meta-analysis of cross-sectional data from the study participants was used to assess the association of physical activity with BMI. The PRS-CSx method was used to develop a multi-ancestry PRS for BMI and evaluate its longitudinal prediction of severe obesity to meet objective 2. For objective 3, the Levene's test, implemented in the OCSA Package, was used to determine candidate gene-interacting variants that exhibited trait variance heterogeneity in the study population. Detailed methods are in the relevant sections for each objective.

Results

Meeting the recommended weekly physical activity levels of at least 150 minutes was associated with a BMI that was 0.80kg/m^2 lower in men (95% CI = -1.14; -0.47) and 0.68kg/m^2 lower in women (95% Ci = -1.03; -0.33). Sex and site-specific differences were also observed in domains of physical activity with an inverse relationship between transport-related physical activity and BMI being observed among men in Agincourt (beta = -1.15 kg/m^2, 95% CI = -2.26; -0.04) and Nanoro (beta = -0.79 kg/m^2, 95%CI = -1.25; -0.33). Work related physical activity was associated with lower BMI in Navrongo men (beta = -0.76 kg/m^2, 95% CI=-1.25; -0.27) and Nanoro women (beta = -0.90 kg/m^2, 95%CI = -1.44; -0.36).

The multi-ancestry PRS demonstrated superior predictive ability, explaining approximately 1.9% of variance in BMI compared to 0.7% and 1.2% explained by two scores developed using single ancestry methods. In addition, over a period of ten years, the multi-ancestry PRS was associated with repeated measures of BMI (β = 1.51 p = < 0.001) and there was significant longitudinal PRS * sex interaction ($P_{interaction}$ = 0.029), prompting subsequent sex-stratified analysis. In the combined analysis of men and women, being in the top 20% of the PRS distribution (top 20) was associated with three times greater hazard of severe obesity (hazard ratio = 2.98, 95% CI = 1.75 - 5.07, p = 5.33e-05) compared to being in the bottom 20% of the PRS distribution (bottom 20). This observation was shown to be driven by women, where being a

woman in the top 20 was associated with 3.5 greater hazard of severe obesity (hazard ratio 3.48, 95% CI = 1.96 – 6.16, p = 1.94e-05) compared to being in the bottom 20 while the associations were not significant in men (hazard ratio = 1.13, 95% CI = 0.24 – 5.37, p = 0.878). Comparison of the associations of dysglycaemia with PRS, BMI and the proteomic score revealed no apparent sex differences in the association between BMI PRS and dysglycaemia for most of the glycaemic markers except for Matsuda Index though men exhibited lower insulin sensitivity compared to women. The proteomic score predicted higher insulin resistance in women than in men.

Gene x lifestyle interaction analysis revealed novel interactions between three genetic variants with diet and lifestyle factors. The effect of the rs557505940 variant on BMI was accentuated by higher fruit intake ($beta_{interaction}$ = 0.03, $P_{interaction}$ = 0.04) in the combined analysis of men and women while higher SES, carbohydrate intake and self-reported physical activity attenuated the effect of rs527747185 ($beta_{interaction}$ = -0.349, $P_{interaction}$ = 0.037), rs3016751 ($beta_{interaction}$ = -0.056, $P_{interaction}$ = 0.035) and rs188275749 ($beta_{interaction}$ = -0.048, $P_{interaction}$ = 0.0001) respectively on BMI in men.

Conclusions

Sex and geographical differences exist in associations between domains of physical activity and BMI. In addition, genetic risk better predicts incident severe obesity in women than in men while proteomic profiles have a weak correlation with PRS and show heterogenous associations with dysglycaemia, fat distribution, nutrient patterns and physical activity between men and women. Novel GXE interactions were also observed. These results underscore the need for further inquiry into the sex differences in genetic risk and environmental factors associated with BMI. Furthermore, a precision approach to obesity prevention and control, paying attention to the sex differences and contextual factors may be more efficient.

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I would like to express my profound gratitude to the following people who have helped me through my PhD journey:

Thanks to my mentor, Dr Tinashe Chikowore who plunged me into this genetic pool and ignited my passion for genetics. Thanks to my other mentors, Dr Lisa Ware and Prof Shane Norris for the constructive guidance. The journey was both exciting and tiring but well worth it and I am grateful for these three for the various roles they played in ensuring I came this far.

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There are some that I may have inadvertently omitted but have played various roles in my PhD journey. Thank you all for your support.

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CHAPTER 1: INTRODUCTION

1.1 Background

Globally, 71% of all deaths are related to non-communicable diseases (NCDs) and 85% of these occur in low and middle-income countries (LMIC) [1]. Excess weight and obesity, now a worldwide problem, pose significant risk for NCDs such as cardiovascular disease, diabetes and some types of cancers [2]. Obesity in South Africa is associated with a low intake of fruit and vegetables and increased animal protein and fat intake coupled with low physical activity levels [3-10]. It is also known that a substantial proportion of the variability in obesity across individuals (body mass index (BMI) (40-70%), waist circumference (76%), and waist-hip-ratio (45%)) may be attributed to genetics [11]. However, guidelines and strategies for the prevention and control of obesity, particularly those on diet and physical activity, adopt a uniform approach that does not take into account individual differences due to behavioural, environmental, and genetic factors. Studies have mainly focused on relationships between diet, physical activity and obesity but more work is still needed to determine how these factors interplay with genetic susceptibility to obesity [12-15]. It is known that one of the key drivers to adopting health behaviours is personal perceived risk and severity of disease or condition [16]. Identifying people who have a higher genetic risk of obesity and using targeted communication approaches to communicate this risk may be a motivator for individuals to engage with interventions differently and at different stages during the life course [17]. The relationships between diet and physical activity with genetic susceptibility to obesity thus warrant further investigation.

1.1.1 Extent of the problem

Global estimates for obesity in 2015 were 11% for men and 15% for women [18]. In 2016, 13% of adults 18 years old and beyond were estimated to be obese, with prevalence being generally higher in high-income countries (Europe, North America, and Oceania) than in low-income countries (South Asia and sub-Saharan Africa (SSA)) countries. Exceptions have been observed, however, in the Pacific Island states where obesity rates of 61% in Nauru and 55% in Palau are higher than expected for their income levels while Japan, South Korea and Singapore levels are much lower

than expected for their income levels. By the year 2030, more than one billion individuals (1 in 5 women and 1 in 7 men) are projected to be obese [19]. In Africa, studies have shown a consistent increase in obesity prevalence, particularly Southern Africa, with more women affected than men and those residing in urban areas having a higher prevalence [2,20].

1.1.2 Study context

Non-communicable diseases (NCDs) are a growing burden responsible for many premature deaths (deaths of individuals between the ages of 30 and 70 years) in South Africa [21,22]. In 2016, about half of all deaths were due to NCDs, namely cardiovascular diseases (CVD) (19%), cancers (10%), diabetes (7%), chronic respiratory diseases (4%) and other NCDs (11%) [21]. In an attempt to address the NCD burden, South Africa developed a strategic plan aimed at addressing the increase in non-communicable diseases 2013-2017. One of the goals was to reduce the burden of obesity and/or overweight by 10% by the year 2020 [22]. However, by the end of the timeframe for the strategy, the country was far from this target as obesity and overweight continued to increase. Between 1998 and 2016, overweight or obesity increased from 56% to 68% in women and 29% to 31% in men [23].

Obesity, a preventable condition which is characterized by excessive fat accumulation, is a complex trait believed to occur as a result of the intricate relationships of environmental factors (e.g. diet and physical activity) and prior genetic susceptibility [24,25]. However, much research work has focused on understanding how changes in diet and physical activity due to urbanization and adoption of Western lifestyles are contributing to the obesity burden [13,15]. There are still gaps in understanding why men have lower levels of obesity compared to women despite them all being exposed to the same obesogenic environment. It also remains to be elucidated if more research in the genetics of this trait will help to answer this phenomenon [25-28].

Limited access to and high costs of genotyping resources have hampered the exploration of the role of genetics in obesity in South Africans in the past.

Nevertheless, prior work in a sample size of 971 black South Africans using European-derived polygenic risk scores (PRS) suggests that higher adult BMI tracks from 13 years of age [29]. However, we know that European-derived PRS has a 4.9-fold lower prediction accuracy in African populations [30]. Due to the H3Africa consortium studies and African Partnership for Chronic Disease Research (APCDR) Network, increased diversity, more financial resources for genomic research as well as more training and professional opportunities for researchers in Africa are now available. In addition, a genotyping array based on data from continental Africans has been developed, which better represents common variants in Africa [31,32]. This presents an opportunity to evaluate the genetic influence on obesity in the context of diet and physical activity patterns in South Africa.

1.2 Literature Review

1.2.1 Introduction

This section covers an appraisal of the literature regarding the definition, burden, consequences and determinants of obesity in adult men and women based on a conceptual framework developed by Scott, Ejikeme, Clottey and Thomas (2012) [33]. It also highlights the evidence of relationships between diet, physical activity and obesity as well as the genetic contribution to obesity. Figure 1:1 shows the outline of the literature review.

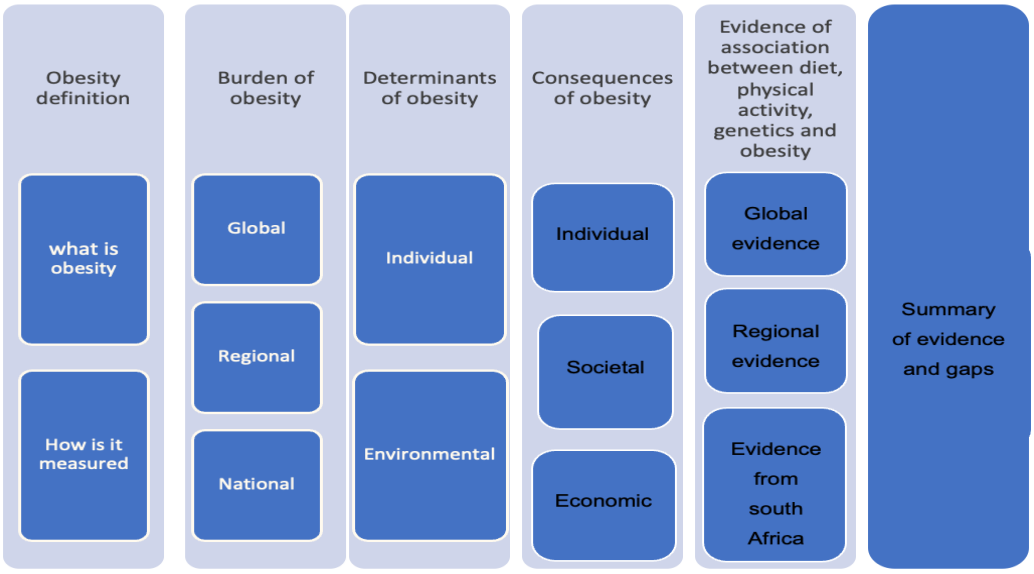

Figure 1.1: Outline of literature review

1.2.2 What is obesity?

Obesity is the excessive accumulation of body fat which is associated with adverse health effects [2]. It is a complex trait believed to arise from the interplay of environmental and genetic factors. Low grade inflammation is also believed to characterise obesity, partly explaining its association with NCDs [34] (See Figure 1:2).

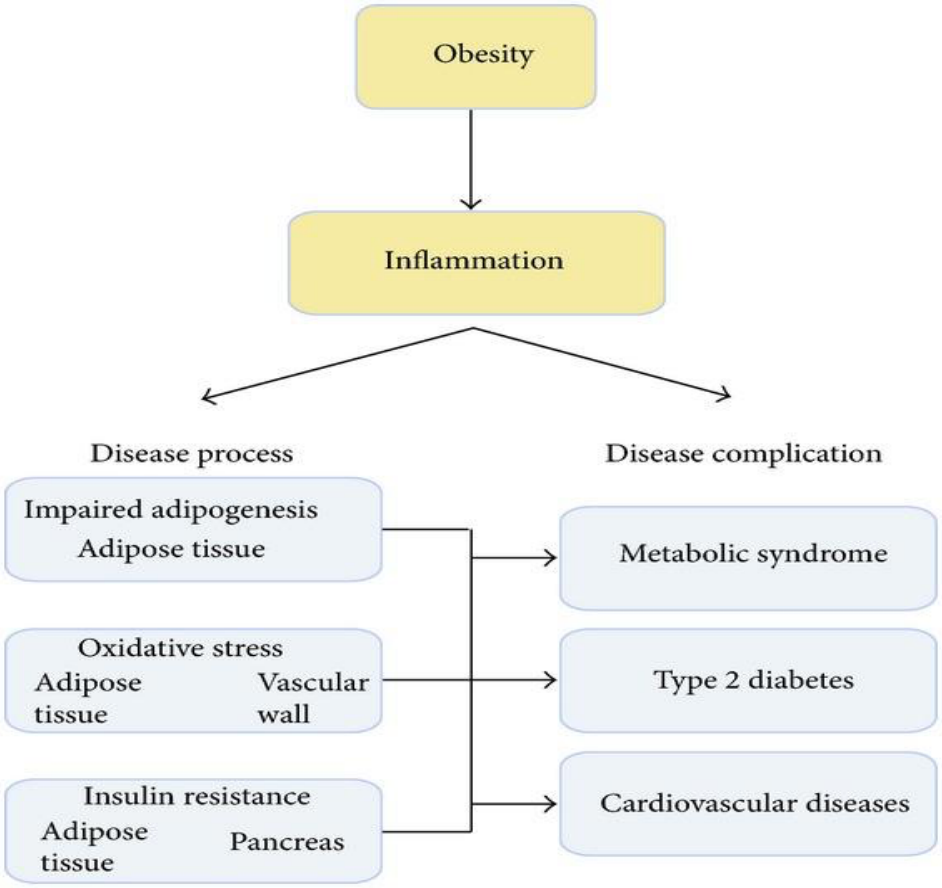

Figure 1.2: Schematic representation of the central role of inflammation in obesity-induced disorders

Inflammation, associated with excessive energy intake during obesity triggers fat tissue structural changes, oxidative stress, and insulin resistance. This is associated with heightened risk of developing metabolic syndrome, type 2 diabetes, and cardiovascular diseases. Source: Paul Holvoet, 2012. Stress in Obesity and Associated Metabolic and Cardiovascular Disorders [34].
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1.2.3 How is obesity measured?

Several methods exist for measuring obesity, the most common being body mass index (BMI). BMI is a simple population level indicator for total body fat, calculated by dividing weight in kilograms by height in metres squared and categorised as follows:

underweight (BMI < 18.5 kg/m2), normal weight (BMI ≥ 18.5 and < 25kg/m2), overweight (BMI ≥ 25 and < 29.9 kg/m2) and obese (BMI ≥ 30 kg/m2) 2. Obesity is further classified into class I (BMI 30 – <35 kg/m2), class II (BMI 35 – <40 kg/m2) and class III (BMI ≥ 40 kg/m2) [2.] Criticisms have been raised against the use of BMI to define obesity. It is argued that BMI is a crude measure which does not consider variations in sex, age and ethnicity and thus has limited generalizability. In addition, it does not differentiate between fat and lean body mass, nor specify the location of adiposity thus limiting the ability to assess metabolic and other health risks, diabetes and coronary heart disease for example. BMI may also overestimate body fat in very muscular people [35-37]. Other measures are therefore also used to complement BMI.

Waist circumference is considered an important measure of central obesity that is useful in stratifying health risk related to obesity alongside BMI [38]. It is particularly useful in individuals classified as having BMI in the normal or overweight ranges [37]. Waist circumference (WC) is determined by placing a measuring tape around the midpoint between the lower rib and top of the iliac crest [39]. Variations in measurements however may exist due to the different recommendations on how to measure WC [40]. A waist circumference of >102cm in men and >88cm in women signifies higher health risk [37] though different ethnic-specific thresholds have however been suggested [41-43]. Another measure of central obesity is waist-to-hip ratio (WHR). This method is however considered to be inferior to waist circumference in measuring total abdominal fat and abdominal visceral fat [44-47]. Waist-to-height ratio (WHtR) is also utilized as a measure of central obesity, though it is not commonly used in screening for obesity. It is reported to be more useful than WC and BMI because of its simplicity and not being age or sex dependant [48] thus it is useful both in children and adults [38,49]. Moreover, in adults, height is constant and has limited influence on WC, enhancing the usefulness of WHtR as it captures the risk conferred by height and waist circumference. It has demonstrated greater ability than WC and BMI in detecting cardiometabolic risk factors [38,50,51]. It is however not recommended for use in children below the age of six [52].

Highly accurate methods exist for measuring body fat. These include computed tomography (CT), magnetic resonance imaging (MRI) and dual-energy x-ray

absorptiometry (DEXA). In addition, underwater weighing (densitometry), bioelectrical impedance analysis as well as isotope dilution (hydrometry) are also used. High cost, lack of portability of some measuring devices, as well as time taken for some of the procedures limit their use. In addition, DEXA is unsuitable for pregnant women while radiation exposure makes CT unsuitable for multiple scans [53]. Skinfold thickness is also used to predict body fat. It is simple to use, portable and inexpensive but has limitations in accuracy and reproducibility [53].

The ease of measuring BMI, its cost efficiency and usefulness in predicting disease risk as well as the strong correlation of BMI with gold standard body fat measures thus confirms its validity in obesity epidemiology [54-56]. Furthermore, the clinical application of BMI has given rise to debates by scholars on the heterogeneity of obesity associations with health outcomes, where metabolic health is believed to be associated with dysfunction rather than just the BMI [57,58]. For example, some individuals may fall into the obese category based on the standard WHO BMI classification, yet they do not possess the metabolic consequences of high BMI. On the other end, some lean individuals may have an unhealthy metabolic profile and typically exhibit higher risk of dysglycaemia comparable to that of obese individuals [59]. The complementary use of various omic profiles such as metabolomics, genomics and proteomics may be useful in unmasking heterogeneity of BMI associations with health outcomes, explaining the differences in metabolic consequences of BMI [60]. However, much work still remains in unmasking BMI heterogeneity.

1.2.4 Burden of obesity in South Africa

South Africa reportedly has the highest rates of obesity in sub-Saharan Africa and it affects men and women disproportionately [23,61]. South African women have higher obesity prevalence (41%) than men (11%) and a rapid increase is apparent in women over the years though in men it appears to be slowing down [62].

1.2.5 Consequences of obesity

Obesity, now a major global health problem, is linked to many leading causes of death which include heart disease, hypertension, stroke, type 2 diabetes mellitus and various cancers [2,63-65]. It has also been reported as one of the prominent causes of mortality in the world, being ranked fifth among the leading causes of death among women and sixth among men in 2019 [66]. Approximately 8% of global deaths and 1.48 million disability adjusted life years (DALYs) in 2017 were ascribed to obesity. In Africa, there was an increase in mortality linked to obesity from 4.5% in 1990 to 8% in 2016 [67]. Overweight and obesity are also reported to be responsible for more deaths than underweight in most countries [2]. Furthermore, psychological disorders related to reduced self-worth, perceived or actual weight discrimination have also been reported in the US, European countries and Australia [65,68-71]. For example, a study representative of US adults revealed greater odds of mood and anxiety disorders as well as substance abuse among those who perceived weight discrimination. More whites reported discriminatory experiences compared to other racial groups [71]. The difference in racial groups possibly is a result of differences in acceptance of body size between whites and other racial groups [72]. Additionally, studies conducted in Africa, particularly South Africa and Senegal, revealed a higher prevalence of chronic diseases among the obese compared to non-obese counterparts [73]. In the Eastern Cape of South Africa, obesity has been found to be significantly associated with arthritis, hypertension and tuberculosis [74]. While obesity may not be a direct cause of these diseases, it increases the risk of their occurrence.

In addition to health consequences, obesity also has economic impacts such as lost productivity, loss of human capital, increased health care costs and disability, estimated to translate to approximately 2.8% of the global Gross Domestic Product (GDP) in 2012 [75]. Estimates of the cost of obesity from eight countries, namely Australia, Brazil, India, Mexico, Saudi Arabia, South Africa, Spain and Thailand, range from 0.8% to 2.4% of the GDP in 2019 [76]. Failure to halt or reduce the growing burden of obesity is projected to result in GDP costs averaging 3.6% for these eight countries by 2060. In 2019, South Africa suffered costs of 1.6% of the GDP, equivalent to ZAR1,800 per capita due to obesity and the total direct health care cost was estimated

at ZAR22,768 million in 2020 [76,77]. In addition, the financial burden of obesity to employers is up to approximately 49% more paid time off work for the obese compared to employees who are not obese [78]. Moreover, studies in Europe and Canada found lower wages and lower participation in the workforce among the obese compared to individuals with normal BMI [69]. Thus, obesity prevention is critical for physical, social and economic well-being at individual, societal and national levels. Understanding how obesity occurs is a first step towards effective prevention and management.

1.2.6 Determinants/risk factors for obesity

Obesity is not merely a consequence of poor diet or sedentary lifestyle but environmental, biological and genetic factors come into play [79]. Various factors have been linked with obesity. These may be presented in a conceptual framework.

1.2.7 Conceptual framework for the development of obesity

The development of obesity in SSA may be conceptualized to occur in the context of interactions of forces in three levels: distal, intermediate and proximate [33].

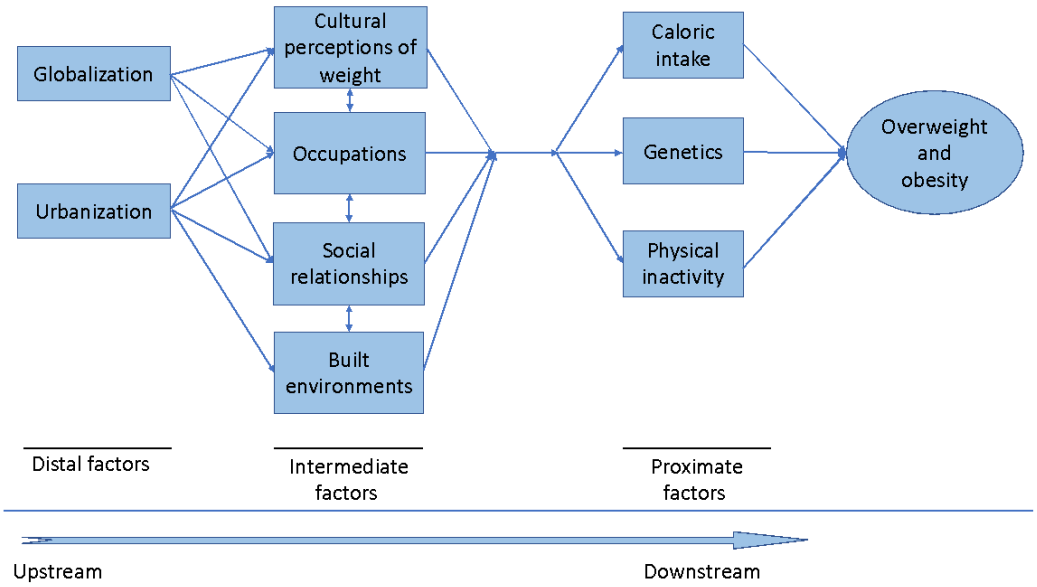


Figure 1.3: A causality continuum for obesity in sub-Saharan Africa
Source: Scott A., Ejikeme C. S., Clottey E. N. and Thomas J. G. (2013). Obesity in sub-Saharan Africa: development of an ecological theoretical framework. Reproduced with permission from Oxford University Press

1.2.7.1 *Distal factors*

Globalization and urbanization are the factors at the macro-environmental level that have been associated with the emergence of obesity. Globalization may be accompanied by positive results such as improved SES, technology and education as well as reduced mortality due to communicable diseases [80-82]. However, it is also associated with disruption in agricultural productivity and increase in consumption of unhealthy low cost processed foods, particularly in urban areas [33,83]. An increase in BMI has been demonstrated with increased economic globalization which may be related to economic inequality between countries though the mechanism still remains to be established [84]. Trade liberalization, an aspect of globalization, is associated with the increase in per capita sales of beverages sweetened with added sugar, consumption of meat and highly processed foods [85,86]. Foreign direct investment, another aspect of globalization, has also been associated with higher soft drink and processed food consumption, particularly in developing countries [87,88]. These factors, together with urbanization and sedentarism, which accompany globalization, may contribute towards the increase in obesity [89].

Urbanization is a significant factor driving the nutrition transition. Rural to urban migration for employment is accompanied by changes in diet and physical activity [81]. Urban migrants tend to shift from traditional food consumption patterns of low fat and high fibre foods to a diet rich in meat, fat, sugar, processed and refined foods thus higher obesity rates have been observed among urban than rural residents [73,81,90,91]. In addition, physical activity is reduced as people adopt sedentary lifestyles and jobs which require less energy [81,92,93]. In studies in Cameroon, urban residents were less physically active and had higher sedentary activity than those from rural areas. Moreover, transition from rural to urban residence was associated with an increase in overweight/obesity prevalence, though the prevalence decreased after 30years of urban residence [94,95]. Urbanization has been cited as one of the major drivers of obesity in South Africa. This has been accompanied by increasing levels of poverty in urban areas, increased consumption of sugar sweetened beverages and lower levels of physical activity [96,97].

1.2.7.2 *Intermediate factors*

These include elements of the built environment, culture and social connections. Physical activity levels may differ with culture, degree of urbanization, economic development and occupations. Moreover, availability and affordability of facilities for leisure physical activity like gyms including safety from traffic or crime may influence the types of physical activity [93,98]. For example, a study in Cape Town, South Africa, revealed that higher perceived safety from crime and traffic as well as availability of cycle and walking paths were associated with increased physical activity. In addition, lower transport-related physical activity was most likely related to vehicle ownership [99]. These results are similar to what was established from a review by Kärmeniemi et.al. (2018) where improvements in the built environment such as walking or cycling infrastructure and perceived safety were associated with levels of physical activity [100]. In addition, poor urban planning and crowding in cities may preclude recreational facilities, sidewalks or result in crowded streets thus reducing physical activity [33].

Changes in occupation have also been observed with globalization and urbanization. Industrialization has accompanied globalization and urbanization. A shift from predominantly manual agricultural occupations to mechanized manufacturing and service occupations has become common resulting in reduced physical activity at work [101]. In addition, the increased use of transportation instead of walking, access to television and other technologies at home or work predispose to higher sedentary activity thus increasing the risk of obesity [81,101,102].

There are also factors related to culture. In SSA, obesity has traditionally not been regarded as a disease like it is in the developed countries. One of the cultural expectations was for women to have big, curvy bodies as a sign of wealth, health, good nutrition and good life. Leanness has been associated with illness, especially HIV infection [33,103]. In Nigeria, Morocco and Tunisia, obesity has been considered a desirable sign of higher social status, fertility and prosperity [104,105]. In South Africa, results from a qualitative study on body size and the threat of obesity revealed that overweight is perceived as normal [106]. In another study, a larger body size was considered as attractive [13]. In addition to culture, social networks have been reported

to influence the development of obesity, where having an obese friend, sibling or spouse is associated with increased obesity risk [107].

1.2.7.3 *Proximate factors*

These are the factors at an individual level, which are influenced by the distal and intermediate factors. At individual level, energy intake, physical activity and genetics influence the risk of obesity, with the environment influencing gene expression [33]. It is believed that obesity has its origins starting in utero and extending to childhood development. Factors like foetal undernutrition, low birthweight, rapid increase in weight gain during infancy and stunting predispose to adult obesity [108-110]. Maternal nutrition and intra-uterine growth retardation may impair foetal insulin metabolism, predisposing the offspring to later life obesity and type 2 diabetes [111]. This aligns with the concept of developmental origins of health and disease (DoHAD) which proposes the influence of environmental conditions during early child development on physiological processes associated with non-communicable diseases (NCDs) later in life [112]. This concept also proposes that when the body repeatedly responds inadequately to environmental stressors such as behavioural, lifestyle or environmental changes, disease risk is ultimately increased. Individuals are thus conditioned early in life to respond in a certain way physiologically to later life environmental challenges [112]. However, the absence of an association between birth weight and genetic risk for obesity has been reported in South Africa, Gambia, England (Avon Longitudinal Study of Parents and Children (ALSPAC) cohort) and Australia (Western Australian Pregnancy Cohort (Raine) Study) [29,113,114]. Moreover, effects of the genetic variants (assessed through an aggregated genetic risk score) on BMI trajectories, are reportedly larger during childhood compared to adulthood and can be observed from as early as one year in the ALSPAC cohort while in South Africa the effects have been found to be more pronounced at about 11 years of age [114-116]. This may reflect the effect of the environment on gene expression.

Demographic factors have also been linked to obesity risk. Age, sex and socio-economic factors contribute to the onset of obesity. Obesity risk tends to increase with age up to about 60 years where it begins to decline [73,105]. For example, in their study

of the prevalence of obesity in Nigeria, Iloh et.al. (2011) found that middle-aged adults (40-64 years) had the highest prevalence of obesity (43.4%) when compared to the younger (24.0%) and elderly adults (≥65 years) (32.6%) [104]. A similar observation was reported from analysis of the US National Health and Nutrition Survey where middle-aged adults (40-59 years) have the highest obesity prevalence compared to the younger and older age groups [65] . South Africa also reports higher obesity rates in the older age groups. Goetjes et. al (2021) found the highest obesity risk in the 46-55- and 56-65-years age groups in South Africa [7,117] .

Globally, women have higher rates of obesity than men and the same scenario is observed in Africa and South Africa in particular [2,20,117]. According to the 2016 South African Demographic and Health Survey, women aged 45-54 (57%) and men ≥65 years (54%) had the highest obesity rates. Though there is still need for more research to establish the reasons for higher obesity in women than men, some factors are indicated to possibly contribute to this gender disparity. Results from a survey in North America showed that women had higher consumption of foods with higher sugar content and lower rates of exercise than men [118]. Moreover, cultural expectations for women to have larger bodies as well as higher likelihood of medical conditions such as thyroid disease, that contribute to weight gain, may contribute to higher obesity rates in women [13,119]. Menopause in women is also associated with weight gain through reduced energy expenditure and physical activity and decreased oxidation of fat [120]. In addition, childhood nutritional deprivation is associated with higher risk of obesity in adult women but not adult men in South Africa, probably due to differential regulation of energy and appetite [121]. Moreover, though nutrient patterns among men and women in South Africa are similar, the associations with adiposity are different [12]. This suggests differential response to the overall diet between men and women, resulting in differences in obesity rates.

Socio-economic status (SES) is also linked to greater obesity risk. Income, education level, occupation or a composite score aggregating multiple factors are commonly used measures of SES [122,123]. In the US, disparities have been observed in obesity prevalence across SES groups though a decrease is apparent over time as prevalence

of obesity increases [7,13,124-127]. Disparities have however been noted between populations in Africa and those in developed countries. While rates of obesity are typically higher in those of higher SES, urban compared to rural residents and higher education in Africa, the reverse is true in some developed countries [128]. This has been attributed to exposure to cheap, poor-quality foods among the poor in Western countries Observations have also differed by SES indicator in a review by Mclaren (2007). Education and occupation were more likely than other indicators to be associated with lower body size among women residing in highly developed countries while income and material possessions were more likely to be positively associated with body size among women in less developed countries (4). In South Africa, findings have been somewhat inconsistent. Analysis of data from three South Africa National Income Dynamics Surveys (SA-NIDS) showed that women in the middle to high and men in the high to highest SES quintiles were more likely to be obese [129]. However, this observation is contrary to what has been observed in another study in Johannesburg where SES factors like having tertiary education, employment and household assets were associated with higher likelihood of obesity in men but not in in women [130].

Other factors such as race, relationship status and smoking are also associated with obesity in South Africa as revealed by analysis of national level data by Goetjes et al. Women of African race as well as married men and women had greater risk of obesity while smoking was inversely associated with obesity [7].

In trying to elucidate the development of obesity in individuals, the concept of energy balance has also been discussed. A positive energy balance, the result of higher energy intake than expenditure through maintenance of life and activity, predisposes to obesity [65,126,131]. Lifestyle modifications, which comprise diet, exercise and modification of behaviour are thus proposed as the cornerstone of obesity prevention and management [127,131]. It is however suggested that efforts to maintain a healthy weight should not only focus on the restriction of calories, but also on what foods are eaten [65].

1.2.8 Associations of Diet with obesity

Diets densely packed with sugar, animal and vegetable fats, which are poor in micronutrients, whole grains, fruits and vegetables, are associated with a higher risk of obesity [33,127]. Thus, typical dietary recommendations designed to promote health often include eating a variety of foods high in legumes, nuts and whole grains but low in salt, fats (especially saturated and trans fats) and free sugars [132]. Diversity is defined as a dietary diversity score of 4 and above [133]. In South Africa, one of the consequences of urbanization has been higher consumption of energy-dense foods, refined carbohydrates, meat, sugar-sweetened beverages and reduced consumption of fruits and vegetables [12,134]. A minimum daily amount of 5 servings of fruit and vegetables is recommended [135]. It is believed that the satiety effect of these foods due to high fibre and water content reduces the consumption of foods high in energy with low nutrient density, contributing towards weight management [136].

Controversies exist regarding the association of fruit and vegetable intake with obesity. Notably, it is debated whether fruit and vegetable consumption independent of total energy intake is efficacious in prevention or control of obesity [137,138]. Some studies propose that increasing intake of fruits and vegetables without paying attention to subsequent reduction in total energy intake may not achieve the goal of reducing obesity [138]. However, in an analysis of three prospective cohorts, an increase in fruit and vegetable intake was inversely associated with change in weight independent of energy intake [139], thereby indicating the feasibility of evaluating the association of fruit and vegetable with traits of interest like obesity as independent dietary variables.

There is emerging evidence that fruits contribute more to reductions in body weight and adiposity compared to vegetables [137]. Studies investigating the role of fruits separate from vegetables in weight or adiposity measures suggest effects attributed to fruits that are not observed for vegetables. For example, in an Eastern Canadian cross-sectional study, combined fruit and vegetable intake was associated with a 12% reduced likelihood of abdominal obesity. However, only fruit intake was inversely associated with anthropometric indices, obesity and fat mass [137]. In addition, the weight reduction observed with increased fruit intake has been reported to be

independent of fibre content or glycaemic load of the fruit, thereby indicating that other constituents of the fruit might be contributing to the reduction in weight [139]. Possible reasons for these observations could be: i) fruits are often eaten raw while vegetables are often cooked with fat thus increasing their energy density, ii) fruits can be used as high fibre-low energy-dense snacks as they typically can be consumed anywhere compared to vegetables, iii) fruits can be used as desserts so are more versatile [140] and iv) it may also be that the mechanism by which fruits regulate adiposity could be different from vegetables. In addition, it is increasingly being recognized that people consume a combination and not individual foods or nutrients, thus studying the nutrient patterns may predict health outcomes better [141].

The Western dietary pattern has been linked to increased risk of obesity. This diet is typically high in processed meat, red meat, fast food, snacks, sweets, condiments and regular soft drinks. On the other hand, the healthy dietary pattern typically comprises higher consumption of fruits, vegetables, nuts, seeds, pulses, eggs, plant fats and fish [142-144]. The higher consumption of energy from fat as opposed to complex carbohydrates is associated with higher BMI [144]. Red and processed meat and fast foods have high saturated fatty acid content which has been associated with greater risk obesity [145,146]. In addition, high intake of snacks which are energy dense, free sugars and soft drinks potentially results in energy imbalance and the development of obesity [147,148]. Studies of nutrient patterns and body composition among men and women in South Africa revealed four dietary patterns, namely the "*plant driven nutrient pattern*, *animal-driven nutrient pattern,* the *Vitamin C, sugar and potassium-driven nutrient pattern* and the *Retinol and Vitamin B12 Driven Nutrient Pattern"* [9,12]. A diet high in animal foods, the animal driven nutrient pattern, was associated with higher BMI in women [9]. More evidence is needed to establish if the same pattern can be observed in men. In addition, some evidence suggests that dietary interventions are more effective if combined with physical activity. However, physical activity, independent of diet, is still considered a useful intervention for reducing obesity [149].

1.2.9 Association of Physical activity with obesity

Physical activity is one of the efficacious interventions for obesity prevention and control [131]. Higher amounts of physical activity and less sedentary behaviour has been reported to help facilitate weight loss and maintenance [150-152]. Results from pooled analyses of data from the US, Jamaica, Africa and six middle income countries have shown lower risk of obesity with MVPA as well as high active travel. Differences have also been observed between men and women, with stronger associations in men than women [4,5]. However, physical activity relationships with BMI or other measures of adiposity may not be so straightforward. Luke et. al. found that a cohort of US young adult men had higher obesity despite higher levels of objectively measured physical activity compared to Jamaican men with lower MVPA who were very lean [10].

In South Africa, some studies report a high prevalence of physical activity alongside a high prevalence of obesity and the precise factors contributing to this situation are not known [153-155]. An example is a study among women in Soweto where most participants met physical activity guidelines (assessed using the "global physical activity questionnaire (GPAQ)") yet 44% of them were obese [154] . In another study 67% of the participants were reported as physically active (assessed using GPAQ) yet obesity prevalence was high (48%) [8]. In addition, in the HealthKick study 81.7% of participants were classified as physically active (assessed using GPAQ) alongside a BMI of ≥25kg/m^2 in 80% of the women and 50% of the men [155]. Contrary to these results, however, the ''Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa'' (HAALSI) found that 57% had low physical activity (assessed using GPAQ) and 58% were obese [15]. Another study assessing physical activity and weight among young adults reported no significant associations between BMI and physical activity levels. Women in this study were found to have low MVPA (accelerometer based), while the mean MVPA for men was 32min in 10minute bouts of physical activity [10]. Thus, this calls for further investigation into the possible explanations.

There are possible reasons for the disparities seen in studies on physical activity and obesity in South Africa. Predominantly, a subjective physical activity assessment method such as the GPAQ is used which may overestimate MVPA as demonstrated in a longitudinal study of pregnant women in South Africa where physical activity was overestimated by 14.8 minutes/day at 14-18 weeks' gestation and by 15.8 minutes/day at 29-33 weeks' gestation [153(54)]. Other factors could be that high reported physical activity may be due to manual work associated with low socio-economic status which impact food choices and obesity [4,7,73] but these assumptions need to be investigated. The use of small sample sizes or cross-sectional nature of most of the studies and possibly genetics could also contribute to the scenario. However limited studies evaluating the role of genetics in the obesity paradox have been done among black South Africans.

1.2.10 Obesity genetics

Genetics have also been implicated in the individual variations in response to obesogenic environments, where genetic mechanisms regulating food intake and energy regulation, among others, may increase risk of obesity [156-160]. Human genetic studies have contributed towards understanding the mechanisms involved in energy homeostasis. Barsh, Farooqi and O'Rahilly proposed that genes primarily determine the susceptibility to obesity but the environment determines its phenotypic expression [161]. Obesity may be classified into 3 categories:

1.2.10.1 Monogenic obesity:

This is characterized by single gene mutations causing rare but severe obesity which manifests at an early age [162]. Monogenic obesity typically results from mutations in genes involved in appetite regulation and homeostasis, such as the leptin gene (LEP) [162], leptin receptor (LEPR) [163], pro-opiomelanocortin (POMC) [164], neuropeptide Y (NPY), melanocortin 4 receptor (MC4R) and prohormone convertase 1 (PCSK1) genes [165-167]. The prevalence of monogenic obesity may range from 5% to 30% of the population [162,168]. In school children of African descent on the Guadeloupe island, the prevalence of monogenic obesity was estimated to be above 15% [169] while it was reported to be 28% among a cohort of Pakistani children [170].

1.2.10.2 *Syndromic obesity:*

This is a form of obesity that coexists with other traits such as neurodevelopmental abnormalities and organ dysfunction [171,172]. It may be the result of a single gene mutation or changes in a chromosomal region [172].

1.2.10.3 *Polygenic obesity:*

This form of obesity is the most common. It is believed to be the additive result of modest contributions of variants from several genes [173]. Ninety-seven loci have been identified which have a role in obesity aetiology through various mechanisms such as affecting energy regulation, adipogenesis and insulin secretion/action [160]. A review of genetic association studies of obesity in Africa revealed associations of genetic variation in the FTO and MC4R genes with obesity in black South Africans, Nigerians and Ghanaians [174]. Several genetic variants are also associated with higher BMI in black South Africans which include variants in the FTO, LEP and MC4R genes [175-177].

1.2.11 The epigenetics of obesity

Over and above the influence of genes on obesity, the role of epigenetics is implicated. Environmental factors, which include physical activity, diet and gut microbiota may influence gene expression through DNA methylation or histone modification without altering DNA sequence [162,178]. These factors are believed to affect all stages of the life cycle. During early child development epigenetic pathways are modified by maternal exposures to effect the development of pathophysiological processes associated with non-communicable diseases (NCDs) later in life [112]. Up to 75% of variation in the methylome in neonates may be explained by interaction between genetic and uterine environmental factors [179]. For example, following maternal lifestyle interventions in pregnant obese Danish women, alterations in DNA methylation and more lean body mass were observed in their offspring, suggesting the possible role of maternal influences on child body composition and possibly child growth [180]. Further, analysis of data from the Isle of Wight (IoW) and ALSPAC cohorts observed associations between DNA methylation in some loci with transition of BMI from overweight/obesity to normal. However, differences in direction of transition were observed between

males and females, with males being more likely to transition to normal compared to females [181].

Among adults, results from studies in Mexican American women and French-Canadian men suggest the role of epigenetics in obesity aetiology [182,183]. In sub-Saharan Africa, adiposity was associated with three epigenome-wide significant loci [184]. However, DNA methylation may not necessarily be the cause of obesity but a consequence thereof as observed in a longitudinal study of the Bogalusa Heart Study (BHS) and Georgia Stress and Heart Study (GSHS) cohorts. Obesity was implicated as the cause of modifications in DNA methylation with time [185]. Similar conclusions were arrived at by Wahl et al., (2017) in their epigenome wide association study using data from three population cohorts [186]. Other evidence points towards the role of histone H3K4 and H3K27 methylation in adipogenesis but evidence on histone modification is still limited [187,188]. More studies are therefore needed to elucidate the epigenetics of obesity.

1.2.12 Genetics, diet, physical activity and obesity interactions

There is general consensus regarding non-homogeneity of response when people adhere to diet and physical activity [189,190]. It is believed that the way the body responds to physical activity and diet differs due to differences in genetic susceptibility to complex traits such as obesity [25,26]. However, the precise genetic factors that interplay with these lifestyle factors are yet to be clarified. The differences in individual response to lifestyle and therapeutic interventions have led to an emerging field of precision medicine which seeks to make sure that people receive interventions that are beneficial to them by taking into account the role of the environment, biology and genetics in modulating individual phenotypic responses [27,28]. This has been motivated by the limitations of the current “one size fits all” intervention approaches which may be of no benefit to certain people and even be detrimental to others as shown in Figure 1:4. Moreover, 40-70% of adiposity in humans may be attributed to genetics [191] hence variability in response to dietary intake may be expected.

Genome-Wide Association Studies (GWAS) have been instrumental in mapping genetic variants associated with numerous traits and a limited number of them have been done in Africa [31]. Recently, polygenic risk scores (PRS) are now being developed to predict complex traits such as obesity. Single nucleotide polymorphisms (SNPs) associated with complex traits are weighted based on their contribution to risk estimated from GWAS and evaluated simultaneously in PRS to predict their effects on a trait [193] thus conferring genetic risk. These may be used to study gene-environment interactions (GXE) or single variants may be used to study these interactions. [25,194,195].

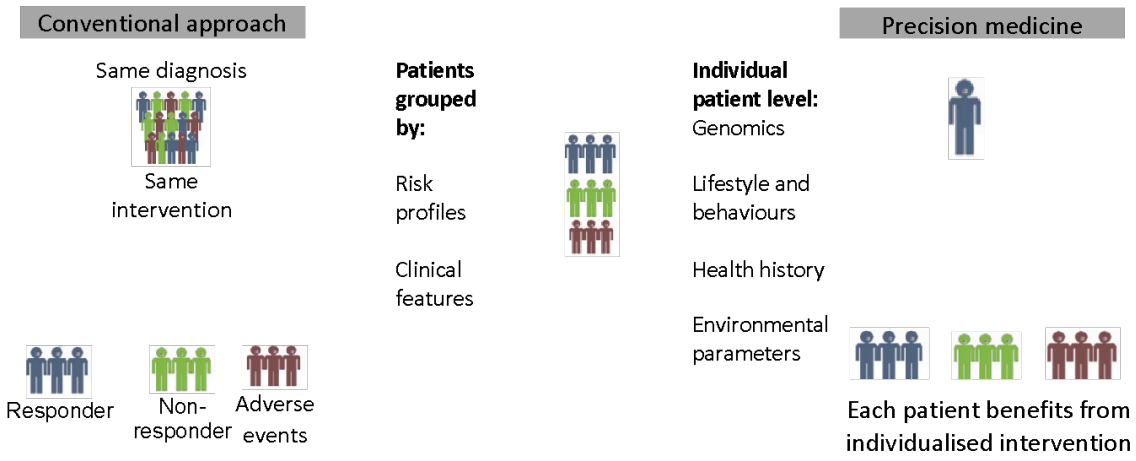


Figure 1.4: Schematic presentation of precision medicine principles illustrating population heterogeneity and potential impacts of appropriate stratification of the population
Adapted from Yilong et.al., 2018 [192] and Agusti et.al., 2017[28].

Studies on the role of physical activity in cardiorespiratory fitness (CRF) have revealed that the CRF response to physical activity is not uniform among individuals, with 47% of the response being attributable to heritability [196,197]. In addition, the European Prospective Investigation of Cancer (EPIC)-Norfolk study revealed that the effect on BMI of BMI increasing alleles is lower by 40% in physically active compared to the physically inactive [190]. Similar results are shown in the "Hispanic Community Health Study/Study of Latinos (HCHS/SOL)" where the genetic risk for obesity (determined using genetic risk scores) appeared to be attenuated by increasing physical activity

and reducing sedentary behaviour [198]. Interactions with dietary intake are not as straightforward.

While evidence consistently shows that physical activity, even at low levels, attenuates the effect of genetic risk on obesity [25,189,190,195] results on dietary interactions are more complex. In a Spanish study, energy intake has been associated with higher body fat mass particularly among people with high genetic risk [199]. People with higher genetic risk also showed a stronger association between total and animal protein intake with higher adiposity while the intake of vegetable protein was protective among those with lower genetic risk [199] . The Malmö Diet and Cancer Study shows no significant role of macronutrient consumption in modifying the influence of genetics on obesity [189]. However, the same study suggests a lower total energy intake and higher fibre intake may be associated with higher genetic susceptibility to obesity and that some obesity loci may regulate food intake though the mechanisms are not clearly understood. More studies on gene-diet interactions reveal interesting insights.

Variable responses to diet interventions for weight loss have led to the conclusion that genes are responsible for an individual's obesity fate. However, evidence suggests that the genetic structure of an individual will not inevitably result in obesity as environmental factors may modify the genetic risk of obesity. In a review focusing on gene-diet interactions, higher intake of free sugars and fried foods was found to be associated with higher BMI in individuals with higher genetic predisposition to obesity in several studies though no significant associations were observed in results from the UK Biobank Study [25]. The same review revealed that genetic variants influence individual adiposity and metabolic response to weight loss, dietary and physical activity interventions. Notably, stronger association of genetics with obesity was observed with increased intake of fried foods in three US cohorts. The FTO variants showed the strongest interactions with consumption of fried food [200]. Some studies have also unmasked the heritability of food preference patterns using structural equation modelling and principal component analysis. For example, twin studies in the Netherlands and United Kingdom show heritability estimates of more than 40% for sweet and high carbohydrate foods, meat and foods with a distinctive taste [201,202]. In

addition, evidence shows a lower risk of total mortality with consumption of three to four servings of fruits and vegetables and legumes (85). However, the guidelines still do not explain individual variations which necessitate differences in doses, requirements and nutrient response (84). As a result, the role of genetic variation in the response to nutrient intake and its relationship with metabolic disease holds much promise in tailored nutrition interventions for the prevention and management of disease (84,89).

In obesity genetics, obesity polygenic risk scores have been developed and tested for predicting obesity in different populations. Of note is the PRS which was developed using variants from 32 loci known to be associated with obesity phenotypes and tested in the "Atherosclerosis Risk in Communities (ARIC)" cohort in the USA [203]. This PRS was reported to strongly predict BMI and obesity among whites in the ARIC cohort over time, though the associations were weaker in blacks [203]. In another study, individuals from the "Framingham Offspring and Coronary Artery Risk Development in Young Adults (CARDIA)" studies were stratified into BMI PRS deciles and 15.6% of those in the top PRS decile developed obesity compared to 5.6% in deciles 2 to 9 and 1.3% in the bottom decile [24]. A limitation of the PRS predictions in these studies is that since these are derived from European populations, they have been noted to be less predictive in Africans. PRSs for several complex phenotypes which include blood pressure, BMI, breast cancer and type 2 diabetes among others were derived from a sample of predominantly European ancestry and tested in multiple ancestry groups. The worst predictive performance of the PRSs was found in an African population [204]. Efforts on obesity and genetics among children to early adulthood by Munthali at al. in 2018 used 971 black South Africans and derived a Genetic Risk Score using data from samples of European ancestry [29]. However, this is likely to be less predictive than that derived from data from an African population. These results suggest that while polygenic risk stratification may help detect individuals whose risk of obesity is higher for intervention, predictive strength of PRS may be population-dependant.

Recently, novel methods have emerged to improve cross-population polygenic prediction of complex traits. Notably, summary statistics from diverse populations may

be integrated into a single multi-ancestry PRS. This Python-based method, termed PRS-CSx, uses diverse populations to enable improved cross-population polygenic prediction. PRS-CSx jointly models SNP effects from different populations thus optimizing effect size estimation and accounting for linkage disequilibrium patterns across the population. A PRS for each discovery sample is calculated before integrating into one through linear modelling [205]. Use of a multi-ancestry PRS has demonstrated superior predictive power for predicting breast cancer in Asian populations and type 2 diabetes in various populations [206,207]. Use of PRS-CSx for PRS construction holds promise for polygenic prediction of obesity in African populations where genetic data is still limited yet the obesity problem continues to rise. However, while they may be robust in stratifying polygenic risk for obesity, polygenic risk scores have been used for studying GXE interactions with limited success in replication. Using variants known to be associated with the complex trait (vQTLs) is believed to be more robust in unmasking GXE interactions. vQTL analysis considers the genetic influence of phenotypic variance thus is able to identify interactions that may otherwise be missed in GWAS analysis [208]. In addition, vQTL analysis averts the burden of multiple testing and may be useful where there are small sample sizes [208-210].

Thus, this literature review highlights various factors that interact to influence the risk of developing obesity. The causality continuum for obesity in sub-Saharan Africa by Scott A., Ejikeme C. S., Clottey E. N. and Thomas J. G. (2013) is applicable in the current study as it articulates the possible interactions of environmental and individual factors in the development of obesity. It highlights how factors such as culture, policy, food and the built environment may influence the development or control of obesity. For example, in South Africa, the increase in obesity gave rise to the sugar-sweetened beverage (SSB) tax whose aim was to reduce the consumption of free sugars, which are implicated in the aetiology of obesity[211,212]. In addition, the cultural environment where overweight is considered to be normal and the propagation of the notion of 'healthy obese' individuals [213] over the years also fits into the conceptual framework of obesity development in South Africa. Moreover, urbanization leading to more sedentary occupations, changes in the built environment leading to fewer green

spaces, heavy traffic and narrow walkways may have resulted in reduced physical activity. The role of genetics may also be studied to enrich the understanding of the factors associated with obesity in South Africa. All these factors may also be discussed in the South African environment thus giving a clearer view of the association of diet and physical activity with obesity in the strata of low and high genetic susceptibility in black South Africans. This study will provide insights that can be validated in clinical trials.

1.3 Summary of literature review and research gaps

Obesity, a complex trait resulting from intricate relationships of environmental and genetic factors, is a growing public health concern in South Africa. It is an important determinant for NCDs such as stroke, diabetes and hypertension. In addition, it is associated with increased economic costs such as increased health care costs and costs due to lost productivity. Several methods exist for measuring obesity which include BMI, waist circumference, waist hip ratio and objective measures of body fat such as CT, DEXA, densitometry and hydrometry. However, due to its ease of measurement, usefulness in assessing total body fat and strong correlation with gold standard measures of body fat, BMI remains a widely used and valid measure of obesity.

Various factors are implicated in the development of obesity. Factors at the macro-environment level such as urbanization and sedentarism are often associated with increased mechanization as people move to urban areas in search of work and work becomes more mechanized and less manual. In addition, globalization is accompanied by the nutrition transition where people move to more meat, sugar and fat consumption with less physical activity. At the intermediate level, the built environment, culture and social connections may influence the risk of obesity. For example, the availability of safe pedestrian pathways or accessibility of gyms likely increases physical activity reducing the risk of obesity. The cultural perception of voluptuous bodies as a sign of wealth, health, good nutrition and fertility normalizes obesity.

At individual level, it is believed that obesity starts in utero and extends to childhood, predisposing to adult obesity. In addition, older people have more likelihood of being obese than younger ones and women tend to be affected more than men. Some factors such as differences in physical activity, food choices or disease, among others, have been reported as possible explanations for the obesity disparities between men and women. More exploration, however, is necessary to determine the precise factors influencing this disparity.

Dietary and physical activity interventions are associated with obesity prevention and management. Diets rich in plant foods and fish which are lower in animal foods, fast foods, free sugars and snacks are associated with lower BMI. Higher physical activity and lower sedentary activity are also associated with lower BMI. However, the obesity paradox in South Africa, where high levels of physical activity are reported alongside high levels of obesity, warrants deeper investigation. This observation suggests that universal recommendations for diet and physical activity may not achieve the desired outcomes. There may be other factors at play.

Genetic factors are implicated in individual differences in responses to adherence to diet and physical activity recommendations. Even at lower intensities, physical activity reportedly attenuates the genetic risk of obesity. However, the gene-diet interaction is more complex, with varied associations being observed for different nutrients. The complex interplay between physical activity, diet and genetic susceptibility to obesity are thus poorly understood. Polygenic risk scores have recently begun to be used to predict genetic risk of complex traits such as obesity. However, genetic studies in Africa are limited. Use of PRS derived from European populations have been shown to have limited predictive capacity for various complex traits in African populations probably due to the complex genetic structure of Africans. Use of multi-ancestry PRSs has demonstrated improved predictivity. Moreover, identification of variants known to influence complex trait variability is known to improve detection of GXE interactions.

Evidence of gene interactions with diet and physical activity in influencing obesity is scarce in African populations. The longitudinal interactions of the same are also not

known, neither is it well understood whether the interactions persist over time. A longitudinal analysis of the association of PRS with obesity from infancy to early adulthood has been conducted in a low income, Black South African population. Results of this analysis suggest that genetic risk of obesity becomes increasingly important from adolescence [93]. It however does not investigate the environmental effects and how they might influence gene expression, neither does it investigate the genetic risk of obesity in adulthood. The Human Hereditary and Health in Africa (H3Africa) consortium has led to setting up of African cohorts that have recruited more than 70 000 research participants from several countries in Africa for genetic studies [90]. This study therefore leveraged on the Africa-Wits-INDEPTH partnership for Genomic studies (AWI-Gen) longitudinal study, which is part of the H3Africa consortium, to use data from 5921 participants in the South African sites to develop PRS for predicting obesity in black South Africans and identify GXE interactions. Furthermore, data from a subset of the AWI-Gen cohort focusing on the determinants of T2D risk in middle-aged black South African (SA) men and women (GSK), was used to explore heterogeneity of associations between BMI and dysglycaemia, diet and physical activity. The analysis is anticipated to be useful as part of the efforts towards tackling the increasing obesity problem in South Africa.

1.4 Aims and objectives

1.4.1 Aim

This study seeks to understand the longitudinal association of diet and physical activity with obesity in the context of individual differences in the level of genetic risk (high versus low) as well as the clinical implications.

1.4.2 Specific Research Objectives

1) To determine the association of physical activity with BMI in middle-aged Black South African men and women
2) To develop a highly predictive genetic risk score for obesity and test its longitudinal predictive ability in middle aged black South African men and women.

3) To determine the gene x lifestyle interactions that influence BMI in Black South African adult men and women.

1.5 Research Questions

Research question 1: What is the association between self-reported physical activity in domains of work, leisure and transport-related physical activity and body mass index in middle aged black South Africans?

Research question 2: Is there a difference in risk for overweight or obesity among middle aged black South African men and women in high and low polygenic risk strata over time?

Research question 3: Do genetic variants associated with BMI modify the association between physical activity and dietary intake with BMI?

CHAPTER 2: EXTENDED METHODOLOGY

2.1 Overview

This study was both a cross-sectional and longitudinal analysis of secondary data from the AWI-Gen cohort and GSK study. This section describes the setting and design of the parent studies providing data for this study as well as procedures and statistical analysis that were conducted to fulfil the objectives of this study.

2.2 AWI-Gen Study

2.2.1 Study design

AWI-Gen is a longitudinal cohort study of 5315 men and 6538 women (recruited when they were aged 29 - 82 years) from six study sites, namely Nanoro, Navrongo, Nairobi, Soweto, Dikgale and Agincourt. AWI-Gen had three study aims at inception, namely (i) capacity building for genomic research, (ii) understanding the "population structure and genetic architecture among the study participants" and (iii) investigating "independent and interacting genomic, environmental and behavioural contributions to body composition and body fat distribution (height, weight, hip and waist circumference, subcutaneous and visceral fat)" [81].

2.2.2 Study setting

Agincourt is a remote rural site in South Africa with a third of the population being immigrants from Mozambique. It is the home of several studies and trials across the life course [82,83]. Nanoro is a Health demographic surveillance system site in rural Burkina Faso which was established to assist the health authorities in setting up and assessing health interventions [84]. Navrongo is also a health demographic surveillance system site and it is located in rural Ghana. Its main function is monitoring and evaluation of the demographics and health interventions among the population of the Kassena-Nankana districts in Northern Ghana where it is located [85]. The Nairobi Urban Health and Demographic Surveillance System site is the other site where the AWI-Gen study is being conducted. It is the first urban demographic and health surveillance site established to study the consequences of urbanization. The Dikgale site is also another health and demographic surveillance system established with the main aim

as being the sampling frame for population studies on non-communicable diseases. It is situated about 40km from Polokwane in South Africa [214]. Soweto is the sixth of the AWI-Gen sites. It is in an urban area, Soweto-Johannesburg, and is the centre of a birth cohort whose recruitment started in 1990. To date, several studies covering the life cycle have been conducted [87]. The focus of this study is on the three sites in South Africa.

2.2.3 Study recruitment and data collection

For the purposes of Objective 1, data from the 6 sites of the AWI-Gen cohort was used. For objective 2, data from 5662 men and women in the three South African study sites, namely Soweto, Dikgale and Agincourt was used while genetic data from 4826 men and women from the same three sites and demographic data from 760 men and women from the Soweto site was used to meet object 3. Individuals with the following characteristics were excluded from the study: pregnancy, parents, children or siblings of existing participants, resident in the region for less than 10 years as well as physical impairments preventing measurement of blood pressure and other anthropometric indices [215]. Recruitment for phase 1 of the study was completed in 2016 and data collection for phase 2 was completed in 2022.

2.3 GSK study

2.3.1 Study design

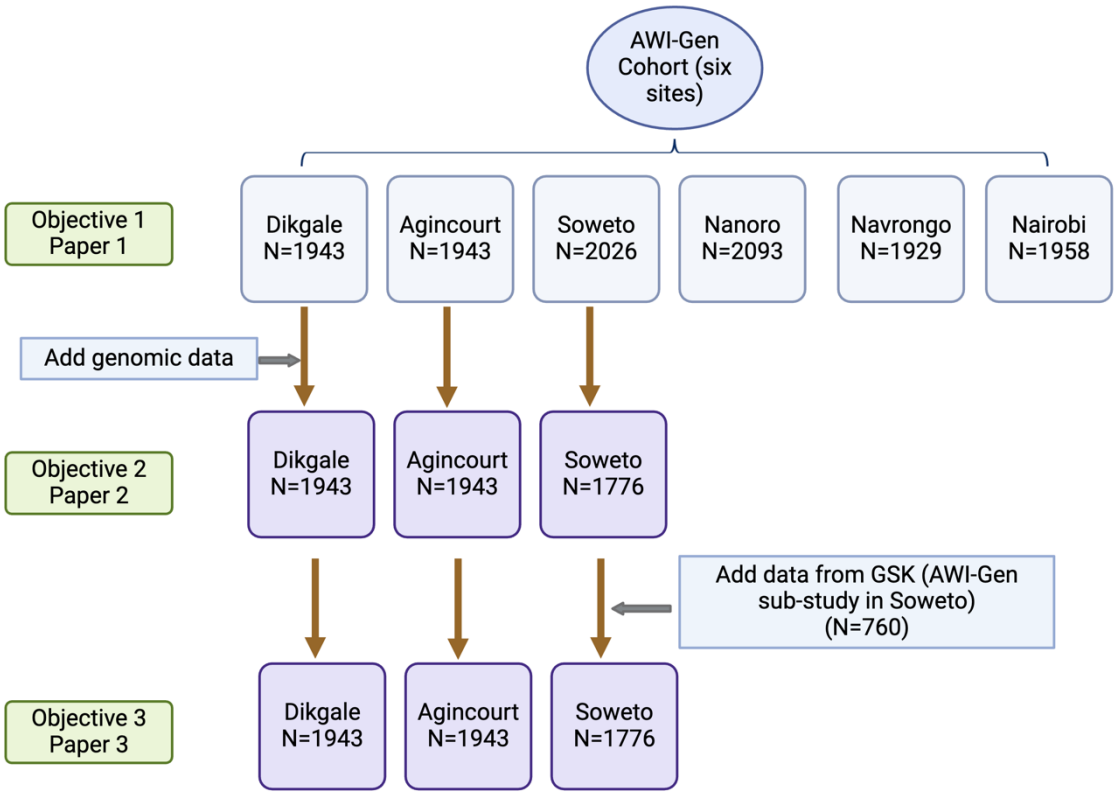
The GSK study was a retrospective cohort study of men and women. The aims were to examine the effect of sex hormonal changes on body fat distribution, insulin sensitivity and secretion as well as the role of inflammatory markers in the context of HIV among middle-aged men and women.

2.3.2 Study setting

The GSK study was conducted in the Developmental Pathways Health Research Unit (DPHRU). DPHRU is an urban research unit located at the Chris Hani Baragwanath Hospital in Soweto, Johannesburg, South Africa.

2.3.3 Study recruitment and data collection

The data was collected from 1025 men and women aged 35 to 65 between January 2017 and July 2018. The men were a random subsample of participants of an African genomics study (www.h3africa.org) whose data were collected in 2014 while the women were randomly selected from the Study of Women Entering and in Endocrine Transition where data collection occurred between 2011 and 2014 . Dietary and proteomic data from 760 men and women were used for objective 2 and 3. See Figure 2.1



Created with BioRender.com

Figure 2.1: Schematic diagram showing the datasets used in each stage of data analysis

2.4 Data collection and management

Trained interviewers and anthropometrists collected data using structured paper questionnaires for AWI-Gen at baseline and for GSK. The data was entered into an electronic data management software, REDCap, which is hosted by the University of the Witwatersrand. For AWI-Gen phase 2 data collection, trained interviewers and anthropometrists used tablets to collect data. The data were entered into REDCap

during data collection. Data on demographics, anthropometry, physical activity, health, smoking, alcohol intake and blood for genotyping were collected. Interviews were conducted using the home language of the participant. Where the participant was comfortable, English was used for the interview. Data cleaning and analysis was conducted as appropriate for each research question.

2.5 Study Measures

A digital scale was used to measure weight while height was measured using a stadiometer. The scale and stadiometer were calibrated every morning before use. Blood samples for genotyping of genomic DNA were collected after an overnight fast and processed using the 2.3million SNP H3Africa genotyping array$_1$ (Illumina, USA), employing the Illumina FastTrack Sequencing Service$_2$ [215]. Quality control included excluding individuals and SNPs with a missingness above specific thresholds, MAF less than 0.01 and Hardy-Weinberg equilibrium (HWE) P-value below 0.0001 as described by Ali et al. (2018) [215]. Imputation was conducted using the Sanger Imputation Server, with the African Genome Resources as reference panel. Poorly imputed SNPs (info scores <0.6, MAF <0.01 and HWE P-value <0.00001) were excluded. The final QC-ed imputed data had 13.98 M SNPs [215].

Details of measurement procedures are discussed in the relevant methods sections. For the three papers, all participants with data available on genetics, physical activity (GPAQ) and BMI at the AWIGEN phase 1 and 2 data collection points were included. In addition, objective physical activity data (measured using accelerometery) from a subsample of 700 participants who participated in the GSK study was also used as well as dietary data from food frequency questionnaires in the GSK study. The influence of genetics on the association of physical activity and diet with BMI was investigated.

2.6 Statistical Methods

2.6.1 Meta-analysis

This was used in the first study to summarize quantitative results from six study sites of AWI-Gen to better understand how domain-specific self-reported physical activity is associated with BMI in adult men and women. Meta-analysis is one of the methods used in aggregating findings from several studies and is useful in summarizing quantitative results into a single estimate. This method was relevant as the data to be summarized was from studies that used the same methodology and thus expected to yield a meaningful summary.

2.6.2 PRS-CSx analysis

This method, which is Python-based, uses continuous shrinkage priors, integrating summary statistics from GWAS in diverse populations. After calculating a PRS for each discovery population, linear modelling is used to integrate the PRSs. This method holds promise in improving polygenic prediction of complex trait in populations with limited genetic data such as Africa where polygenic prediction of complex traits using PRS derived from European populations is 4.5-fold less predictive for several complex traits [30].

2.6.3 Cox proportional hazard analysis

Cox proportional hazard analysis was used in the second study to determine the risk of overweight or obesity in men and women over time. The Cox proportional hazards model is a regression model which assumes constant relative hazard over time and independence of time to event among individuals [216].

2.6.4 Variance quantitative trait locus (vQTL) analysis

This method was used in the third study to identify GXE interactions in the study population. Variance QTL (vQTL) analysis is a statistical method used in genetics to identify genetic loci that contribute to the variability in quantitative traits such like weight, height, blood pressure, etc [210]. Since both genetic and environmental factors are associated with complex traits, identifying the genetic variants underlying complex

trait variance has the potential to help understand their aetiology and form the basis for precision medicine [217].

2.7 Ethics

This study was nested in the ongoing AWI-Gen studies that have obtained ethical clearance from the Wits HREC (M121029). Some data was also used from the GSK study that has obtained ethical clearance from the Wits HREC (M160604). The PhD student focused on the genetic and environmental factors and obtained ethical clearance from the Wits HREC (M210166). RedCap, an electronic data management tool hosted by the University of Witwatersrand, was used for data collection and only accessed by authorised study personnel. All secondary data that the PhD student had access to was anonymised to protect participant privacy. Electronic equipment which was used had a password that is only known by the user. Participants were reimbursed transport costs incurred during their participation in the study and offered refreshments at the study sites. Covid-19 safety protocols, which were developed at each study site, were also observed for all staff and study participants.

2.8 Candidate's role in the study

The PhD student administered interviews and anthropometric measurements in the AWI-Gen phase 2 at the Soweto site. In addition, she conducted data quality control, cleaning and analysis prior to report writing.

CHAPTER 3: Physical activity and its association with body mass index: a cross-sectional analysis in middle-aged adults from four sub-Saharan African countries

Analysis in this chapter was published in Muti M, Ware LJ, Micklesfield LK, Ramsay M, Agongo G, Boua PR, Kisiangani I, Cook I, Gómez-Olivé FX, Crowther NJ, Kabudula C, Norris SA, Chikowore T. Physical activity and its association with body mass index: A cross-sectional analysis in middle-aged adults from 4 Sub-Saharan African countries. J Phys Act Health.2023;20(3):217–225.
https://doi.org/10.1123/jpah.2022-0539

3.1 Abstract

Background: This study aimed to explore association of self-reported physical activity domains of work, leisure, and transport-related physical activity and body mass index (BMI) in 9388 adult men and women from the Africa-Wits-INDEPTH partnership for Genomic (AWI-Gen) study in Africa. Africa-Wits-INDEPTH partnership for Genomic is a large, population-based cross-sectional cohort with participants from 6 sites from rural and urban areas in 4 sub-Saharan African countries.

Methods: A sex-stratified meta-analysis of cross-sectional data from men and women aged 29–82 years was used to assess the association of physical activity with BMI.

Results: Overall, meeting physical activity guidelines of at least 150 minutes per week was associated with 0.82 kg/m2 lower BMI in men (β = −0.80 kg/m2; 95% confidence interval [CI] = −1.14 to −0.47) and 0.68 kg/m2 lower BMI in women (β = −0.68 kg/m2; 95% CI = −1.03 to −0.33). Sex and site-specific differences were observed in the associations between physical activity domains and BMI. Among those who met physical activity guidelines, there was an inverse association between transport-related physical activity and BMI in men from Nanoro (Burkina Faso) (β = −0.79 kg/m2; 95% CI = −1.25 to −0.33) as well as work-related physical activity and BMI in Navrongo men (Ghana) (β = −0.76 kg/m2; 95% CI = −1.25 to −0.27) and Nanoro women (β = −0.90 kg/m2; 95% CI = −1.44 to −0.36).

Conclusions: Physical activity may be an effective strategy to curb rising obesity in Africa. More studies are needed to assess the impact of sex and geographic location-specific physical activity interventions on obesity.

3.2 Introduction

Obesity is one of the major risk factors for cardio-metabolic diseases [218]. It is projected that in Africa, by 2030, 27 million men and 72 million women will be obese, an increase from 8 million men and 26 million women in 2010 [19]. Physical activity (PA) is a vital lifestyle intervention for reducing obesity [2,219-222]. However, more studies are needed in Africa to understand the physical activity patterns of men and women and their association with BMI.

Total time spent in physical activity is accrued from various physical activity domains (namely work, leisure and transport) and varies among communities and countries [223,224]. High-income countries have higher levels of leisure-time physical activity (LTPA) (28% of total PA) compared to the low, lower-middle and upper-middle income countries (4%, 8%, and 13% respectively) [223]. Work-related physical activity has a higher contribution to total PA in the low and lower-middle income countries (57%) compared to the upper-middle and high-income countries (44%–47%) [223]. Most evidence on the association between physical activity and BMI is based on the leisure-time physical activity (LTPA) domain in US and European populations [149,221,225]. However, work and transport-related PA are highly prevalent in Africa, accounting for 95% of overall physical activity in 22 countries, compared to 5% for LTPA [226]. This might be due to differences in culture, levels of urbanization, economic development and climate between low-and-middle income and high-income countries. In addition, access to and affordability of facilities for LTPA such as gyms may determine the types of physical activities in which Africans engage [93,98]. Dugas et al. (2014 and 2017) explored the association between physical activity (self-reported and accelerometry-based) on BMI in adults of African origin. Inconsistent associations were found between time spent in moderate-to-vigorous physical activity (MVPA) and BMI while higher baseline MVPA levels were not significantly associated with future weight changes.

Some scholars argue that inconsistencies in the association between physical activity and BMI may be because physical activity alone is insufficient to influence BMI but

more benefits would be realized if complemented with other interventions such as diet [227,228]. Nevertheless, evidence is fairly consistent on the association of higher physical activity with lower BMI [229-232]. However, though physical activity is known to be associated with lower BMI, the reverse may also be true as bidirectional causal relationships between physical activity and BMI have been observed in a Mendelian randomization study [233] and higher BMI has been seen to result in less transport-related physical activity [234]. Nevertheless, there remains, a lack of evidence on the impact of domain-specific physical activity on BMI, particularly on the African continent as patterns of physical activity in work, leisure and transport-related physical activity domains differ across regions of the world [223]. Therefore, we aimed to describe and compare physical activity domains between middle-aged men and women from East, West and South African countries and evaluate the association between time spent in these physical activity domains with BMI.

3.3 Materials and Methods

3.3.1 Study population and setting

We used data from 9388 men and women aged 29 - 82 years recruited across five sites in the Africa-Wits-INDEPTH partnership for Genomic studies (AWI-Gen), a large, population-based cross-sectional cohort from rural and urban areas in four sub-Saharan African countries [215,235]. Four of the sites were health and demographic surveillance sites (HDSS) in West Africa (Nanoro HDSS [236], Burkina Faso and Navrongo HDSS in the Navrongo Health Research Centre, Ghana [237]), East Africa (African Population and Health Research Center HDSS, Nairobi, Kenya [23827]) and South Africa (Dikgale HDSS [214]) The fifth site was located in the MRC/Wits Developmental Pathways for Health Research Unit, Soweto, also in South Africa [239]. Participants were recruited at random into the AWI-Gen study. The recruitment process is described in detail in an earlier publication [215]. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the University of the Witwatersrand Human Research Ethics Committee (Medical) (M210166). The AWI-Gen study data was collected under ethical approval from the same committee (M121029), and written informed consent was obtained from all

participants. Those who could not read or write had the consent form read before they affixed a thumbprint and a third party signed as a witness [215].

3.3.2 Data collection

Face-to-face interviews were conducted at study sites in different countries to obtain data on physical activity and demographic variables.

3.3.3 Anthropometric measurements

Weight was measured with a calibrated digital scale to the nearest 0.1kg, and height was measured to the nearest 0.01cm using a wall-fixed digital stadiometer (Holtain, Wales) [215]. BMI was calculated and categorised as follows: underweight (BMI < 18.5 kg/m^2), normal weight (BMI ≥ 18.5 and < 25kg/m^2), overweight (BMI ≥ 25 and < 30 kg/m^2) and obese (BMI ≥ 30 kg/m^2) [240].

3.3.4 Socio-demographics and physical activity

Education was categorized as no formal education, completion of primary, secondary or tertiary education. Household assets in working order were used to categorize socioeconomic status (SES) into quintiles based on the demographic and health survey method [241,242].

Physical activity was measured in three domains, namely occupational, transport-related and leisure-time physical activity, using the Global Physical Activity Questionnaire (GPAQ) [240,243]. Total time spent in each physical activity domain was a sum of the minutes spent per week in moderate and vigorous-intensity physical activity (MVPA) in that domain. Total MVPA in minutes per week was calculated as MVPA time accumulated in the three domains. Total MVPA was classified based on the WHO guidelines for physical activity. Those with MVPA ≥ 150 minutes/week were classified as meeting guidelines, and those with MVPA <150 minutes/week were classified as not meeting guidelines [224]. Sitting time in hours per day from the GPAQ was used to measure sedentary time. Sleeping time was not included in the analysis [243].

3.3.5 Statistical analysis

Data was exported to R version 4.0.0, cleaned and checked for normality using the Shapiro Wilcoxon test. Cleaning was conducted for the physical activity data using the GPAQ analysis guide. In addition, observations lying outside +/- 1.5 SD of the mean were removed. For sitting time, participants with sitting hours above 24 hours per day were removed.

In the first stage of analysis (data analysis stage 1, Figure 3:1), the data was split into sites. Descriptive statistics were used to describe the participants' characteristics, exposures and outcomes, including physical activity patterns in the different study sites. Median and interquartile ranges (IQR) were used to describe the non-normally distributed variables. Mann-Whitney test for continuous data and chi-square test for categorical data were used to test the differences between men and women and between sites. To determine the proportion of time spent in each physical activity domain, the total MVPA for each participant was calculated, followed by the percentage of time spent in each domain before getting the mean of these percentages for each domain. Linear regression modelling was conducted to determine the association between meeting physical activity guidelines (predictor) with BMI (outcome) across the sites. After that, a meta-analysis was completed in the meta package of R using summary statistics from linear regression to determine the associations in the total sample. Models were adjusted for age, education level and SES.

In stage 2 of the analysis (Figure 3:1), only those who met physical activity guidelines were included. Leisure-time, work and transport-related physical activity were classified as low (<120 minutes/week) and moderate-to-high (>120 minutes/week), an adaptation of the work by Holtermann et al. (2021) [244]. Linear regression models were used to obtain effect sizes, with BMI as an outcome and physical activity domain as a predictor while adjusting for age, educational level and socioeconomic status (SES). Alcohol intake and smoking status were not included in the models since alcohol intake data for Soweto was not collected and the prevalence of smoking among Nanoro women was 0% [245]. We then aggregated the effect sizes of the associations between physical activity domain (as the predictor) and BMI (as the outcome) across the study

sites using the fixed-effects model, assuming that the actual effect of physical activity on BMI was the same in all the sites. This enabled us to determine departure from this assumption as indicated by the I^2, which is a measure of heterogeneity [246]. Effect sizes in the meta-analysis are labelled as standardized mean differences (SMD) by default since they were pre-calculated for each study while weight denotes the percent weight that is attributed to each study by the model [247].

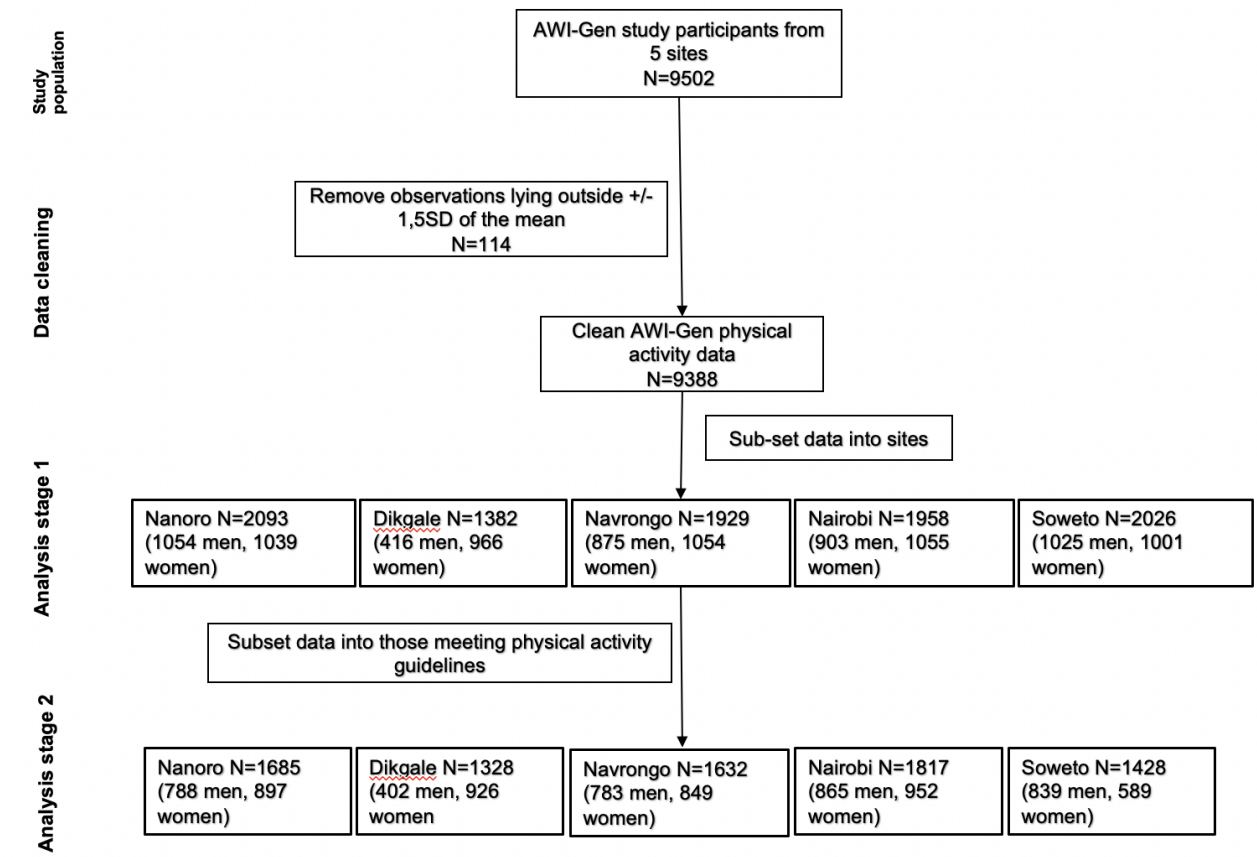


Figure 3.1: Schematic presentation of data handling procedures for the analysis of the physical activity in four African countries

3.4 Results

3.4.1 Characteristics of study participants

The median age of the study participants was 50 years for both men and women (IQR: 45, 55) (Table 3:1). Education level was significantly different between men and women in all study sites except for Dikgale (rural South Africa). In all the study sites,

BMI was higher in women than men except for Nanoro (rural Burkina Faso), where the median BMI was 21.1 kg/m^2 for men and 19.8 kg/m^2 for women. Women in Soweto (urban South Africa) had the highest median BMI (32.9 kg/m^2), while women in Nanoro had the lowest (19.8 kg/m^2). The median sitting time was 8 hours per day (IQR = 5.5; 11.5) among men and 7.7 hours (IQR = 5.5; 11.0) among women, and this difference was statistically significant ($p<0.001$). More than 80% of the total sample of men (86.1%) and women (82.4%) met the weekly physical activity guidelines of at least 150 minutes of MVPA per week. This trend was consistent in all sites except Nanoro, where more women than men (86.3% vs. 74.8%; $p < 0.001$) met the physical activity guidelines (Table 3:1).

3.4.2 Patterns of physical activity by domain

Most of the physical activity time at all sites was spent on work and transport-related physical activity, with LTPA contributing the least to total MVPA (Figure 3:2). Transport-related PA accounted for most of the time spent in MVPA in Soweto and Nairobi men and women. However, there were sex differences in the physical activity domains in which most of the time was spent at the other sites. Thus, in Dikgale and Nanoro, women spent most of their time in work-related PA while men spent most of their time in transport-related PA. In Navrongo, women spent a similar amount of time in work and transport-related PA, while men spent most of their time in work-related PA (Figure 3:2).

3.4.3 Association between meeting physical activity guidelines and BMI

Compared to not meeting guidelines, meeting physical activity guidelines of at least 150 minutes MVPA per week was significantly associated with lower BMI in Soweto and Nanoro men (Figure 3:3A) and in Nanoro and Dikgale women (Figure 3:3B). In the meta-analysis, this was associated with a 0.80 kg/m^2 lower BMI in the total sample of men (β = -0.80, 95% CI = -1.14 – -0.47) (Figure 3:3A), and 0. 68 kg/m^2 lower BMI in the total sample of women (β = -0.68, 95% CI = -1.03 – -0.33) (Figure 3:3B).

Table 3:1 Background characteristics of participants in sites from 4 African countries

Table 1 Background Characteristics of Participants in Sites From 4 African Countries

Variable	Combined AWI-Gen sites		Dikgale		Soweto		Nanoro		Navrongo		Nairobi	
Number of participants	Men (n = 4273)	Women (n = 4935)	Men (n = 416)	Women (n = 966)	Men (n = 1025)	Women (n = 1001)	Men (n = 1054)	Women (n = 1039)	Men (n = 875)	Women (n = 1054)	Men (n = 903)	Women (n = 1055)
Age, y	50 (45, 55)	50 (45, 55)	52 (45, 58)	52 (46, 58)	49 (44, 55)	49 (44, 54)	50 (44, 55)	50 (45, 55)	50 (46, 55)	52 (47, 56)***	48 (44, 53)	48 (44, 53)
	$P < .001$		$P = .010$		$P < .001$		$P < .001$		$P < .001$		$P < .001$	
SES quintiles, n (%)												
First quintile	466 (10.9)	876 (17.1)	76 (18.3)	106 (11.0)	25 (2.4)	207 (20.7)	136 (12.9)	202 (19.4)	134 (15.3)	216 (20.5)	95 (10.5)	145 (13.7)
Second quintile	725 (17.0)	1260 (24.6)	94 (22.6)	214 (22.2)	97 (9.5)	389 (38.9)	218 (20.7)	189 (18.2)	145 (16.6)	198 (18.8)	171 (18.9)	270 (25.6)
Third quintile	781 (18.3)	960 (18.8)	55 (13.2)	136 (14.1)	157 (15.3)	162 (16.2)	194 (18.4)	213 (20.5)	159 (18.2)	208 (19.7)	216 (23.9)	241 (22.8)
Fourth quintile	916 (21.4)	966 (18.9)	79 (19.0)	219 (22.7)	267 (26.0)	79 (7.9)	184 (17.5)	203 (19.5)	210 (24.0)	247 (23.4)	176 (19.5)	218 (20.7)
Fifth quintile	1383 (32.4)	891 (17.4)	112 (26.9)	290 (30.0)	479 (46.7)	9 (0.9)	320 (30.4)	227 (21.8)	227 (25.9)	184 (17.5)	245 (27.1)	181 (17.2)
	$P < .001$		$P = .125$		$P < .001$		$P < .001$		$P < .001$		$P < .001$	
Education level, n (%)												
No education	1734 (32.7)	1734 (32.7)	30 (7.2)	103 (10.9)	8 (0.8)	2 (0.3)	765 (72.9)	961 (93.3)	535 (61.3)	813 (77.5)	33 (3.7)	114 (10.8)
Primary	1510 (28.5)	2397 (38.0)	151 (36.3)	338 (35.7)	116 (11.5)	635 (81.0)	181 (17.2)	58 (5.6)	195 (22.3)	173 (16.5)	456 (50.5)	668 (63.3)
Secondary	1781 (33.6)	1211 (19.2)	219 (52.6)	480 (50.7)	738 (72.9)	146 (18.6)	87 (8.3)	9 (0.9)	116 (13.3)	54 (5.1)	392 (43.4)	269 (25.5)
Tertiary	282 (5.3)	93 (1.5)	16 (3.8)	26 (2.7)	150 (14.8)	1 (0.1)	17 (1.6)	2 (0.2)	27 (3.1)	9 (0.9)	22 (2.4)	4 (0.4)
	$P < .001$		$P < .001$		$P < .001$		$P = .026$		$P = .054$		$P < .001$	
Employment status, n (%)												
Employed	3439 (69.6)	3669 (59.7)	166 (41.0)	292 (30.9)	657 (64.9)	543 (54.6)	991 (98.4)	921 (99.5)	554 (63.7)	621 (59.4)	801 (96.9)	896 (90.8)
Unemployed	1505 (30.4)	2473 (40.3)	239 (59.0)	654 (69.1)	355 (35.1)	451 (45.4)	16 (1.6)	5 (0.5)	316 (36.3)	425 (40.6)	26 (3.1)	91 (9.2)
	$P < .001$		$P < .001$		$P < .001$		$P < .001$		$P < .001$		$P < .001$	
BMI category, n (%)**												
Underweight	722 (14.3)	563 (9.0)	82 (19.7)	33 (3.4)	105 (10.3)	6 (0.6)	182 (17.3)	322 (31.0)	165 (18.9)	138 (13.1)	106 (11.7)	41 (3.9)
Normal	3058 (60.4)	2300 (36.8)	247 (59.4)	203 (21.0)	452 (44.1)	112 (11.2)	717 (68.0)	645 (62.1)	644 (73.6)	709 (67.3)	569 (63.0)	347 (32.9)
Overweight	916 (18.1)	1353 (21.7)	74 (17.8)	248 (25.7)	288 (28.1)	216 (21.6)	130 (12.3)	59 (5.7)	56 (6.4)	161 (15.3)	179 (19.8)	332 (31.5)
Obese	369 (7.3)	2029 (32.5)	13 (3.1)	481 (49.8)	179 (17.5)	666 (66.6)	25 (2.4)	12 (1.2)	10 (1.1)	46 (4.4)	49 (5.4)	335 (31.8)
Meeting physical activity guidelines, n (%)	3677 (86.1)	4213 (82.4) ***	402 (96.6)	926 (95.9)	839 (81.9)	589 (58.8)***	788 (74.8)	897 (86.3)***	783 (89.5)	849 (80.6)***	865 (95.8)	952 (90.2)***
Total sitting hours												
median (Q1; Q3)	8 (5.5; 11.5)	7.7 (5.5; 11.0) ***	7.3 (5.5; 11.1)	7 (5.4; 12.0)	10 (7.0; 13.1)	9 (6.0; 12.0)	7.1 (5.0; 11.0)	8 (6.0; 10.2)*	6.8 (5.0; 9.4)	6.3 (5.0; 9.0)*	13 (8.0; 16)	12.2 (8.0; 17.0)
Proportion spending > 8 h sitting	2381 (51.4)	2620 (49.2)*	13 (40.6)	22 (44.9)	692 (67.9)	585 (58.7)***	507 (48.3)	569 (55.0)**	329 (36.5)	438 (40.3)	581 (75.8)	691 (75.4)

Abbreviations: BMI, body mass index; SAS, socioeconomic status.
*$P < .05$. **$P < .01$. ***$P < .001$.

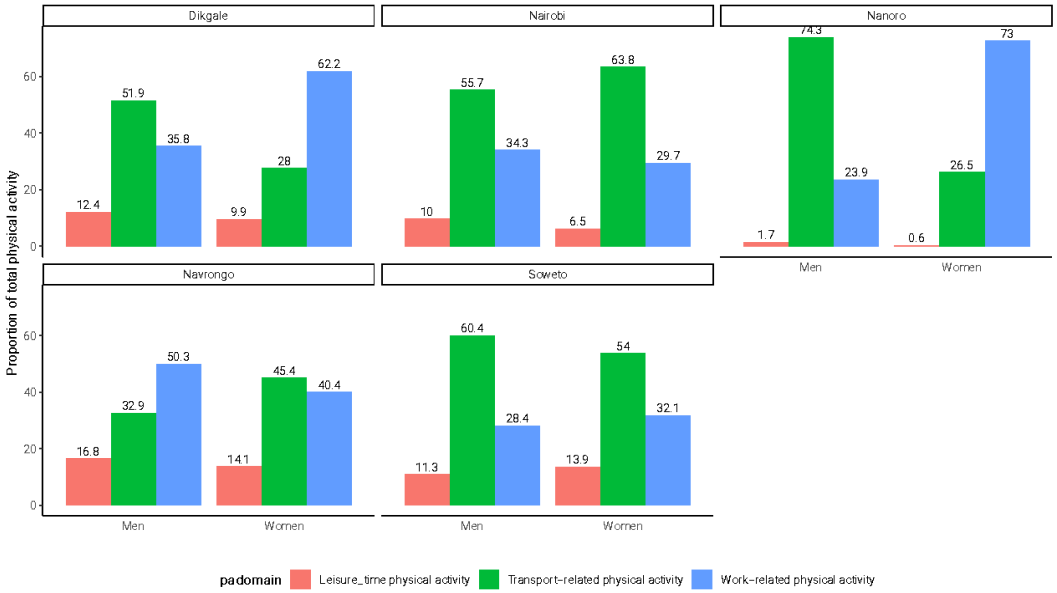


Figure 3.2: The proportion of total MVPA spent on leisure, transport and work-related physical activity among men and women in five study sites from 4 African countries

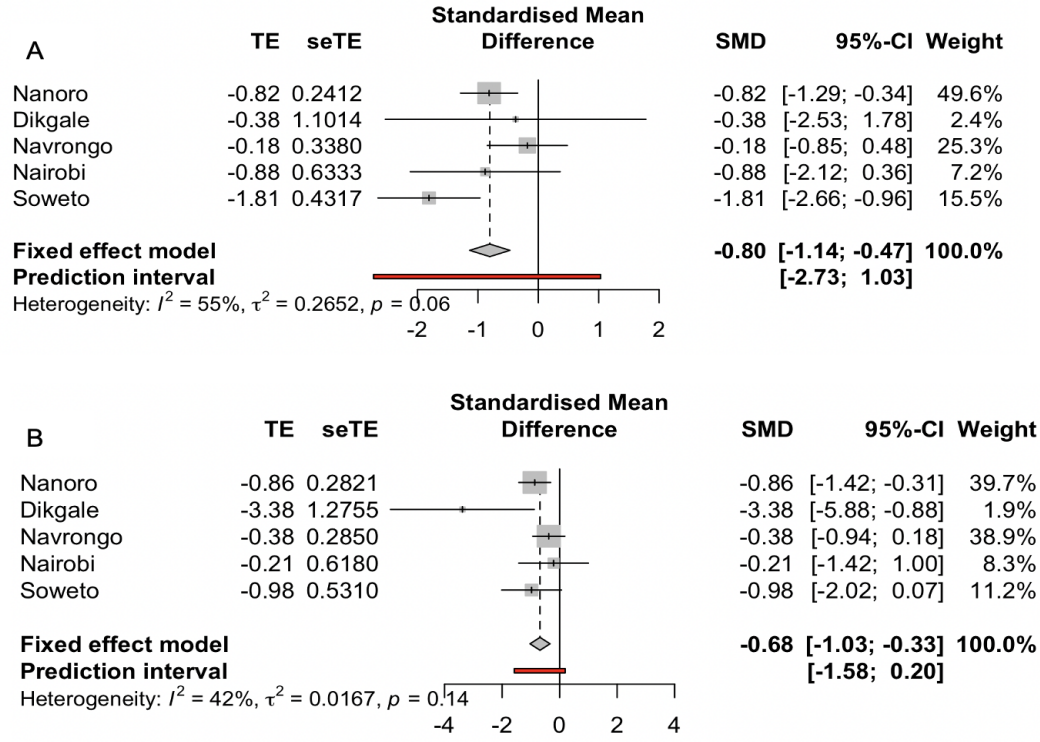


Figure 3.3: Meta-analysis of the association between meeting physical activity guidelines and BMI in six sites in 4 African countries

A. Site specific metanalysis in men **B.** Site specific metanalysis in women. TE = estimate, seTE = standard error of the estimate. SMD=standardized mean difference (effect size). Models were adjusted for age, education and socio-economic status.

3.4.4 Meta-analysis of the association between time spent in different domains of physical activity with BMI in men and women meeting physical activity guidelines

Overall and at the different sites, among those meeting physical activity guidelines, there were no statistically significant associations between leisure-time physical activity and BMI in either men (Figure 3:4A) or women (Figure 3:4B). In the whole sample BMI was significantly lower in men participating in moderate-high (>120 minutes/wk) transport-related physical activity (Figure 3:4C) (β = -0.33, 95%CI = -0.66 – -0.01) and work-related physical activity (Figure 3:4E) (β = -0.32, 95% CI = -0.59 – -0.05) compared to men participating in low (< 12 minutes) physical activity within these domains.

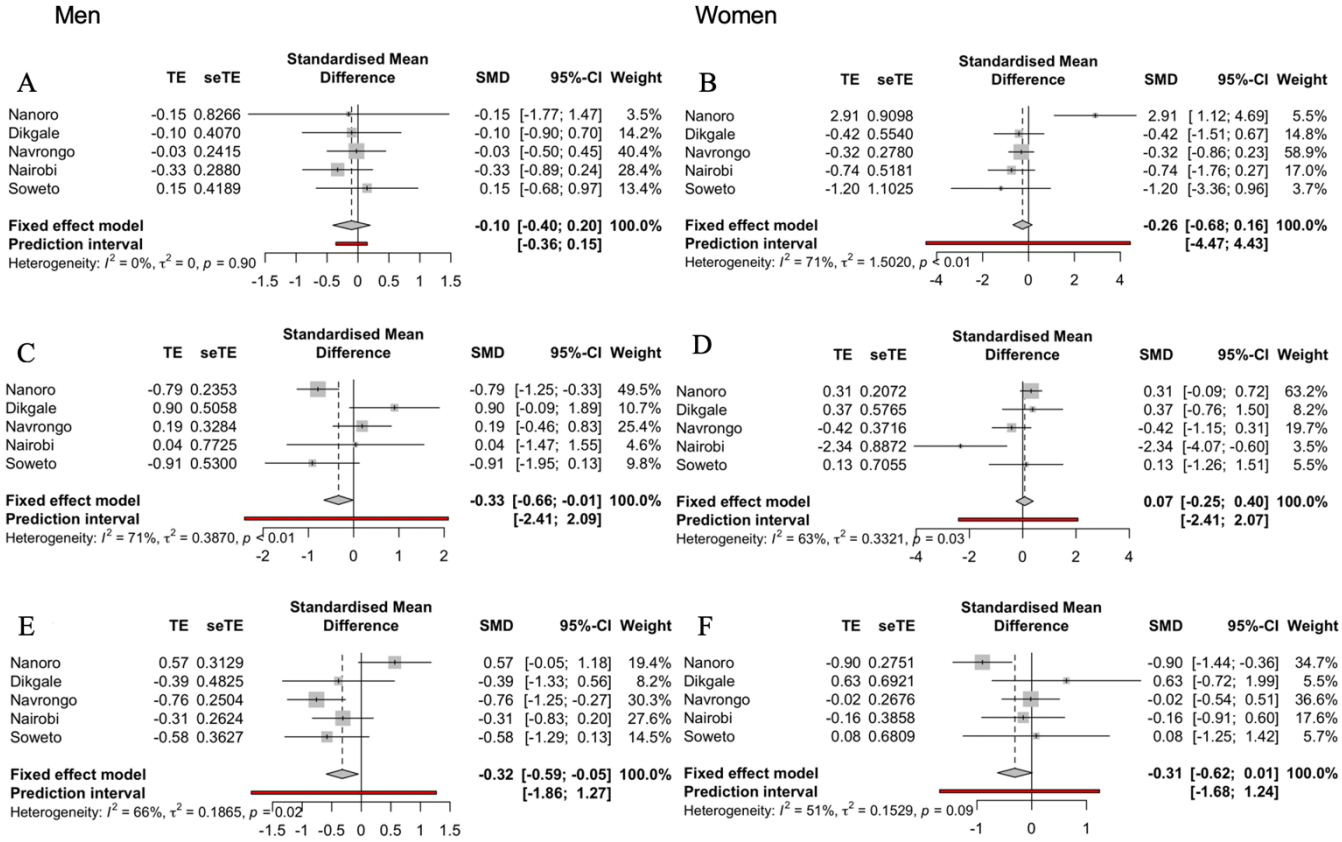


Figure 3.4: Analysis of the association between domain-specific physical activity and BMI among men and women in four African countries

A. Site specific metanalysis of leisure-related physical activity in men; **B.** Site specific metanalysis of leisure-related physical activity in women; **C.** Site specific metanalysis of transport-related physical activity in men; **D.** Site specific metanalysis of transport-related physical activity in women; **E**. Site specific metanalysis of work-related physical activity in men; **F.** Site specific metanalysis of work-related physical activity in women. TE = estimate, seTE = standard error of the estimate. Models were adjusted for age, education and socio-economic status.

In the different study sites BMI was lower in Nanoro men who participated in moderate-high (>120 minutes) transport-related physical activity compared to their low activity counterparts (β = -0.79, 95% CI = -1.25 – -0.33) (Figure 3:4C). In addition, >120 minutes (moderate-to-high) of work-related physical activity in Navrongo men who met physical activity guidelines was associated with 0.76 kg/m^2 lower BMI compared to those who did <120 minutes (low work-related physical activity) (β = -0.76, 95% CI = -1.25 – -0.27) (Figure 3:4E). In Nanoro, when compared to women with <120 minutes work-related physical activity, women who did >120 minutes of work-related physical activity had 0.90 kg/m^2 lower BMI (β = -0.90, 95% CI = -1.44 – -0.36) (Figure 3:4F) and in Nairobi women who met physical activity guidelines, moderate-to-high (>120 minutes) compared to low (<120 minutes) transport-related physical activity was associated with 2.34 kg/m^2 lower BMI (β = -2.34, 95% CI = -4.07 – -0.06) (Figure 3:4D). In Nanoro, > 120 minutes LTPA was associated with 2.91kg/m^2 higher BMI compared to < 120 minutes LTPA (β = 2.91, 95% CI = 1.12 – 4.69) (Figure 3:4B) but less than 1% of the total MVPA was spent in LTPA in these women.

3.5 Discussion

Our study evaluated the association between self-reported physical activity and BMI in a large African cohort of middle-aged men and women from urban and rural sites in East, West and South Africa. We found that although the prevalence of meeting physical activity recommendations was high (above 80%) in both men and women, it was higher in the men than the women (83.9% vs. 80.5%, p <0.001). Time spent in work and transport-related physical activity contributed the most to total MVPA with leisure time physical activity contributing very little at the sites. Meeting physical activity guidelines was associated with lower BMI in the whole sample of men and women, and this was driven by men in West (Nanoro) and South Africa (Agincourt and Soweto) and women in West Africa (Nanoro) and South Africa (Dikgale). Moreover, among those meeting physical activity guidelines, >2 hours of work and transport-related PA were associated with lower BMI in men but not women and regional variations were observed.

The higher prevalence of men meeting PA guidelines compared to women and the majority of time spent in work (47.0%) and transport-related physical activity (43.5%) supports data from 22 African countries where 83.8% of men and 75.7% of women met the global World Health Organization (WHO) physical activity guidelines, and the largest proportion of total physical activity was during work (48.6%) or transport (46.3%) [226]. A comparison of domain-specific physical activity patterns in 104 countries also revealed higher work and transport-related physical activity in these domains in low-income compared to high-income countries [223]. Sex differences in physical activity participation, which were shown at all but one site in our study, have been corroborated using objectively measured physical activity in some of the same participants from the Soweto site [248]. Higher work and transport-related physical activity could arise from work in Africa typically involving manual labour. It is also possible that the transport cost may be too high for a significant proportion of the studied population. As a result, they opt to walk or use other means of non-motorized transport, consistent with observations from an earlier study in Nairobi, where walking to work or using other non-motorized means were the primary forms of transportation [4,249].

We found that compared to not meeting guidelines, meeting physical activity guidelines was associated with 0.82 kg/m^2 lower BMI in men and 0.68 kg/m^2 lower BMI in women and site differences were also apparent. Meeting physical activity guidelines was associated with lower BMI only among men from two sites (Nanoro and Soweto) and women in two sites (Nanoro and Dikgale). Findings from studies in Africa have shown inconsistent results. While complying with physical activity guidelines of at least 150 minutes per week of MVPA was associated with lower BMI in a sample of younger Black South African women from urban Cape Town (26 ± 7 years old), no association was found in another study in a rural population of South African men (28.4 ± 17.6 years old and women (40.1 ± 20.7 years old) [250,251]. Therefore, these findings and observations from our study suggest that complex context-specific factors may confound the association between physical activity and BMI. These may include physical activity intensity, where physical activity performed at a higher intensity may be associated with lower BMI [252]. Conversely, higher BMI may be contributing to lower physical activity as observed in a Mendelian randomization study by Carrasquilla et al.

(2021), where higher MVPA was causal for lower BMI and at the same time higher BMI was causal for less physical activity. In addition, Kroesen and De Vos (2020) found lower physical activity as a consequence of higher BMI [233,234]. Alternatively, depending on the stage of the epidemiologic transition, the domains contributing most to total MVPA and subsequent associations may differ [4]. For example, in our study, men and women in Soweto and Nairobi (urban sites) spent most of their time in transport-related physical activity while women in rural sites of Dikgale and Nanoro spent most of their time in work-related physical activity. Diet, obesity category and other socio-cultural and genetic factors among participants in the different sites may also confound the association between physical activity and BMI [130,253]. In a study of obese and non-obese individuals, highly significant associations between physical activity and BMI in the obese but weak associations in non-obese individuals were apparent [254]. However, this does not seem to be the case in our study as the sites with the highest obesity prevalences do not necessarily show significant associations. Further inquiry is warranted to unpack possible reasons for these regional differences.

We also observed inverse associations between work and transport-related physical activity and BMI in the total sample of men but not women. Site-specific results showed inverse associations between BMI with transport-related physical activity in Nairobi women and men in Nanoro, where participants spent the most time in transport-related physical activity. These findings are corroborated in other studies where more transport-related physical activity has been reported in lean compared to overweight or obese men, and high use of active travel is generally associated with lower BMI [4,5]. Work-related physical activity was also associated with lower BMI in Navrongo men and Nanoro women in our study and these have the highest proportion of MVPA as work-related compared to the other sites. High work-related physical activity has been associated with lower obesity risk [125,255].

This study was not without some limitations. Firstly, it was a cross-sectional study of middle-aged adults therefore we can only report associations between physical activity and BMI and cannot infer causal relationships or comment on other age groups. The relationship between physical activity and BMI may be bidirectional but this can only

be validated by additional studies in this population. Secondly, we used self-reported physical activity measures, which are likely to result in over-reporting of physical activity. However, the GPAQ is helpful as a population-level physical activity surveillance tool as it has good validity compared with population surveillance data [256,257]. The strengths of our study include that we used a large sample size to determine the association of physical activity in the different domains with BMI in an African context.

3.6 Conclusions

We have demonstrated regional and sex-specific variation across five communities in four African countries in patterns of physical activity when assessing activity in work, travel and leisure domains and their association with BMI. These results show that BMI varies significantly across regions and sexes, and physical activity alone may be insufficient to reduce BMI. There is, therefore, a need for more context-specific physical activity recommendations. Further inquiry into other factors not included in the study that may confound the association between physical activity and BMI is warranted since this was a cross-sectional study. It also remains to be determined what intensity and duration of different domains of physical activity offer the most significant benefits.

CHAPTER 4: POLYGENIC PREDICTION OF BMI IN SOUTH AFRICANS OF AFRICAN ANCESTRY

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The work in this chapter is a draft manuscript prepared for publication.

4.1 Abstract

Polygenic prediction of body mass index is under-studied in continental Africans while proteomic profiling to examine the heterogeneity in associations of obesity with dysglycaemia is yet to be explored. Here, we developed a multi-ancestry BMI polygenic risk score (PRS) and evaluated its longitudinal prediction of severe obesity. We then used proteomic markers previously validated in a European population to define obesity classes and evaluate associations with dysglycaemia. We demonstrate the ability of a multi-ancestry PRS to reveal sex differences in predicting incident risk of severe obesity and associations with the obesity classes. Moreover, we show that associations of proteomic defined obesity classes with dysglycaemia, diet and physical activity are heterogeneous between men and women, thereby revealing the complexity of the interplay of genetics, proteomics, diet and physical activity in relation to obesity. More multi-omic studies are required to further evaluate this phenomenon in Africa.

4.2 Introduction

Overweight and obesity represent significant determinants of non-communicable diseases (NCDs) and contributed to more than 160 million preventable deaths in 2019 [1]. If no effective measures are implemented, projections indicate that by 2030, approximately 1 in 7 men and 1 in 5 women worldwide will be obese [19]. In Africa, obesity occurs more in women than in men and it is anticipated that by 2030, 7.8% of men and 20.4% of women will be obese, with South Africa having the highest burden (50% of adults projected to be obese) [19,21]. However, insulin sensitivity and beta cell function are lower in Black South African men but they have stronger associations of adiposity with type 2 diabetes compared to women [258]. The mechanisms underlying these observations are nevertheless not well understood.

Polygenic prediction holds promise in determining those susceptible to obesity earlier and unravelling its underlying pathophysiology, thereby facilitating the development of tailored interventions. However, it has been demonstrated that PRS derived in European ancestry populations have 4.5-fold less predictive accuracy in African ancestry individuals than European ancestry individuals for a spectrum of complex traits [30]. Recent efforts in integrating GWAS summary statistics from multiple ancestries have shown a potential to improve cross-population polygenic prediction in diverse populations [205]. This approach has been applied mainly to African Americans and is yet to be implemented in continental African populations that are genetically different from African Americans. Evidence on the longitudinal polygenic prediction of obesity is scarce thus the demand for more comprehensive research in Africa.

Understanding the predicted genetic risk of BMI is an initial step in addressing the complex issues of obesity. It is often argued that BMI crudely measures body composition, without differentiating between fat and lean body mass, nor does it specify the location of adiposity thus limiting the ability to assess metabolic and other health risks like diabetes and coronary heart disease [35-37]. Obesity is reported to be heterogeneous, with varied cardiometabolic risk profiles for the same BMI [259]. To advance the capacity for personalized interventions, use of omic profiles that go

beyond body composition may therefore be an essential stride to further elucidate the heterogeneity of obesity associated health risk.

Preliminary work with regards to metabolomic and proteomic profiling of obesity is gaining momentum in European ancestry populations where attempts have been made to explain the possible source of heterogeneity in the associations between BMI and health outcomes. Some scholars have employed linear models to predict BMI using the metabolome, extracting residuals to classify individuals above or below a certain threshold as either overestimated (OE) or underestimated (UE) and those within the threshold as either normal weight, overweight or obese, based on the standard WHO classification. Association of these classes with health outcomes revealed higher risk of mortality and cardio-metabolic disease in individuals metabolically predicted as obese yet with a normal observed BMI [259,260], implying the role of metabolic changes in this heterogeneity. Watanabe et al. (2023) went further to demonstrate how proteomics can reveal heterogeneity in the associations of BMI with insulin production, insulin resistance and waist circumference among European ancestry individuals whose proteomic-inferred BMI was concordant with the measured BMI compared to those who were discordant [59,60]. It is, however, not known if these proteomic markers are associated with BMI, genetic susceptibility in the form of PRS or if they can be used to explain obesity heterogeneity, particularly between men and women in South Africa. We, therefore, set out to develop multi-ancestry PRS of BMI, evaluate its predictivity of severe obesity over ten years and evaluate the association of proteomic defined obesity with PRS and dysglycemia.

4.3 Methodology

4.3.1 Study participants

Black men and women between the ages of 40 and 60 years (n= 5269) from the three South African study sites of AWI-Gen, namely Soweto, Dikgale and Agincourt were included in this study [235]. Pregnancy, being a parent, sibling or child of existing participants, having lived less than 10 years in the region as well as having physical impairments interfering with blood pressure and other anthropometric indices

measurement constituted exclusion criteria from the study [215]. Data was also used from men and women recruited into the GSK study on determinants of T2D.

4.3.2 Ethical clearance

AWI-Gen and GSK obtained ethical clearance to conduct the studies from the University of the Witwatersrand Human Research Ethics Committee (Medical) (Protocol Number M170880 and Protocol Number M160604 respectively) and this study has ethical clearance from the same committee (Protocol Number: M210166). Participants provided written informed consent.

4.3.3 Demographic variables

Questionnaires were used to collect data on sex and age at each study site. Data were stored and managed using the Research Electronic Data Capture (REDCap) tool, a web-based electronic system hosted by the University of the Witwatersrand [235].

4.3.4 Anthropometric measurements

A digital scale (Kendon Medical, SA) was used to measure weight and a wall-fixed digital stadiometer (Holtain, Wales) was used to measure height [215].

4.3.5 BMI classification

BMI was classified as follows: underweight (BMI < 18.5 kg/ m^2), normal weight (BMI ≥ 18.5 and < 25kg/m^2), overweight (BMI ≥ 25 and < 29.9 kg/m^2), obese (BMI ≥ 30 kg/m^2 and < 40 kg/m^2, severe obese ≥ 40 kg/m^2) [261].

4.3.6 Genotyping and quality control

Genotyping of genomic DNA was done using the H3Africa genotyping $array_1$ (Illumina, USA), employing the Illumina FastTrack Sequencing $Service_2$. Detailed quality control is described elsewhere [215]. In summary, individuals with a missing SNP calling rate >0.05, SNPs with genotype missingness >0.05, MAF <0.01 and Hardy-Weinberg equilibrium (HWE) P-value <0.0001 were removed as well as non-autosomal, mitochondrial and ambiguous SNPs unmatched to the GRCh37 references alleles or

strands [215]. The Sanger Imputation Server was used for imputation, with the African Genome Resources as reference panel. Poorly imputed SNPs (info scores <0.6, MAF <0.01 and HWE P-value <0.00001) were excluded. The final QC-ed imputed data had 13.98 M SNPs [215].

4.3.7 Sample collection and analysis

Blood plasma was collected from participants after a 10-12 hour overnight fast. OLINK proteomics AB (Uppsala, Sweden) was used for proteomic analysis. Cardiovascular disease (CVD) panels II and III (www.olink.com/downloads) were used and these included 184 biomarkers related to multiple biological processes. Normalized protein expression (NPX) values were used for reporting results of the analysis. Performance of the proteomic assays was checked against four internal standards [262]. Serum insulin and C-peptide concentrations were determined from fasting blood plasma using the Immulite 1000 Immunoassay System (Siemens Healthcare Diagnostics, Tarrytown, New, York, USA). The standard oral glucose tolerance test (OGTT) was employed to determine plasma glucose levels in participants. A fasting blood sample was collected after which each participant was asked to drink a solution of 75g of glucose dissolved in 250ml of water. Thereafter, blood samples (5ml) were obtained every 30minutes for two hours. Blood plasma concentrations were then determined using Randox RX Daytona Chemistry Analyser (Randox Laboratories Ltd, London, UK) [263].

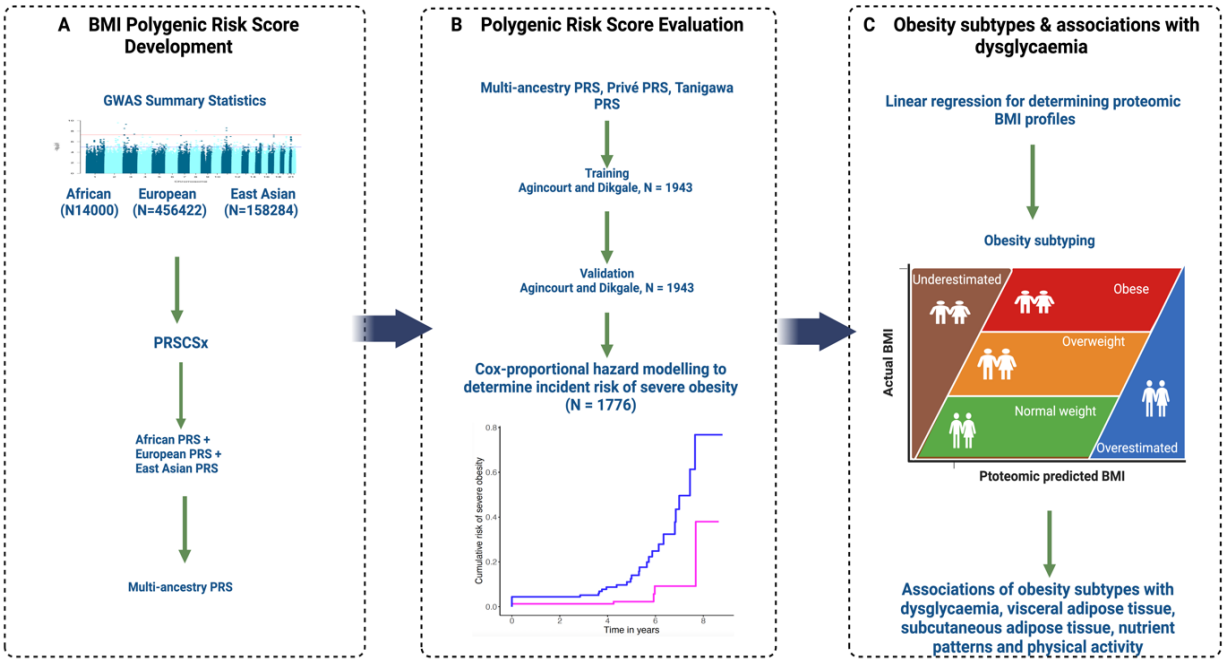
4.3.8 Dietary Data collection and analysis

Data on food, including fruit and vegetable intake was collected using a food frequency questionnaire with the aid of household measures and food models to estimate portion sizes. The FoodFinder3 (SAMRC, Cape Town, South Africa) software [283] was employed to estimate amounts of nutrients consumed (plant protein, animal protein, saturated fatty acids, total carbohydrate, added sugar and total dietary fibre) as described previously [12]. Nutrient patterns data, obtained from principal component analysis of the GSK dietary data [12] was used in the analysis.

4.3.9 PRS development and replication

We constructed a multi-ancestry polygenic risk score using the Python-based PRS-CSx method and compared its performance with two other PRSs developed using single ancestry methods that were accessed through the PRS Catalog (Figure 4:1A). PRS-CSx uses diverse populations to enable improved cross-population polygenic prediction. Using continuous shrinkage priors, GWAS summary statistics from various populations are integrated, thus optimizing effect size estimation and accounting for linkage disequilibrium (LD) patterns across the populations. A PRS for each discovery sample is calculated before integrating through linear modelling [205]. Summary statistics of African, East Asian and European individuals were extracted for use in developing the PRS. The 1000 Genomes Project Phase 3 samples were used to construct reference panels, selected based on greater population diversity (includes Luhya from Kenya, Yoruba and Esan in Nigeria, among others https://www.coriell.org/1/NHGRI/Collections/1000-Genomes-Project-Collection/1000-Genomes-Project). The global shrinkage parameter phi thresholds (phi=auto and phi= 1e-2) were used in the discovery dataset (the one half of the randomized dataset named “validate”) to compute multiple PRSs and identify SNPs that significantly predicted BMI. The PRS was evaluated for predictivity using linear regression models. Source and reference files were downloaded as per instructions from https://github.com/getian107/PRScsx.

Training, validation and replication data sets were obtained from splitting the study population. The training dataset comprised 1943 participants from Agincourt and Dikgale data and the validation dataset comprised another 1943 participants from the same sites after randomly splitting the data into two (Figure 4:1B). Randomization was achieved using R software version 4.1.1. Soweto (n=1776) was used as the replication dataset. Data from a subset of participants from AWI-Gen who were enrolled into the GSK study was used to explore the associations with proteomic markers (Figure 4:1C).



Created with BioRender.com

Figure 4.1: Overview of PRS development, obesity risk prediction and evaluation of obesity heterogeneity among adult Black men and women in South Africa

A. Development of a multi-ancestry PRS in Black South African men and women. **B.** Evaluation of the predictivity of the multi-ancestry BMI PRS in comparison with two others developed using single ancestry methods and longitudinal prediction of risk of severe obesity. Participants were classified into the top and bottom 20% of the PRS and the cumulative risk of severe obesity between the two categories assessed using the Cox proportional hazards model. Models were adjusted for age, sex and five genetic principal components. **C.** Evaluation of the heterogeneity of obesity associations with dysglycaemia. Proteomic-predicted BMI was determined using linear regression models and heterogeneity of associations assessed using associations with dysglycaemia, visceral adipose tissue and sub-cutaneous adipose tissue.

For the first score used to compare with the multi-ancestry PRS, model weights by Tanigawa et al (2022), were obtained from PRS developed for 813 traits using the batch screening iterative lasso (BASIL) algorithm on data from 260,704 unrelated individuals in the UK Biobank. The PRS models were tested for transferability in 6497 Africans in the same cohort (this was in addition to transferability assessment in East Asians, non-British whites and South Asians) [264]. We named this score Tanigawa score. Model weights for the second PRS score by Privé et al (2022) were derived using the LDPred2 to construct polygenic risk scores for 245 traits using the UK

Biobank data. Transferability of the scores was assessed on nine groups of different ancestries from the same cohort [265]. We named this score the Privé score.

4.4 Statistical analysis

Linear regression was used to evaluate the predictivity of the PRSs. Models were adjusted for age, sex and population stratification (five genetic principal components). PRS quintiles for the best predictive PRS (as determined by the highest PRS R2) was used to stratify the risk of overweight or obesity and the bottom 20% used as the reference. Differences between groups (continuous variables) were assessed using the students t-test. The chi-square test was employed for the binary variables.

PRS and longitudinal prediction of BMI

Linear regression was used to evaluate the cross sectional PRS x sex interactions, with age, sex and genetic principal components as covariates. The model explaining the most variation was selected. Longitudinal PRS x sex interaction was determined using generalised estimating equations, adjusting for age, sex and population stratification.

The Cox proportional hazards model, adjusted for age, sex and three genetic principal components, was used to predict the longitudinal risk of obesity using the 'survival' package of the R statistical software. Models for men and women were adjusted for age and three genetic principal components. Participants were divided into extremes of the PRS distribution (top 20% and bottom 20%) and risk of severe obesity was compared between these two strata, first in the combined data for men and women then for men and women separately.

Association of plasma proteins with PRS and implications for glucose tolerance

Proteomic markers identified to be associated with BMI in European populations [60] were checked for transferability by evaluating if there were significant associations with BMI in the South African dataset ($p< 0.05$) and if the effect size was in the same direction. Models were adjusted for age and sex. We computed a proteomic score by

including the proteomics in the same model and using the residuals to represent this score. The proteomic score was used to determine obesity subtypes by checking deviance of the predicted from actual BMI indicated by the residuals. Deviance from actual BMI was defined as +/-1 kg/m^2 of the residuals and facilitated the classification of obesity sub-types. Classifications of normal weight (NW) (BMI <25 kg/m^2), overweight (OW) (BMI 25–30 kg/m^2) or obese (OB) (BMI >30 kg/m^2), based on measured BMI, were used for participants with BMI between -1 and +1 kg/m^2. Those whose BMI was outside the error margin were either classified as overestimated (OE) (i.e. actual BMI – proteomic predicted BMI > 1 kg/m^2) or underestimated (UE) (i.e. actual BMI – proteomic predicted BMI < -1 kg/m^2). Linear regression was used to evaluate the association of these sub-types with dysglycaemia in men and women (using glycaemic markers as the outcome and adjusted for age). Similar models were also used to evaluate the association of PRS and BMI with dysglycaemia in men and women, adjusted for age, and five genetic principal components. Further analysis was also conducted to determine the associations of diet (using nutrient patterns derived from GSK data) and physical activity (using global physical activity questionnaire (GPAQ) data from AWI-Gen and accelerometry data from GSK). Models were adjusted for age. In these analyses, all variables were mean-centred and variance-scaled using the scale function in R.

4.5 Results

Firstly, we employed the PRS-CSx method to develop a multi-ancestry PRS using summary statistics from European (N=456422), Asian (N=158284), and African (N=14000) populations (Figure 1, Methods). We then evaluated its predictivity of BMI in comparison to two previously developed PRSs (Tanigawa and Privé scores) derived using single ancestry methods (Figure 1, Methods). The multi-ancestry PRS was the most highly predictive, explaining approximately 1.9% of the variation in BMI in our replication dataset (N=2035) compared to 1.2% explained by the Privé score and 0.7% by the Tanigawa score (Table 4:1).

Thereafter, we sought to establish the longitudinal prediction of the Multi-ancestry PRS and its association with incident severe obesity (Methods). The multi ancestry PRS was associated with repeated measures of BMI over a ten-year period (Beta = 1.51, p = < 0.001). Furthermore, a significant PRS * sex interaction for BMI, which was sustained over the study period, was observed from the evaluation using generalised estimating equations ($P_{interaction}$ = 0.029) (Supplementary Table 1). Subsequent analysis was therefore conducted separately in men and women.

We divided the study population into the extremes of the PRS distribution (Top 20% and Bottom 20%), first to assess the BMI distribution in men and women then evaluate differences in polygenic risk between the extremes of the PRS distribution (Methods). Over the ten-year period, women had higher BMI than men and BMI of those in the top 20% was higher than that of those in the bottom 20% of the PRS distribution (Figure 4:2).

To determine how much the multi-ancestry PRS predicts incident severe obesity, we used the Cox-proportional hazards model (Figure 4:3, Methods). We noted significant differences in risk of developing severe obesity between men and women who were in the top 20% compared to those in the bottom 20% of the PRS distribution (Figure 4:3A). In the total study population, those in the top 20% had 3 times higher hazard of incident severe obesity (hazard ratio = 2.98, 95% CI = 1.75 - 5.07, p = 5.33e-05) compared to those in the bottom 20%. We went further to determine what was driving the observed results and noted that they were driven by women. Women in the top 20% had almost 3.5 times greater hazard of incident severe obesity (hazard ratio = 3.48, 95% CI = 1.96 – 6.16, p = 1.94e-05) compared to those in the bottom 20% (Figure 4:3C) while there was no difference in hazard among men (hazard ratio = 1.13, 95% CI = 0.24 – 5.37, p = 0.878) (Figure 4:3B). (See Supplementary Table 2 for model outputs).

Table 4:1 Comparison of predictivity of three polygenic risk scores for BMI in South Africa

PRS Parameter	Multi-ancestry PRS	Tanigawa score (Tanigawa et al., 2022)	Privé score (Privé et al., 2022)
Method	PRS-CSx	Batch screening iterative lasso (BASIL)	LDPred2
Training dataset (N=1942)			
Number of SNPs	13976041		
PRS variance (R2)	0.0107		
P value	< 2.2e-16		
Validation dataset (N=1942)			
Number of SNPs	13976041	27126	110153
PRS variance (R2)	0.0092	0.0036	0.0020
P value	2.2e-16	< 2.2e-16	< 2.2e-16
Replication dataset (N=2035)			
Number of SNPs	13976041	27126	110153
PRS variance (R2)	0.0186	0.0074	0.0120
P value	< 2.2e-16	< 2.2e-16	< 2.2e-16

* Models were corrected for age, sex and population stratification (five principal components used).
SNP – single nucleotide polymorphism

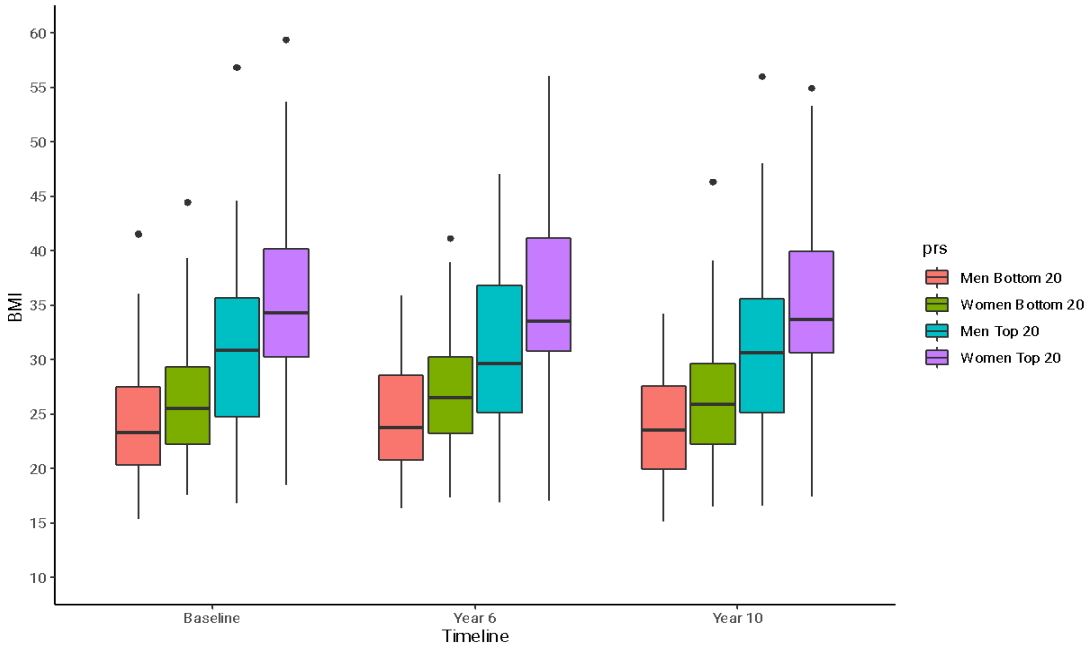


Figure 4.2: Mean BMI among men and women in the top and bottom 20% over 10 years in Soweto, South Africa

Participants were divided into extremes of the PRS distribution (top 20% and bottom 20%). The median BMI and interquartile range were determined for the PRS strata over the data collection points.

We then leveraged the levels of plasma proteins to predict BMI using linear regression models and evaluate associations with fat distribution and dysglycemia in our study population. This was achieved through replication of the association of 14 proteomic markers with BMI from a European ancestry population, previously validated by Watanabe et al., 2023 [60] (Figure 4:4A, Supplementary Table 3). A full model containing the proteins significantly associated with BMI was then used to predict BMI and compute a proteomic score (Methods). The model explained more variation in BMI compared to the PRS (67% vs 1.9%) (Table 4:1, Supplementary Table 4). In addition, we observed a weak correlation between the BMI PRS and the proteomic score (Figure 4:4B).

Following establishment of a model to predict BMI using plasma proteins, we explored its potential application in BMI classification. Participants were split into five categories with those having residuals within +/- 1.0 kg/m^2 being considered concordant with the measured BMI (Methods). These constituted 74% of our study population and were categorized into normal, overweight or obese based on the WHO standard (Methods). The outliers comprised individuals whose residuals (measured BMI - proteomic predicted BMI) was lower -1 kg/m^2 (Underestimated (UE)) and those whose residuals were higher than +1 kg/m^2 (Overestimated (OE)) (Figure 4:5A and Methods). We found that for the combined men and women analysis, individuals in the OE category had normal BMI (mean = 24.48 (3.91) kg/m^2) while those in the UE category exhibited BMI typical of obesity (mean = 35.03 (10.94) kg/m^2) (Figure 4.5B). Analysis by sex showed that women in the OE category had BMI similar to overweight (mean = 24.97 (4.01) kg/m^2) and men exhibited normal BMI (mean = 24.02 (3.80) kg/m^2) while women in the UE category had BMI consistent with severe obesity (mean = 43.37 (6.43) kg/m^2) and men had BMI similar to overweight (mean = 27.44 (8.37) kg/m^2). We also observed that in men, the range of BMI in the UE category was from underweight to obese (Supplementary Figure 1).

In view of the observed discrepancies between measured and proteomic predicted BMI, we postulated that these differences may have clinical significance in metabolic

risk profiling. Using BMI classes as the predictor, we assessed their associations with dysglycaemia, visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT). Compared to those with normal weight, being in the OE category was associated with higher polygenic risk of increased BMI (β = 0.43 standard deviations (SD), 95% CI = 0.08-0.78, p = 0.017) in men while in women, the UE category was marginally associated with higher polygenic risk of increased BMI (β = 0.49 SD, 95% CI = 0.003 0.97, p = 0.049). Moreover, differences in associations with dysglycaemia between the OE and normal weight categories were more apparent in men than in women. Being in the OE category for men was associated with more insulin production (fasting c peptide: β = 0.99 SD, 95% CI = 0.71-1.26, p = 7.12e-12), higher insulin resistance (HOMA-IR: β = 0.52 SD, 95% CI = 0.27-0.77, p = 4.32e-05), elevated 2-hour glucose (β = 0.50 SD, 95% CI = 0.17-0.83, p = 003) and lower insulin sensitivity (Matsuda index: β = -1.02 SD, 95% CI = 1.35e-08, p = 1.35e-08) compared to being of normal weight. (Figure 4:5C). In women, notable differences between the OE and normal weight classes were apparent in the associations with insulin production and insulin sensitivity where being in the OE category was associated with higher insulin production (Fasting c-peptide: β = 0.85 SD, 95% CI = 0.33-1.37, p = 0.001) and lower insulin sensitivity (Matsuda index: β = -1.37 SD, 95% CI = -1.79 - -0.95, p = 4.82e-10) than being of normal weight (Supplementary Figure 2).

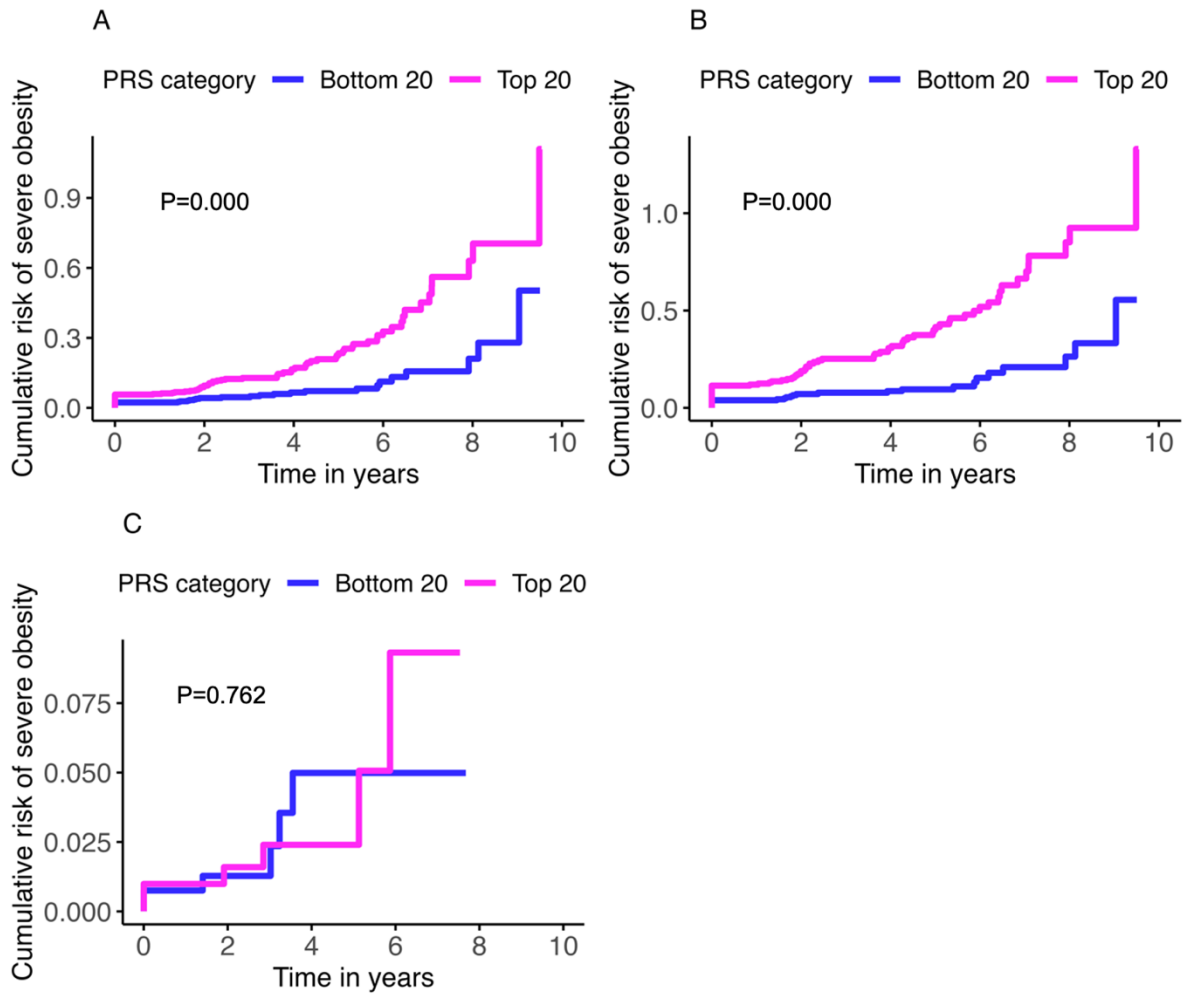


Figure 4.3: Cumulative risk of severe obesity over 10 years by PRS strata among adult men and women in Soweto, South Africa

A. Cumulative risk of severe obesity in the combined analysis of men and women. Hazard models were adjusted for age, sex and three principal components. **B.** Cumulative risk of severe obesity among men. **C.** Cumulative risk of severe obesity among women. Participants were divided into extremes of the PRS distribution (top 20% and bottom 20%) and Cox proportional hazards models used the to assess the risk of severe obesity over 10 years. Hazard models were adjusted for age, sex and three genetic principal components in the combined analysis of men and women. For the separate men and women models, hazard models were adjusted for age and three genetic principal components.

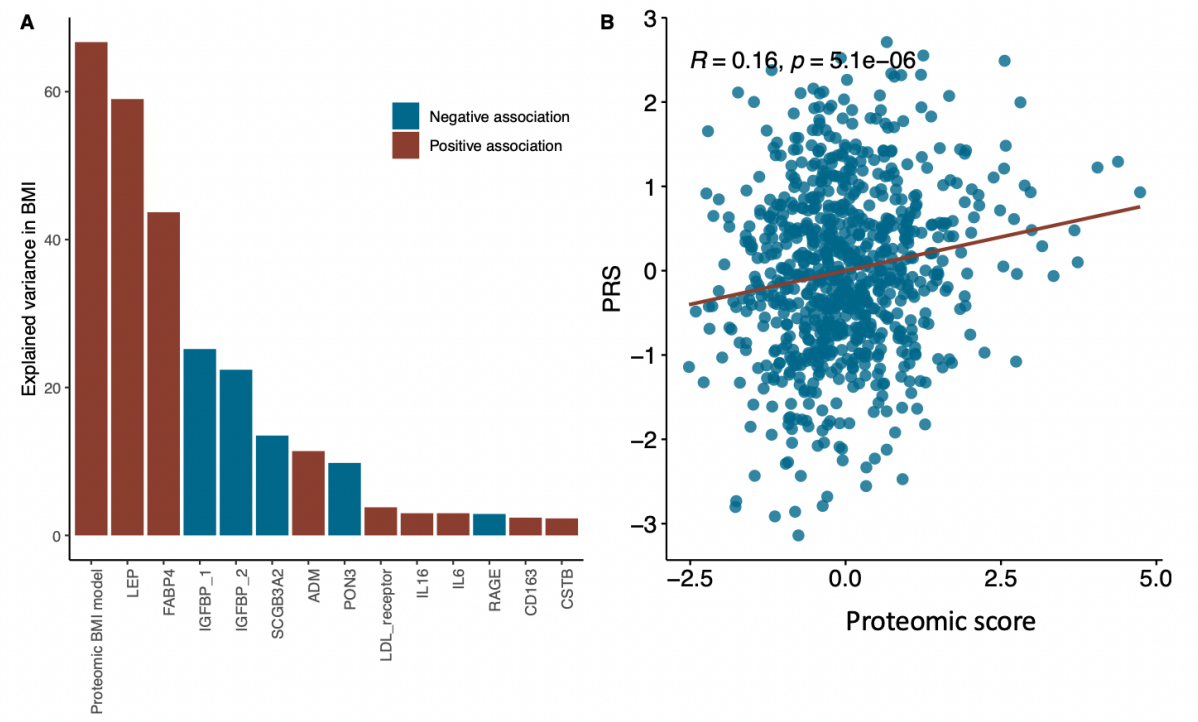


Figure 4.4: Proteomic prediction of BMI and correlation between BMI PRS and proteomic score among adult Black men and women in Soweto, South Africa
A. Univariate explained variance in BMI by each protein. Linear models were run with scaled BMI as the outcome and each protein as a covariate. **B.** Correlation between BMI PRS and proteomic score. BMI was regressed on 14 proteins with age and sex as covariates. Residuals of the model were used to compute a proteomic score.

Drawing from prior findings on the possible influence of lifestyle on omic-inferred BMI [60], we went further to determine how nutrient patterns and physical activity may influence the BMI categories. We conducted linear regression with BMI categories as the outcome (Methods). In men, the plant-driven nutrient pattern was associated with lower obesity (β = -0.50 SD, 95% CI = -0.87 - -0.12 SD, p = 0.009), while the retinol driven nutrient pattern was associated with higher proteomic predicted BMI (β = 0.43 SD, 95% CI = 0.06 - 0.80 SD, p = 0.022) and lower obesity in both the self-reported physical activity (β = -0.33 SD, 95% CI = -0.63 - -0.02 SD, p = 0.036) and accelerometry-based physical activity (β = -0.61 SD, 95% CI = -0.92 - -0.29 SD, p = 0.0002) (Figure 4.5D). No significant associations were observed in women.

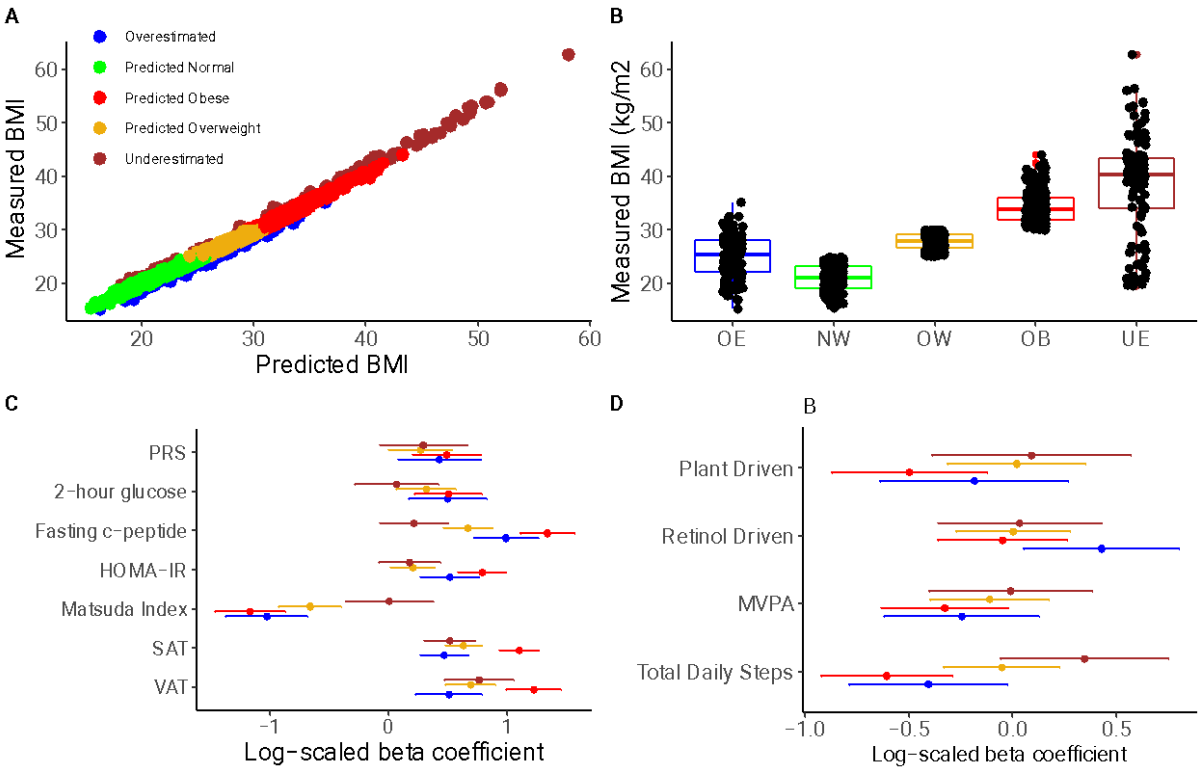


Figure 4.5: Proteomic profiling of obesity and its heterogeneity among adult Black men and women in Soweto, South Africa

A. Correlation between measured BMI and proteomic predicted BMI. BMI was regressed on 14 proteins with age and sex as covariates. Residuals of the model were used to classify obesity into proteomic predicted BMI categories. Individuals with residuals (Actual BMI – Predicted BMI) > 1.0 kg/m^2 were classified as overestimated (OE), those with residuals < -1.0 kg/m^2 were underestimated (UE), the rest were classified according to their BMI as normal weight (NW) BMI < 25 kg/m^2), overweight (OW) (BMI 25 – 30kg/ m^2) and obese (OB) (BMI > 30 kg/m^2). **B.** Differences in BMI among groups of proteomic predicted BMI. **C**. Association of proteomic predicted BMI with glycaemic profiles, visceral adipose tissue and subcutaneous adipose tissue in men. **D**. Association of proteomic predicted BMI with nutrient patterns and physical activity in men. MVPA – moderate-to-vigorous physical activity, Plant driven – plant driven nutrient pattern, Retinol driven - Retinol and Vitamin B12 Driven Nutrient Pattern. Total daily steps were obtained from accelerometry. All variables were scaled and age was used as a covariate in the linear models.

We then went on to hypothesize that heterogeneity observed in the associations between dysglycaemia and predicted BMI categories in men and women could be because of differences in sensitivities of BMI, PRS and predicted BMI to detect

associations. We therefore used linear regression to assess the association of dysglycaemia with each of PRS, BMI and the proteomic score. There were no apparent distinctions between men and women in the association between BMI polygenic risk and dysglycaemia for most of the glycaemic markers except for Matsuda Index. However, men exhibited lower insulin sensitivity compared to women (Figure 4:6). In contrast, the proteomic score was associated with higher insulin resistance in women compared to men. Moreover, BMI was associated with higher subcutaneous fat and waist circumference in men compared to women while the proteomic score was associated with higher visceral fat and waist circumference in women compared to men (4:6).

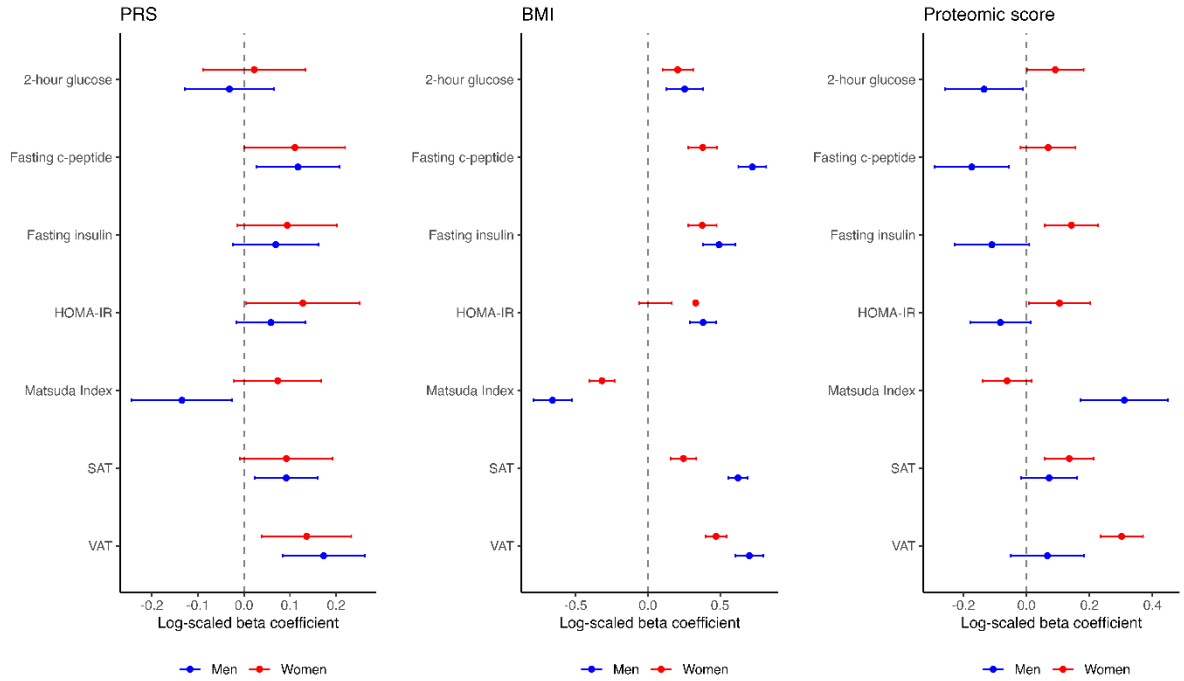


Figure 4.6: Heterogeneity of associations of PRS, BMI and proteomic score with dysglycaemia

PRS depicts the prediction of dysglycaemia using the multi-ancestry PRS, BMI depicts the BMI prediction of dysglycaemia and Proteomic score shows the proteomic prediction of dysglycaemia. The models for PRS were adjusted for age and 3 genetic principal components while models for BMI and Proteomic score were adjusted for age.

4.6 Discussion

We set out to develop multi-ancestry PRS of BMI, evaluate its predictivity of severe obesity over ten years and evaluate the association of proteomic defined obesity with

PRS and dysglycemia. The multi-ancestry PRS for BMI exhibited enhanced BMI risk prediction compared to two PRSs constructed from single ancestry discovery methods and was associated with repeated BMI measures. We also observed a three-fold hazard of severe obesity among those in the top PRS 20% compared to those in the bottom 20% with a higher than 3-fold hazard in women over a ten-year period. Further, sex differences were observed in the associations between proteomic predicted BMI categories and dysglycaemia, VAT, SAT, nutrient patterns and physical activity. Integrating proteomic markers into obesity prediction highlights that molecular changes may explain sex-specific heterogeneity in associations between obesity and metabolic outcomes such as T2D.

The multi-ancestry PRS had superior predictive capacity compared to those derived from single discovery methods. This enhanced prediction has been attributed to the ability of a multi-ancestry PRS to account for population-specific linkage disequilibrium (LD) patterns and the continuous shrinkage [205]. We however note that the single-ancestry PRS used for comparison were from European ancestry populations [264,265] as these were publicly available. As a result, a single ancestry PRS from a discovery dataset of continental Africans may perform differently. In addition, though our multi-ancestry PRS performed better than the single-ancestry PRSs, its predictivity was much lower than reported in a similar study among Koreans ($R^2 = 0.255$) [266] This may be attributed to the fact that our discovery dataset comprised a higher proportion of European ancestry individuals (72.6%) compared to those of African ancestry (2.2%) and the individuals of African ancestry were not from South Africa. This means BMI prediction is likely to be lower since the discovery populations are likely to have different genetic architecture from South Africans in our study[267] and Wang et al. (2023) have shown that higher representation of the target population in the discovery data improves polygenic prediction in the target population [268].

While the use of PRS as continuous variable yielded low predictivity, significant differences were noted between the top and bottom 20% tails of the PRS distribution when predicting obesity outcomes. Incident severe obesity was 3.5 times higher for women in the top 20% of the PRS distribution compared to those in the bottom 20%

but in men it was not statistically significant. This is probably because of the differences in prevalence of severe obesity across the sexes (0.75% vs 8.11% at baseline, 1.16% vs 7.89% at first follow up visit and 0.50% vs 7.68% at the second follow up visit). It may also suggest that the higher prevalence of obesity in women is probably genetically driven. The low predictive ability of the continuous PRS may also strengthen the argument for the exploration of complementary use of other omic profiles e.g. proteomics in predicting BMI traits.

Sex differences in the BMI distribution of proteomic-predicted BMI were also apparent in our analysis, where men in the UE category were typically overweight as opposed to the obesity observed in women. This has not been reported before as previous reports did not specify the sex distributions so it is unknown whether the reported results were driven by one sex or not [59,269]. Further, the associations of the categories with dysglycaemia and PRS revealed different patterns in men and women, a possible indicator that BMI in men is more sensitive to environmental changes compared to women. Alternatively, other omic profiles may be at play, particularly in women. An example may be investigating the metabolome, which is reportedly more prone to perturbations than the proteome [60]. Thus, more studies in Africans are warranted.

Differences were seen in the associations of PRS, BMI, proteomic score and BMI categories with dysglycaemia. Of particular interest are the sex differences that are apparent when using the proteomic score or BMI categories in the linear models. These may be attributed to the ability of proteomic profiling to reveal hidden metabolic disease risk that is not apparent using measured BMI. Scholars are increasingly investigating the role of multi-omics in unmasking heterogeneity of associations of BMI with health outcomes, arguing that the use of BMI alone is insufficient to explain adverse associations in some individuals otherwise classified as normal weight thereby suggesting underlying molecular changes apart from changes in measured BMI [59,60,269]. From our analysis, BMI is associated with dysglycaemia in men and women while proteomic profiling reveals the sex differences. However, though the BMI PRS is useful in stratifying the risk of obesity, particularly in women, higher genetic susceptibility to higher BMI does not necessarily translate to associations with

dysglycaemia. We also observed associations of the proteomic predicted BMI categories with physical activity, the plant-driven nutrient pattern and the retinol and vitamin B12-driven nutrient pattern in men but not in women, suggesting the differential roles of diet and physical activity on proteomic and BMI profiles in men and women. This implies that diet and physical activity interventions may need to be differentiated in men and women. However, the hypothesis still needs to be tested.

Our study has some limitations. The discovery dataset had low representation of African populations thus potentially limiting predictive capacity of the multi-ancestry PRS and subsequent clinical utility. Future studies with larger representation of continental Africans are therefore required. In addition, the discovery of methods for better PRS prediction of BMI in populations may be useful. We also only replicated those proteins previously validated in Europeans. It is, therefore, still unknown which other proteins are associated with BMI in Africans. We also do not know how other omic profiles like metabolomics would predict BMI in Africans. Studies with larger datasets of Africans with different omic markers (proteomics, metabolomics, etc) could yield more insights.

4.7 Conclusion

Our study suggests that a multi-ancestry BMI PRS is more useful in predicting incident severe obesity in African women but not in men. However, the low predictivity overall (approximately 2%) limits its clinical utility. Risk stratification using the top and bottom tails of the PRS distribution appears to be more useful for predicting obesity risk. We also show the usefulness of European derived proteomic makers in unmasking the heterogeneity that exists in associations between BMI with dysglycemia among men but not among women. This suggests the utility of complementing genetic risk profiling with proteomics to improve clinical utility. Further, associations of the proteomic predicted BMI categories with dietary patterns and physical activity were apparent in men but not in women. Thus, proteogenomic analysis highlights the need to look more into sex differences when tackling obesity. Interventions for prevention and control of obesity in men need to focus more on environmental variables while in women more

focus should be directed towards understanding the pathways that influence expression of genes involved in obesity, identifying those at greater genetic risk and developing appropriate preventive or therapeutic strategies. More African studies are however needed to validate these conclusions.

CHAPTER 5: GENE-LIFESTYLE INTERACTIONS FOR BMI AS A MEASURE OF OBESITY IN BLACK SOUTH AFRICANS

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The work in this chapter is a draft manuscript prepared for publication.

5.1 Abstract

Introduction: The prevalence of obesity is increasing due to the interaction of a genetic predisposition in the presence of obesogenic environmental factors. However, the precise genetic variants interacting with diet and physical activity are not well understood in black Africans.

Methods: Genetic data from three South African sites of the AWI-Gen cohort (N=4826) was used to determine candidate gene-interacting variants that exhibited trait variance heterogeneity using the Levene's test implemented in the OCSA package. Linear regression, adjusting for age, sex and three genetic principal components, was used to assess and replicate interactions of diet and physical activity with vQTLs on BMI, as a marker of adiposity in 760 men and women from the GSK study.

Results: Significant interactions for BMI were identified for rs557505940 with fruit intake (P_{int} = 0.001), rs527747185 with SES (P_{int} = 0.0009), rs3016751 with carbohydrate intake (P_{int} = 0.0009), and rs188275749 with physical activity (P_{int} = 0.0019).

Conclusion: vQTL analysis holds promise in identifying GXE interactions among Black Africans.

5.2 Introduction

Overweight and obesity, typically measured using the body mass index (BMI), are major risk factors for cardio-metabolic diseases [2], with obesity affecting 11% of adult men and 47% of women in South Africa [117]. It is reported that weight-related disease conditions exerted a health care cost of between ZAR 30 million and ZAR 36 million in 2020, the bulk of the cost being due to hypertension and type 2 diabetes [77]. The intricate relationships between genetics and lifestyle factors such as diet and physical activity is believed to significantly affect the body mass index (BMI) and related comorbidities. BMI is a highly heritable trait, with estimates from twin studies ranging from 40 -70% while genome-wide SNP heritability has been estimated between 16-54% [160,270,271]. To date, an excess of 500 loci associated with BMI have been identified in genome-wide association studies (GWAS), mostly among individuals of European ancestry [160,272,273]. Consequently, gene x environment (GXE) interactions for obesity have been reported in several studies among Europeans and Americans where for example genetic predisposition (measured using a 32 BMI associated variant genetic risk score) to higher BMI was accentuated by higher intake of sugar-sweetened beverages and fried foods and BMI polygenic risk scores (PRS) had significant interactions with diet and physical activity [190,200,274-278]. However, there is a dearth of similar studies in African populations.

In spite of the existence of several reports on GXE interactions, the success in replicating these observed interactions has been limited both in Europeans and in LMICs [279,280]. Possible reasons include heterogeneity of methods used in the different studies, confounding, small effect sizes of GXE interactions, shortcomings with adjusting for multiple testing, population structure and error in measurement of exposure variables [208]. Thus, the role of environmental factors and variability in the penetrance of genetic effects on complex traits like obesity remains poorly understood. As variance quantitative trait loci (vQTL) analysis is believed to be more robust in unmasking GXE interactions it has been proposed as a complement to GWAS in identifying novel variants associated with complex traits, as well as a way of exploring GXE interactions [209]. vQTL typically identifies variants associated with the variability,

as opposed to just the mean of quantitative traits thus is more likely able to capture differences in variance that is exhibited in interactions [281]. As a result, testing the vQTLs may identify loci concealing underlying GXE interactions for quantitative traits [209]. Since this approach has not been evaluated in African populations, our aim was to assess the usefulness of vQTLs in unravelling the interactions of genetic variation with diet and physical activity that may affect BMI in a continental African setting.

5.3 Methods

5.3.1 Study population

Genomic data from 4825 black men and women (29 to 82 years old) from three South African sites of the Africa of the Wits-INDEPTH partnership for Genomic Studies (AWI-Gen) collected between 2011 and 2015 was used [235]. Data was also used from a subset of this cohort (760 men and women) who were enrolled into a sub-study on the determinants of Type 2 diabetes mellitus risk (GSK) between 2017 and 2018. Details on criteria for inclusion into AWI-Gen are described elsewhere [215].

Ethical clearance for AWI-Gen and GSK studies was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical) (Protocol Number M170880 and Protocol Number M160604 respectively). Written informed consent was obtained from the study participants. We obtained ethical clearance for this analysis from the same committee (Protocol Number: M210166).

5.3.2 Socio-demographic variables

In-person interviews were used to collect data, which included age at enrolment, sex, employment status (classified as employed or not employed, highest level of education (classified as no formal education, primary, secondary and tertiary) and socioeconomic status (SES). The sum of household assets in working order was used to derive SES quintiles using the DHS methodology as described elsewhere [282].

5.3.3 Dietary data

A food frequency questionnaire was employed to collect data on food, including fruit and vegetable intake in the GSK study. Household measures and food models aided

in estimating portion sizes. Amounts of nutrients consumed (plant protein, animal protein, saturated fatty acids, total carbohydrate, added sugar and total dietary fibre) were estimated using the FoodFinder3 (SAMRC, Cape Town, South Africa) software [283]. The process has been described previously [12]. Nutrient patterns data, obtained from principal component analysis of the GSK dietary data [12] was also used in the analysis.

5.3.4 Anthropometric measurements

Weight measurements were collected using a digital scale (Kendon Medical, SA) while a digital wall mounted stadiometer (Holtain, Wales) [215] was used to measure height to the nearest 0.1cm. These measurements were taken in light clothing and bare foot. BMI was calculated as weight (kg)/height squared (in metres).

5.3.5 Physical activity measurements

Total time spent in moderate-to-vigorous physical activity (MVPA), measured using the global physical activity questionnaire (GPAQ) as reported in the AWI-Gen study, was calculated by summing time spent in three domains, namely occupational, transport-related and leisure-time physical activity [243]. Objective physical activity (reported as total steps) was collected in the GSK study using accelerometry with the activPAL (PAL Technologies, Glasgow, Scotland) worn on average for 5 to 7 days. The data was processed using ActivPAL 3M software [271].

5.3.6 Blood collection, genotyping and quality control

Blood for DNA analysis was collected after an overnight fast and processed according to the set standard procedures. Manual or automated procedures were used for isolation and purification of genomic DNA as described by Ali et al. (2018). The Illumina FastTrack Sequencing Service$_2$ was used for genotyping and quality control included excluding individuals and SNPs with a missingness above specific thresholds MAF less than 0.01 and Hardy-Weinberg equilibrium (HWE) P-value below 0.0001 as described by Ali et al. (2018) [215].

5.3.7 Data analysis

The R statistical package version 4.1.1 was used to compute the descriptive characteristics of the participants stratified by sex. Continuous data was compared using the students' T test while the chi square test was used for categorical data.

5.3.7.1 *VQTL analysis*

BMI was first transformed through inverse-rank normalization and this was done in the combined dataset then in men and women. Thereafter, to determine vQTLs associated with BMI, a genome-wide mean-based Levene's test was applied using vQTL module of OSCA-0.46.1 package to extract variants known to be associated with BMI from the South African genomic data. The Levene's test was conducted in the combined dataset for men and women then separately to obtain vQTLs for men and vQTLs for women. The SNPs that met genome-wide significance (p = 5e-08) were prioritized as vQTLs for interaction analysis to identify GXE interactions. Thereafter, distance clumping using +/- 500kb window was performed to determine the lead vQTLs.

5.3.7.2 *Interaction analysis*

This was conducted in two stages, first using the combined data for men and women (combined analysis) then separately for men and women. Data was randomly split by half to create the discovery and replication datasets using CaTools package in R statistical software. The discovery and validation datasets were merged with the demographic and dietary data from Soweto and GSK to evaluate interactions of the PRS with self-reported physical activity (MVPA), objective physical activity (total daily steps) and dietary data (measured by fruit, vegetable, nutrient intake and nutrient patterns, plant protein, animal protein, saturated fatty acids, total carbohydrate, added sugar and total dietary fibre). Linear models were used with BMI as the outcome and age, sex and 3 genetic principal components as covariates (Figure 5:1). Interaction analysis was conducted in the combined data and separately for men and women.

Results that were found to be statistically significant in the discovery datasets were replicated in the replication datasets. To adjust for multiple testing, significant

interactions were depicted by dividing 0.05 by the number of tests performed. If results remained statistically significant in the discovery dataset, the summary statistics from the discovery and datasets were meta-analysed to confirm that the results were not by chance.

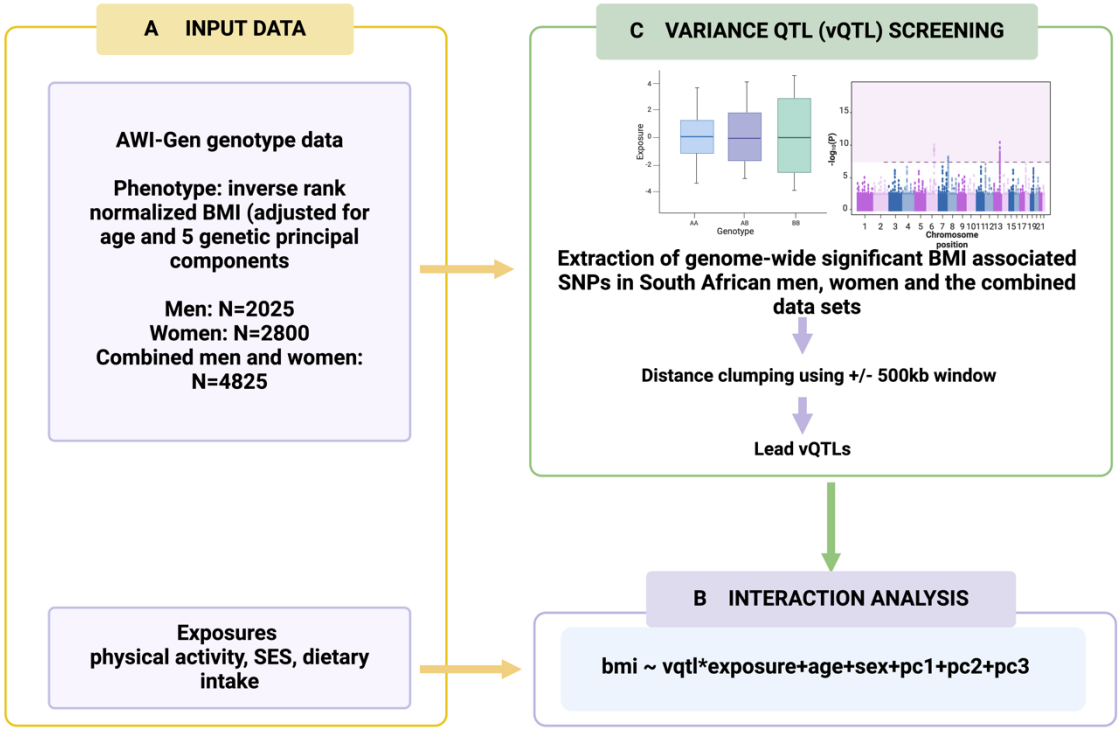

Figure 5.1: Process diagram for determining gene-lifestyle interactions of BMI in South African adult men and women

Genomic data from 4825 men and women from the AWI-Gen cohort was used to screen for vQTLs using the Levene's test to identify variants associated with BMI in Black South African men and women. Distance clumping using +/- 500kb window was performed to determine the lead vQTLs which were then used to determine interactions with diet and physical activity variables for BMI.

5.4 Results

Table 5:1 shows the characteristics of the study participants. No differences in the mean age and amount of fruit intake were observed among the study participants. However, women exhibited higher BMI (mean = 30.91 (7.55)) compared to men (mean

= 24.15 (5.45)). More men (49.2%) than women (38.8%) were employed and men engaged in more MVPA (median = 740 minutes; q1, q3 = 24, 1680)) per week compared to women (median = 630 minutes, q1,q3 (150, 1500).

Table 5:1 Background characteristics of men and women participating in the South African sites of the AWI-Gen (A) and GSK (B) studies.

A. Variable	Women (N=3413)	Men (N=2503)	Total (N=5916)	p value
BMI Mean (SD)	30.9 (7.6)	24.2 (5.5)	28.1 (7.5)	< 0.001
Age in years Mean (SD)	53 (9)	54 (10)	53 (9)	0.273
Highest level of education (n, %)				< 0.001
No formal education	723 (22.7)	403 (16.1)	1126 (19.8)	
Primary	1504 (47.1)	682 (27.3)	2186 (38.4)	
Secondary	886 (27.8)	1199 (47.9)	2085 (36.6)	
Tertiary	79 (2.5)	217 (8.7)	296 (5.2)	
Employed: Yes (n, %)	1254 (38.8)	1124 (49.2)	2378 (43.1)	< 0.001
SES				< 0.001
Median	8.00	9.00	8.00	
Q1, Q3	6.00, 10.00	6.00, 12.00	6.00, 11.00	
MVPA (self-reported)				< 0.001
Median	630.00	740.00	690.00	
Q1, Q3	150.00, 1500.00	240.00, 1680.00	180.00, 1560.00	
B. Variable	**Women (N=346)**	**Men (N=414)**	**Total (N=760)**	**p value**
Plant protein (g)				< 0.001
Mean (SD)	28.2 (12.9)	22.7 (12.4)	25.7 (13.0)	
Animal protein (g)				< 0.001
Mean (SD)	30.8 (21.3)	23.7 (15.6)	27.6 (19.3)	
Saturated FA (g)				0.012
Mean (SD)	17.5 (10.3)	15.7 (8.6)	16.7 (9.6)	
Total Carbohydrate (g)				< 0.001
Mean (SD)	270.7 (124.3)	229.2 (103.7)	251.8 (117.2)	
Added sugar (g)				0.107
Mean (SD)	48.0 (38.7)	52.7 (41.0)	50.1 (39.8)	
Total dietary fibre (g)				< 0.001
Mean (SD)	19.9 (9.4)	17.6 (8.5)	18.8 (9.1)	
Total Number of Steps				< 0.001
Median	10105.0	8805.0	9379.0	
Q1, Q3	7336.5, 12909.5	6574.3, 11204.8	7029.5, 12180.3	
Vegetables (g)				0.046
Mean (SD)	154.8 (119.1)	139.0 (89.0)	147.6 (106.7)	
Fruit (g)				0.846

5.4.1 VQTL Analysis

In the vQTL analysis using the OSCA package, 30 SNPs met the genome-wide significance threshold of p = 5e-08 in the combined analysis while in men there were 15 SNPs and 11 SNPs in women but these SNPs did not overlap. However, after distance clumping, there were seven, eight and twenty-four lead vQTLs in women, men and the combined analysis respectively (Supplementary Table 5), i.e. these vQTLs were considered to be the most strongly associated with BMI within specific genomic regions.

5.4.2 Interaction analysis

Using the discovery data for the combined analysis, higher fruit intake accentuated the effect of rs557505940 on BMI (P_{int} = 0.04) and this finding was replicated in the replication dataset. Pooled results from the discovery and replication datasets similarly showed that higher fruit intake accentuated the effect of rs557505940 on BMI (P_{int} = 0.001). Conversely, in men the effect of rs3016751 (P_{int} = 0.0009) and rs188275749 (P_{int} = 0.0019) on BMI was attenuated by carbohydrate intake and self-reported physical activity, respectively. These interactions were also statistically significant in the replication dataset but no interactions in women were replicated. Further, meta-analysis of the significant interaction results revealed consistent results (Table 5:2). The interaction plots are shown in Figure 5.2. Variants rs527747185 and rs557505940 are intronic variants while rs3016751 is an intergenic variant (Supplementary Table 5).

Table 5:2 Summary of significant gene x environment interactions on BMI in adult South Africans from Soweto

	Discovery			Replication			Metanalysis		
Interaction term	**beta**	**se**	**P value**	**beta**	**se**	**P value**	**beta**	**se**	**P value**
Combined analysis (N)			334			351			
rs557505940*Fruit	0.03	0.014	0.04	0.025	0.01	0.015	0.027	0.008	0.001
Men (N)			202			182			
rs3016751*Total Carbohydrate	-0.056	0.026	0.035	-0.041	0.016	0.014	-0.045	0.014	0.0009
Men (N)			446			455			
rs188275749*MVPA (self-reported)	-0.048	0.013	0.0001	-0.007	0.003	0.046	-0.009	0.003	0.0019

Models were adjusted for age, sex and three principal components.

Figure 5:2 shows the interaction plots. Variants rs188275749 and rs557505940 are intronic variants while rs3016751 is an intergenic variant.

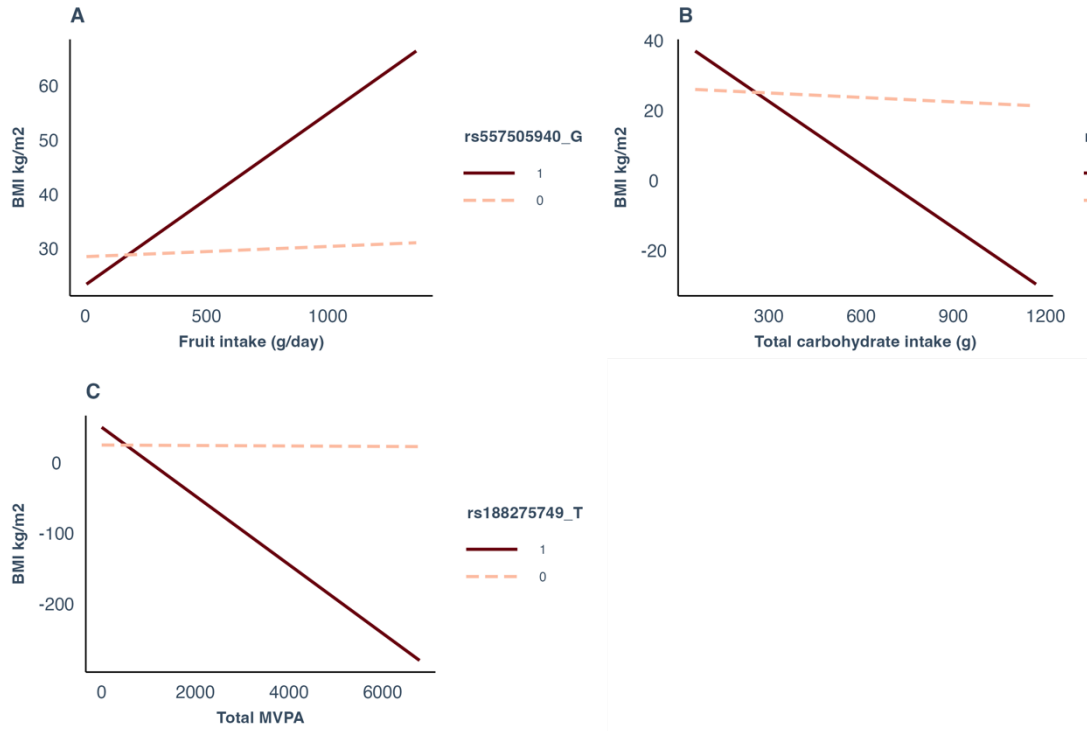

Figure 5.2: Interaction plot illustrating the influence of genotype and lifestyle factors (diet and physical activity) on BMI

Interaction plots illustrating the influence of genotype and lifestyle factors on BMI. **A**. Interaction plot showing the influence of the variant rs557505940 on the association between fruit intake and BMI. **B.** Interaction plot showing the influence of the variant rs3016751 on the association between total carbohydrate intake on BMI. **C**. Interaction plot showing the influence of the variant rs188275749 on the association between total carbohydrate intake and BMI. The bold line represents the influence for those carrying the effect allele of the variant while the dashed line shows the influence for those without the effect allele.

5.5 Discussion

This analysis was aimed at assessing the gene-lifestyle interactions for BMI in a continental African population by leveraging the variance heterogeneity of vQTLs. Novel gene-lifestyle interactions for three vQTLs with physical activity, fruit

and carbohydrate intake whose interaction co-efficients were directionally consistent in the replication dataset and meta-analysis were observed.

The interaction of the rs557505940 variant with fruit intake was replicated in the combined analysis while in men interactions of the rs3016751 variant with carbohydrate intake and rs188275749 with self-reported physical activity for BMI were identified. The variant rs557505940 is in the LOC105372747 gene whose role is largely unknown as it has not been fully annotated. However, a variant in this gene, rs2827976, has been implicated in metabolic syndrome in women [284] a possible indication of this gene's role in obesity biology which needs further inquiry. The variant rs3016751 is in the LOC105369309 gene, a long non-coding RNA (lncRNA) gene [285] while the rs188275749 is a novel variant which still needs to be characterized. LncRNAs play a key role in gene expression [286,287]. More studies to determine the population distribution of these variants in African populations and their pathways in influencing BMI are needed.

Meta-analyses of studies from European, Asian and American populations found interaction of variants of the FTO and SEC16B loci with physical activity [280,288] contrary to our findings where significant interactions of variants were identified in different loci. This suggests that genetic variant interactions with environmental factors for BMI and other obesity related traits are probably population-specific [9]. It is likely that different environmental exposures will alter the expression of different genes, ultimately modifying pathways that specific genes operate to produce specific phenotypes [289]. As a result, in different populations, different genetic variants are likely to manifest interactions. Alternatively, as is the case from results observed in our analysis, differences in genetic architecture implies different genetic pathways influencing BMI. Continental Africa is known to have higher genetic diversity [290] thus it is possible that there are still a lot of unknown variants that interact with the environment to produce the varying phenotypes.

This analysis was not without weaknesses. The small sample size may have led to the inability to detect some GXE interactions. However, the use of vQTL analysis averts

the burden of multiple testing which is common in gene x environment interaction studies [208] and enabled detection of three novel gene x environment interactions for BMI. Further analysis using all the six sites of the AWI-Gen cohort could yield some useful insights.

5.6 Conclusion

This study identified novel variants that may have a critical role in obesity aetiology. Further studies to determine the prevalence of these variants and their role in influencing BMI in African populations is warranted. Further, replication of these findings and use of larger sample sizes may also unmask other GXE interactions that have significant implications in the prevention and control of obesity in continental Africans.

CHAPTER 6: INTEGRATED DISCUSSION AND CONCLUSION

In this chapter is a summary the key findings in line with objectives of the thesis, reflections on relevance of research in the African context and proposed areas for future research. The strengths and limitations are also highlighted.

6.1 Summary of Objectives and Key Findings

The aim of this thesis was to provide evidence of predictivity of a BMI PRS on obesity as well as GXE interactions and the clinical implications thereof. This was achieved through exploring three objectives results of which are summarized in Table 6:1.

6.2 Emerging themes from the findings

In this section, the methodological and empirical themes that emerged in the design and analysis of the studies that constitute this thesis are discussed.

6.2.1 Methodological themes

Various quantitative methods, considered to best answer the different research questions, were used. Quantitative methods are often criticised for lacking the human element hence the inability to determine human experiences and context that influence the findings [291]. In addition, relationships among variables may be oversimplified, particularly non-linear complex relationships and some variables which may influence the phenomenon under study may be missed thus influencing the impact observed. However, they have advantages which include the ability to test hypotheses, objective data can be collected, quantification of impact, generalizability to wider populations and ability to compare results across studies and to determine causal associations [292]. Much as each research question in this thesis was answered using a quantitative approach, there was no uniform quantitative method applicable to each one of them. Each method used has its strengths and limitations hence the decision to settle for a specific method was painstaking. Table 6:2 summarizes the strengths and limitations of the quantitative methods applied to meet the specific objectives in this thesis.

Table 6:1 Summary of key study findings

Objective, research question and hypothesis	Key findings
Objective 1: To determine the association of physical activity with BMI in middle-aged black South African men and women. **Research question 1**: What is the association of self-reported physical activity domains of work, leisure and transport-related physical activity and body mass index in middle aged black South Africans?	• Dikgale men spent most of their physical activity time (51.9%) in transport-related physical activity while the women engaged most in work-related physical activity (62.2%). In Soweto, most physical activity time was spent in transport-related physical activity for both men (55.7%) and women (63.8%). • In the overall sample meeting physical activity guidelines was associated with 0.80kg/m^2 (95% CI = -1.14 – -0.47) lower BMI in men and 0.68kg/m^2 (95% CI = -1.03 – -0.33) lower BMI in women. For South Africa meeting physical activity guidelines was associated with 1.81 kg/m^2 (95% CI = -2.66; -0.96) lower BMI in Soweto men and 3.38 kg/m^2 (95% CI = -5.88; -0.88) lower BMI among women from Dikgale. • Among those who met physical activity guidelines, transport-related physical activity was associated with 0.79 kg/m^2 (95%CI = -1.25; -0.33) lower BMI in Nanoro (West Africa) • Among those who met physical activity guidelines, work-related physical activity was associated with 0.76 kg/m^2 (95% CI=-1.25; -0.27) lower BMI in Navrongo men (West Africa) and 0.90 kg/m^2 (95%CI = -1.44; -0.36) lower BMI in Nanoro women

Objective 2: To develop a highly predictive genetic risk score for obesity and test its predictive ability in middle aged black South Africans **Research question 2**: Is there a difference in risk for overweight or obesity among middle aged black South African men and women in high and low polygenic risk strata over time?	• Higher predictivity of the multi-ancestry PRS, which explained approximately 1.9% of the variance in BMI compared to 0.7% explained by the Tanigawa score and 1.2% by the Privè score was observed. • Over 10 years, polygenic risk of higher BMI was associated with approximately 1.51 kgm2 higher BMI (β = 1.51 kg/m^2 p = < 0.001) with longitudinal sex interactions ($P_{interaction}$ = 0.029), suggesting sex differences in polygenic risk of higher BMI. This was substantiated in subsequent analysis. • Those in the top 20% of the PRS distribution had 3 times greater hazard of severe obesity (hazard ratio = 2.98, 95% CI = 1.75 - 5.07, p = 5.33e-05) and this observation was driven by women. Almost 3.5 times greater hazard of severe obesity was observed for women in the top 20% (hazard ratio = 3.48, 95% CI = 1.96 – 6.16, p = 1.94e-05) compared to those in the bottom 20% but there was no difference observed in men. • The overestimated (OE) category of proteomic predicted BMI was associated with higher polygenic risk of increased BMI (β = 0.43 standard deviations (SD), 95% CI = 0.08-0.78, p = 0.017) in men while in women, the UE category was marginally associated with higher polygenic risk of increased BMI (β = 0.49 SD, 95% CI = 0.003 0.97, p = 0.049). This suggests that genetic factors influencing BMI may have some impact on the proteomic profile.

	• For men, being in the OE category of proteomic predicted BMI was associated with more insulin production (fasting c peptide: β = 0.99 SD, 95% CI = 0.71-1.26, p = 7.12e-12), higher insulin resistance (HOMA-IR: β = 0.52 SD, 95% CI = 0.27-0.77, p = 4.32e-05), elevated 2-hour glucose (β = 0.50 SD, 95% CI = 0.17-0.83, p = 003) and lower insulin sensitivity (Matsuda index: β = -1.02 SD, 95% CI = 1.35e-08, p = 1.35e-08) compared to being of normal weight • The plant-driven nutrient pattern was associated with lower obesity (β = -0.50 SD, 95% CI = -0.87 - -0.12 SD, p = 0.009), while the retinol driven nutrient pattern was associated with higher proteomic predicted BMI (β = 0.43 SD, 95% CI = 0.06 - 0.80 SD, p = 0.022) and lower obesity in both the self-reported physical activity (β = -0.33 SD, 95% CI = -0.63 - -0.02 SD, p = 0.036) and accelerometry-based physical activity (β = -0.61 SD, 95% CI = -0.92 - -0.29 SD, p = 0.0002). No significant associations were observed in women. • The proteomic-predicted BMI classes unmask heterogeneity of associations between BMI and dysglycaemia between men and women which are not apparent when using measured BMI.
Objective 3: To determine the gene x lifestyle interactions that influence BMI in Black South African adult men and women.	• Novel diet and physical activity interactions with BMI associated variants were observed.

Research question 3: Do genetic variants associated with BMI modify the association of physical activity and dietary intake with BMI?	• The effect of the rs557505940 variant on BMI was accentuated by higher fruit intake ($beta_{interaction}$ = 0.03, $P_{interaction}$ = 0.04) in the combined analysis of men and women • Higher carbohydrate intake and self-reported physical activity attenuated the effect of rs3016751 ($beta_{interaction}$ = -0.056, $P_{interaction}$ = 0.035) and rs188275749 ($beta_{interaction}$ = -0.048, $P_{interaction}$ = 0.0001) respectively on BMI in men.

Table 6:2 Strengths and limitations of the quantitative methods applied to meet the specific objectives in this thesis

	Meta-analysis	PRS-CSx	Cox-proportional hazards modelling	vQTL analysis
Strengths	Combining data from 5 study sites increased statistical power of our study to detect associations between physical activity and BMI. Meta-analysis allowed for examination of consistency of associations between physical activity and BMI across the studies by examining heterogeneity. This helped explore potential sources of differences observed in the associations. Generalizability of the results obtained in this analysis to African populations is possible as results were pooled from different regions. External validity is also enhanced.	The use of summary statistics from diverse populations, accounting for population-specific LD and continuous shrinkage priors potentially facilitated improved predictivity of the multi-ancestry PRS, particularly in this population that has limited genetic data	The Cox proportional hazards model does not assume a constant rate over time so was suitable in this analysis where obesity may change with time. The flexibility of this model allowed use of multiple covariates that may affect the hazard of severe obesity	Use of variants associated with the variability of BMI enhanced the likelihood of detecting hidden GXE interactions. The use of vQTLs in GXE interaction analysis is advantageous where the exposure variable is poorly measured [209]. In this analysis, we cannot rule out the possibility of measurement bias particularly for self-reported physical activity and dietary data which were not objectively measured. The use of vQTL analysis enhances the chances of detecting GXE interactions.
Limitations	The quality of results from meta-analysis depends on the availability of complete and accurate data. Data from	The summary statistics used were of predominantly European ancestry individuals so despite the multi-ancestry	The Cox proportional hazards model can handle censored data, in this case those that did not develop severe	This approach is limited by the lack of large discovery data sets from which the Levene test can be applied to discover candidate gene-

	Agincourt was excluded from the meta-analysis due to missing leisure-time physical activity data. this could impact the observed associations. Heterogeneity of data collection techniques, which impacts on data quality, cannot be ruled out. While efforts were made to standardize methods for data collection, the possibility of differences in measurement and interview skills cannot be ignored. Due to differences in populations and settings, factors confounding the association between physical activity and BMI may differ across the included studies. This complexity was however not explored in the analysis.	PRS having enhanced predictivity, it could probably have better predictivity if there was more representation of African ancestry individuals	obesity. In the event that there are numerous censored events as in this analysis where only a few men developed severe obesity (failure events), the precision of estimates is compromised. Related to this limitation, if the failure events are few, the ability to handle multiple covariates can lead to overfitting and unstable estimates as was the case for men in this analysis.	interacting variants. With the increase in African genomic data sets, more candidate gene interacting variants will be discovered in the future.

6.2.2 Empirical themes

A review of relevant literature and data analysis for the studies included in this thesis revealed pertinent themes. The overarching theme is that of paying particular attention to population groups in designing diet and physical activity interventions for obesity prevention and control. In this era of precision medicine, blanket interventions may be ineffective in addressing the issues at hand. Globally, is known that generally women have higher BMI than men yet diet and physical activity recommendations for addressing obesity have ignored this fact [132,224,293,294]. The same is true for South Africa where the food-based dietary guidelines and guidelines for NCD prevention and control do not consider sex differences [117,295].

From the analysis in this thesis, regional and sex-specific variation across five communities in four African countries in patterns of work, transport and leisure related physical activity domains and their association with BMI were apparent. However, the intensity and duration of different domains of physical activity that offer the most substantial benefits have not yet been established. Reverse causality in the associations between physical activity and BMI can also not be ruled out. Meanwhile, more context-specific physical activity recommendations are likely to be more beneficial than the current blanket recommendations.

Results from analyses conducted in studies in this thesis further reveal the differences in genetic risk for severe obesity, genetic influence on proteomic profiles and GXE interactions between men and women. Scholars have argued that BMI is a crude measure of obesity that does not differentiate between fat and lean body mass. Nevertheless, BMI remains a valid measure of obesity due to its simplicity, ability to predict disease risk and strong correlation with gold standard body composition measures [54,56,296,297]. It has been further argued that BMI associations with health outcomes are heterogeneous, manifesting varied cardiometabolic outcomes for the same BMI [259]. The use of multi-omics (genomics, metabolomics, proteomics) holds promise in unmasking the heterogeneity associations between BMI and health outcomes and improving screening for the prevention and management of obesity-

related conditions [60,269]. This steers us to think more contextually about the interventions that would be of more benefit as well as identify possible mechanisms for differences in obesity between men and women, which is the idea behind precision medicine. Applying precision thinking in obesity prevention and control is likely to move us further towards achieving sustainable development goal 3, which aims at global health and well-being by 2030. In the context of results presented in this thesis, it may be helpful to further consider the possibility that while in women BMI PRS can clearly stratify the hazard of severe obesity, in men the genetic risk may be expressed better through the proteomic profiles. This probably implies that interventions for women may be targeted at identifying those at higher genetic risk of higher BMI and designing appropriate interventions while for men, a focus on the genetic influences on the proteomic profiles may yield insights into appropriate interventions.

6.2.3 Conceptual framework

This section reflects on the conceptual framework applied in this study. Scott A., Ejikeme C. S., Clottey E. N. and Thomas J. G. (2013) proposed that overweight and obesity are a culmination factors in the macro-environment; intermediate factors which include the built environment, social and cultural factors as well as factors at individual level (proximate factors). Results presented in this thesis demonstrate how the individual level factors are associated with obesity. While the scope could not determine causal associations, it was possible to apply this conceptual framework to determine associations of the proximate factors, namely diet, physical activity and genetics with obesity. Some of the intermediate factors could be inferred to as possible factors contributing towards higher or lower BMI. For example, the sex and regional differences in the associations between different physical activity domains and BMI could be related to intermediate factors like occupations. We observed higher work-related physical activity in this study, as is typical in low-income compared to high-income countries [223] and this likely influences associations with BMI.

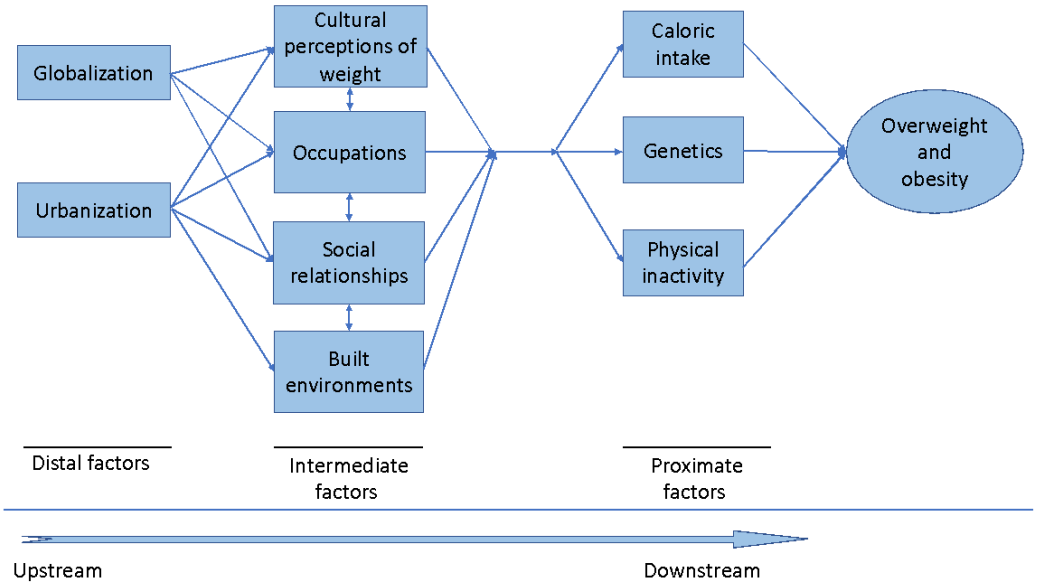

Figure 6.1: A causality continuum for obesity in sub-Saharan Africa
Source: Scott A., Ejikeme C. S., Clottey E. N. and Thomas J. G. (2013). Obesity in sub-Saharan Africa: development of an ecological theoretical framework. Reproduced with permission from Oxford University Press

The role of genetics was also demonstrated in use of the PRS to predict risk of higher BMI as well as stratifying risk of severe obesity in women. While further inquiry into the GXE interactions is still required, some novel variants that influence the associations between diet, physical activity and BMI were discovered. The conceptual framework becomes applicable in this context, demonstrating the complex interactions of factors at individual level in obesity aetiology. Furthermore, the observed association of proteomic predicted BMI categories with PRS and subsequent associations with dysglycaemia suggest that this conceptual framework can be further expanded to include the consequences of obesity.

An in-depth analysis of the conceptual framework applied in this thesis provides insight that it is not adequate to just focus on the proximate factors in the obesity discourse as there are complex interactions of the factors at all the levels [33]. Focus on the other factors was out of the scope of this thesis. However, subsequent inquiry into the gaps identified can begin to consider the intermediate and distal factors. For example, it is

known that environmental factors may influence gene expression [162,178] and analysis contributing to this thesis has shown that a BMI PRS can stratify women into high or lower risk of severe obesity but it was beyond our scope to determine what environmental factors influence gene expression to enable development of severe obesity.

6.2.4 Implications

Results presented in the studies in this thesis are the first to demonstrate the regional and sex-specific associations of physical activity domains with BMI in Africa. The weakness of blanket physical activity recommendations for obesity prevention, regardless of sex and social context is therefore confirmed. Before designing physical activity recommendations, the intermediate factors influencing physical activity must be understood.

This thesis also provides novel evidence in the African context for superior predictivity of a multi-ancestry PRS and stratification of severe obesity risk in women. While larger studies may be required to determine if similar stratification can be obtained in men, it is clear from this analysis that there may be strong genetic influences for severe obesity in women. Further understanding of obesity aetiology in women may need to include identification of women at higher genetic risk and the factors influencing obesity-related gene expression.

This thesis also provides novel empirical evidence that genetic risk of higher BMI among men in an African context may be expressed through the influence on proteomic profiles. Furthermore, proteomic profiles in men are significantly associated with dysglycaemia, an observation which was not seen in women. Therefore, a study of the genetics of obesity in men may need to focus more on proteomic profiles and gene expression, or rather the environmental factors that may be influencing obesity in men. More studies however need to be done to determine the underlying mechanisms influencing obesity prevalence and risk of cardio-metabolic diseases in men and women.

These results therefore underscore the need for considering men and women separately in the discourse on obesity prevention and control. Further, rather than just focusing on diet and physical activity, further inquiry into genetic factors influencing food choices and molecular pathways influencing development of obesity must be done. This is expected to contribute towards more robust preventive and therapeutic interventions.

6.3 What this thesis adds to the body of scientific knowledge

Findings from this thesis add some insights into the scientific inquiry of obesity.

1. Sex and regional differences in the association between physical activity domains with BMI were found, implying the need to pay attention to these factors in developing physical activity guidelines in the prevention and management of obesity.
2. While the multi-ancestry BMI PRS explains only a small proportion of the variation in predicting BMI, stratification using tails of the PRS distribution holds promise in identifying at risk individuals in a continental African population.
3. This thesis findings also add to the body of knowledge regarding the heterogeneity of associations between BMI and health outcomes using proteomic profiling. Findings suggest a possible role of proteomics in the sex-differences in BMI.
4. The findings herein also revealed novel variants interacting with diet and physical activity for BMI in continental Africans

6.4 Further research

From this research, various research gaps have been noted and these include:

5. In the analysis of the association between physical activity domains and BMI, further inquiry into other factors such as diet, SES, medications and health conditions not included in the study that may confound the associations is warranted. Moreover, it remains to be determined whether it is the physical activity level that results in BMI level or the BMI determines physical activity levels.

6. Assessment of genetic risk on obesity over time was only conducted in the South African dataset. Further study and validation in other African populations, given the wide genetic variation in Africans [29], is therefore warranted.

7. Interesting insights were gleaned from the associations of proteomic predicted BMI classes with dysglycaemia, fat distribution, nutrient patterns and physical activity. More inquiry into the different omic profiles associated with BMI should yield greater insights into obesity aetiology and probably better explain the sex differences in obesity prevalence and associated cardio-metabolic risk profiles.
8. Gene x lifestyle interaction analysis in African populations is still scarce. Further interrogation of vQTL analysis in African populations may thus yield findings useful in obesity aetiology.

9. Work also needs to be done to establish the causal associations between obesity phenotypes and health outcomes.

6.5 Limitations and strengths

A key strength of this study is the availability of longitudinal data that enabled modelling of genetic risk of obesity over a period of ten years. Also having data from five sites to assess the association of physical activity domains and BMI revealed regional and sex patterns that had not been previously known in Africa. In addition, the availability of proteomic, glycaemic and fat profiles enabled the assessment of clinical implications of genetic risk of higher BMI. Though it was possible to assess the longitudinal associations of PRS with obesity over time, the results cannot be generalized to African populations due to differences in genetic architecture, necessitating further inquiry in other African populations. Moreover, the methods used did not allow determination of causality.

Small sample size may mask GXE interactions that may be present in the study population. However, the use of vQTLs was instrumental in revealing some novel interactions that may be useful in informing obesity prevention and control. In addition,

dietary and MVPA data used was self-reported. Self-reported data is prone to recall bias, which may result in over or underestimation of effects. Efforts were however made to use models to aid recall in collecting dietary data. In the interaction analysis, objective physical activity data collected using accelerometry was also used for comparison. Another limitation was that dietary data was only from an urban population, thus also limiting generalizability to the whole of South African adult men and women or to Africa.

6.6 Conclusions

Associations of physical activity with BMI differ by physical activity domain, sex and geographical location. In addition, complex mechanisms are at play in obesity aetiology, with genetic risk being sustained over time and better predicting incident severe obesity in women than in men. Proteomic profiles show heterogenous associations with dysglycaemia, fat distribution, nutrient patterns and physical activity between men and women and novel GXE interactions were observed. Thus in light of the very vivid sex differences observed in this analysis, a precision approach to obesity prevention and control, paying attention to the sex differences and contextual factors may be more efficient. Further study as highlighted in the previous section is warranted.

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Appendices

Appendix 1: Muti M, Ware LJ, Micklesfield LK, Ramsay M, Agongo G, Boua PR, Kisiangani I, Cook I, Gómez-Olivé FX, Crowther NJ, Kabudula C, Norris SA, Chikowore T. Physical activity and its association with body mass index: A cross-sectional analysis in middle-aged adults from 4 Sub-Saharan African countries. J Phys Act Health. 2023;20(3):217–225

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ORIGINAL RESEARCH

Physical Activity and Its Association With Body Mass Index: A Cross-Sectional Analysis in Middle-Aged Adults From 4 Sub-Saharan African Countries

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Background: This study aimed to explore association of self-reported physical activity domains of work, leisure, and transport-related physical activity and body mass index (BMI) in 9388 adult men and women from the Africa-Wits-INDEPTH partnership for Genomic (AWI-Gen) study in Africa. Africa-Wits-INDEPTH partnership for Genomic is a large, population-based cross-sectional cohort with participants from 6 sites from rural and urban areas in 4 sub-Saharan African countries. ***Methods:*** A sex-stratified meta-analysis of cross-sectional data from men and women aged 29–82 years was used to assess the association of physical activity with BMI. ***Results:*** Overall, meeting physical activity guidelines of at least 150 minutes per week was associated with 0.82 kg/m^2 lower BMI in men ($\beta = -0.80$ kg/m^2; 95% confidence interval [CI], −1.14 to −0.47) and 0.68 kg/m^2 lower BMI in women ($\beta = -0.68$ kg/m^2; 95% CI, −1.03 to −0.33). Sex and site-specific differences were observed in the associations between physical activity domains and BMI. Among those who met physical activity guidelines, there was an inverse association between transport-related physical activity and BMI in men from Nanoro (Burkina Faso) ($\beta = -0.79$ kg/m^2; 95% CI, −1.25 to −0.33) as well as work-related physical activity and BMI in Navrongo men (Ghana) ($\beta = -0.76$ kg/m^2; 95% CI, −1.25 to −0.27) and Nanoro women ($\beta = -0.90$ kg/m^2; 95% CI, −1.44 to −0.36). ***Conclusions:*** Physical activity may be an effective strategy to curb rising obesity in Africa. More studies are needed to assess the impact of sex and geographic location-specific physical activity interventions on obesity.

Keywords: obesity, MVPA, physical activity domain, Africa

Obesity is one of the major risk factors for cardio-metabolic diseases.[1] It is projected that in Africa, by 2030, 27 million men and 72 million women will be obese, an increase from 8 million men and 26 million women in 2010.[2] Physical activity (PA) is a vital lifestyle intervention for reducing obesity.[3–7] However, more studies are needed in Africa to understand the PA patterns of men and women and their association with body mass index (BMI).

Total time spent in PA is accrued from various PA domains (namely work, leisure, and transport) and varies among communities and countries.[8,9] High-income countries have higher levels of leisure-time PA (LTPA) (28% of total PA) compared with the low, lower-middle, and upper-middle income countries (4%, 8%, and 13%, respectively).[8] Work-related PA has a higher contribution to total PA in the low and lower-middle income countries (57%) compared with the upper-middle and high-income countries (44%–47%).[8] Most evidence on the association between PA and BMI is based on the leisure-time PA (LTPA) domain in US and European populations.[6,10,11] However, work and transport-related PA are highly prevalent in Africa, accounting for 95% of overall PA in 22 countries, compared with 5% for LTPA.[12] This might be due to differences in culture, levels of urbanization, economic development, and climate between low- and middle-income and high-income countries. In addition, access to and affordability of facilities for LTPA such as gyms may determine the types of physical activities in which Africans engage.[13,14] Dugas et al[15]

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explored the association between PA (self-reported and accelerometry based) on BMI in adults of African origin. Inconsistent associations were found between time spent in moderate to vigorous physical activity (MVPA) and BMI while higher baseline MVPA levels were not significantly associated with future weight changes.

Some scholars argue that inconsistencies in the association between PA and BMI may be because PA alone is insufficient to influence BMI but more benefits would be realized if complemented with other interventions such as diet.[16,17] Nevertheless, evidence is fairly consistent on the association of higher PA with lower BMI.[18–21] However, though PA is known to be associated with lower BMI, the reverse may also be true as bidirectional causal relationships between PA and BMI have been observed in a Mendelian randomization study[22] and higher BMI has been seen to result in less transport-related PA.[23] Nevertheless, there remains, a lack of evidence on the impact of domain-specific PA on BMI, particularly on the African continent as patterns of PA in work, leisure, and transport-related PA domains differ across regions of the world.[8] Therefore, we aimed to describe and compare PA domains between middle-aged men and women from East, West, and South African countries and evaluate the association between time spent in these PA domains with BMI.

Materials and Methods

Study Population and Setting

We used data from 9388 men and women aged 29–82 years recruited across 5 sites in the Africa-Wits-INDEPTH partnership for Genomic studies (AWI-Gen), a large, population-based cross-sectional cohort from rural and urban areas in 4 sub-Saharan African countries.[24,25] Four of the sites were health and demographic surveillance sites (HDSS) in West Africa (Nanoro HDSS,[26] Burkina Faso, and Navrongo HDSS in the Navrongo Health Research Centre, Ghana[27]), East Africa (African Population and Health Research Center HDSS, Nairobi, Kenya[28]), and South Africa (Dikgale HDSS[29]) The fifth site was located in the MRC/Wits Developmental Pathways for Health Research Unit, Soweto, also in South Africa.[30] Participants were recruited at random into the AWI-Gen study. The recruitment process is described in detail in an earlier publication.[25] The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the University of the Witwatersrand Human Research Ethics Committee (Medical; M210166). The AWI-Gen study data were collected under ethical approval from the same committee (M121029), and written informed consent was obtained from all participants. Those who could not read or write had the consent form read before they affixed a thumbprint and a third party signed as a witness.[25]

Data Collection

Face-to-face interviews were conducted at study sites in different countries to obtain data on PA and demographic variables.

Anthropometric Measurements

Weight was measured with a calibrated digital scale to the nearest 0.1 kg, and height was measured to the nearest 0.01 cm using a wall-fixed digital stadiometer (Holtain Ltd).[25] BMI was calculated and categorized as follows: underweight (BMI < 18.5 kg/m^2), normal weight (BMI ≥ 18.5 and <25 kg/m^2), overweight (BMI ≥ 25 and < 30 kg/m^2), and obese (BMI ≥ 30 kg/m^2).[31]

Sociodemographics and PA

Education was categorized as no formal education, completion of primary, secondary, or tertiary education. Household assets in working order were used to categorize socioeconomic status into quintiles based on the demographic and health survey method.[32,33]

PA was measured in 3 domains, occupational, transport-related, and leisure-time PA, using the Global Physical Activity Questionnaire (GPAQ).[31,34] Total time spent in each PA domain was a sum of the minutes spent per week in moderate- and vigorous-intensity PA (MVPA) in that domain. Total MVPA in minutes per week was calculated as MVPA time accumulated in the 3 domains. Total MVPA was classified based on the World Health Organization guidelines for PA. Those with MVPA ≥ 150 minutes per week were classified as meeting guidelines, and those with MVPA <150 minutes per week were classified as not meeting guidelines.[9] Sitting time in hours per day from the GPAQ was used to measure sedentary time. Sleeping time was not included in the analysis.[34]

Statistical Analysis

Data were exported to R (version 4.0.0), cleaned, and checked for normality using the Shapiro–Wilcoxon test. Cleaning was conducted for the PA data using the GPAQ analysis guide. In addition, observations lying outside ±1.5 SD of the mean were removed. For sitting time, participants with sitting hours above 24 hours per day were removed.

In the first stage of analysis (data analysis stage 1, Figure 1), the data were split into sites. Descriptive statistics were used to describe the participants' characteristics, exposures, and outcomes, including PA patterns in the different study sites. Median and interquartile ranges (IQRs) were used to describe the non-normally distributed variables. Mann–Whitney test for continuous data and chi-square test for categorical data were used to test the differences between men and women and between sites. To determine the proportion of time spent in each PA domain, the total MVPA for each participant was calculated, followed by the percentage of time spent in each domain before getting the mean of these percentages for each domain. Linear regression modeling was conducted to determine the association between meeting PA guidelines (predictor) with BMI (outcome) across the sites. After that, a meta-analysis was completed in the meta-package of R using summary statistics from linear regression to determine the associations in the total sample. Models were adjusted for age, education level, and socioeconomic status.

In stage 2 of the analysis (Figure 1), only those who met PA guidelines were included. Leisure-time, work, and transport-related PA were classified as low (<120 min/wk) and moderate to high (>120 min/wk), an adaptation of the work by Holtermann et al.[35] Linear regression models were used to obtain effect sizes, with BMI as an outcome and PA domain as a predictor while adjusting for age, educational level, and socioeconomic status. Alcohol intake and smoking status were not included in the models since alcohol intake data for Soweto was not collected and the prevalence of smoking among Nanoro women was 0%.[36] We then aggregated the effect sizes of the associations between PA domain (as the predictor) and BMI (as the outcome) across the study sites using the fixed-effects model, assuming that the actual effect of PA on BMI was the same on all the sites. This enabled us to determine departure from this assumption as indicated by the I^2, which is a measure of heterogeneity.[37] Effect sizes in the meta-analysis are labeled as standardized mean differences by default since they were

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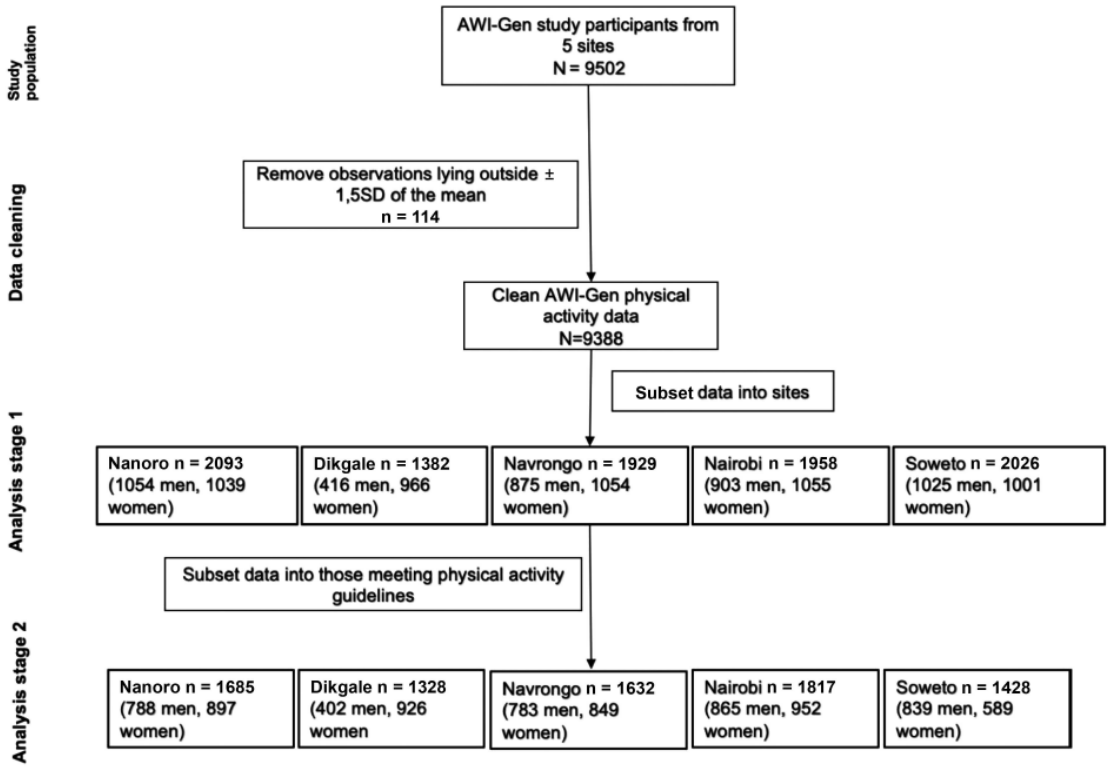

Figure 1 — Schematic presentation of data handling procedures for the analysis of the physical activity in 4 African countries. AWI-Gen indicates Africa-Wits-INDEPTH partnership for Genomic.

precalculated for each study while weight denotes the percentage weight that is attributed to each study by the model.[38]

Results

Characteristics of Study Participants

The median age of the study participants was 50 years for both men and women (IQR: 45, 55; Table 1). Education level was significantly different between men and women in all study sites except for Dikgale (rural South Africa). In all the study sites, BMI was higher in women than men except for Nanoro (rural Burkina Faso), where the median BMI was 21.1 kg/m^2 for men and 19.8 kg/m^2 for women. Women in Soweto (urban South Africa) had the highest median BMI (32.9 kg/m^2), while women in Nanoro had the lowest (19.8 kg/m^2). The median sitting time was 8 hours per day (IQR = 5.5; 11.5) among men and 7.7 hours (IQR = 5.5; 11.0) among women, and this difference was statistically significant ($P < .001$). More than 80% of the total sample of men (86.1%) and women (82.4%) met the weekly PA guidelines of at least 150 minutes of MVPA per week. This trend was consistent in all sites except Nanoro, where more women than men (86.3% vs 74.8%; $P < .001$) met the PA guidelines (Table 1).

Patterns of PA by Domain

Most of the PA time at all sites was spent on work and transport-related PA, with LTPA contributing the least to total MVPA (Figure 2). Transport-related PA accounted for most of the time spent in MVPA in Soweto and Nairobi men and women. However, there were sex differences in the PA domains in which most of the time was spent at the other sites. Thus, in Dikgale and Nanoro, women spent most of their time in work-related PA while men spent most of their time in transport-related PA. In Navrongo, women spent a similar amount of time in work and transport-related PA, while men spent most of their time in work-related PA (Figure 2).

Association Between Meeting PA Guidelines and BMI

Compared with not meeting guidelines, meeting PA guidelines of at least 150 minutes MVPA per week was significantly associated with lower BMI in Soweto and Nanoro men (Figure 3A), and in Nanoro and Dikgale women (Figure 3B). In the meta-analysis, this was associated with a 0.80 kg/m^2 lower BMI in the total sample of men (Figure 3A), and 0. 68 kg/m^2 lower BMI in the total sample of women (Figure 3B).

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Table 1 Background Characteristics of Participants in Sites From 4 African Countries

Variable	Combined AWI-Gen sites		Dikgale		Soweto		Nanoro		Navrongo		Nairobi	
Number of participants	Men (n = 4273)	Women (n = 4935)	Men (n = 416)	Women (n = 966)	Men (n = 1025)	Women (n = 1001)	Men (n = 1054)	Women (n = 1039)	Men (n = 875)	Women (n = 1054)	Men (n = 903)	Women (n = 1055)
Age, y	50 (45, 55)	50 (45, 55)	52 (45, 58)	52 (46, 58)	49 (44, 55)	49 (44, 54)	50 (44, 55)	50 (45, 55)	50 (46, 55)	52 (47, 56)***	48 (44, 53)	48 (44, 53)
SES quintiles, n (%)	$P < .001$		$P = .010$		$P < .001$		$P < .001$		$P < .001$		$P < .001$	
First quintile	466 (10.9)	876 (17.1)	76 (18.3)	106 (11.0)	25 (2.4)	207 (20.7)	136 (12.9)	202 (19.4)	134 (15.3)	216 (20.5)	95 (10.5)	145 (13.7)
Second quintile	725 (17.0)	1260 (24.6)	94 (22.6)	214 (22.2)	97 (9.5)	389 (38.9)	218 (20.7)	189 (18.2)	145 (16.6)	198 (18.8)	171 (18.9)	270 (25.6)
Third quintile	781 (18.3)	960 (18.8)	55 (13.2)	136 (14.1)	157 (15.3)	162 (16.2)	194 (18.4)	213 (20.5)	159 (18.2)	208 (19.7)	216 (23.9)	241 (22.8)
Fourth quintile	916 (21.4)	966 (18.9)	79 (19.0)	219 (22.7)	267 (26.0)	79 (7.9)	184 (17.5)	203 (19.5)	210 (24.0)	247 (23.4)	176 (19.5)	218 (20.7)
Fifth quintile	1383 (32.4)	891 (17.4)	112 (26.9)	290 (30.0)	479 (46.7)	9 (0.9)	320 (30.4)	227 (21.8)	227 (25.9)	184 (17.5)	245 (27.1)	181 (17.2)
Education level, n (%)	$P < .001$		$P = .125$		$P < .001$		$P < .001$		$P < .001$		$P < .001$	
No education	1734 (32.7)	1734 (32.7)	30 (7.2)	103 (10.9)	8 (0.8)	2 (0.3)	765 (72.9)	961 (93.3)	535 (61.3)	813 (77.5)	33 (3.7)	114 (10.8)
Primary	1510 (28.5)	2397 (38.0)	151 (36.3)	338 (35.7)	116 (11.5)	635 (81.0)	181 (17.2)	58 (5.6)	195 (22.3)	173 (16.5)	456 (50.5)	668 (63.3)
Secondary	1781 (33.6)	1211 (19.2)	219 (52.6)	480 (50.7)	738 (72.9)	146 (18.6)	87 (8.3)	9 (0.9)	116 (13.3)	54 (5.1)	392 (43.4)	269 (25.5)
Tertiary	282 (5.3)	93 (1.5)	16 (3.8)	26 (2.7)	150 (14.8)	1 (0.1)	17 (1.6)	2 (0.2)	27 (3.1)	9 (0.9)	22 (2.4)	4 (0.4)
Employment status, n (%)	$P < .001$		$P < .001$		$P < .001$		$P = .026$		$P = .054$		$P < .001$	
Employed	3439 (69.6)	3669 (59.7)	166 (41.0)	292 (30.9)	657 (64.9)	543 (54.6)	991 (98.4)	921 (99.5)	554 (63.7)	621 (59.4)	801 (96.9)	896 (90.8)
Unemployed	1505 (30.4)	2473 (40.3)	239 (59.0)	654 (69.1)	355 (35.1)	451 (45.4)	16 (1.6)	5 (0.5)	316 (36.3)	425 (40.6)	26 (3.1)	91 (9.2)
BMI category, n (%)**	$P < .001$		$P < .001$		$P < .001$		$P < .001$		$P < .001$		$P < .001$	
Underweight	722 (14.3)	563 (9.0)	82 (19.7)	33 (3.4)	105 (10.3)	6 (0.6)	182 (17.3)	322 (31.0)	165 (18.9)	138 (13.1)	106 (11.7)	41 (3.9)
Normal	3058 (60.4)	2300 (36.8)	247 (59.4)	203 (21.0)	452 (44.1)	112 (11.2)	717 (68.0)	645 (62.1)	644 (73.6)	709 (67.3)	569 (63.0)	347 (32.9)
Overweight	916 (18.1)	1353 (21.7)	74 (17.8)	248 (25.7)	288 (28.1)	216 (21.6)	130 (12.3)	59 (5.7)	56 (6.4)	161 (15.3)	179 (19.8)	332 (31.5)
Obese	369 (7.3)	2029 (32.5)	13 (3.1)	481 (49.8)	179 (17.5)	666 (66.6)	25 (2.4)	12 (1.2)	10 (1.1)	46 (4.4)	49 (5.4)	335 (31.8)
Meeting physical activity guidelines, n (%)	3677 (86.1)	4213 (82.4) ***	402 (96.6)	926 (95.9)	839 (81.9)	589 (58.8)***	788 (74.8)	897 (86.3)***	783 (89.5)	849 (80.6)***	865 (95.8)	952 (90.2)***
Total sitting hours												
median (Q1; Q3)	8 (5.5; 11.5)	7.7 (5.5; 11.0) ***	7.3 (5.5; 11.1)	7 (5.4; 12.0)	10 (7.0; 13.1)	9 (6.0; 12.0)	7.1 (5.0; 11.0)	8 (6.0; 10.2)*	6.8 (5.0; 9.4)	6.3 (5.0; 9.0)*	13 (8.0; 16)	12.2 (8.0; 17.0)
Proportion spending > 8 h sitting	2381 (51.4)	2620 (49.2)*	13 (40.6)	22 (44.9)	692 (67.9)	585 (58.7)***	507 (48.3)	569 (55.0)**	329 (36.5)	438 (40.3)	581 (75.8)	691 (75.4)

Abbreviations: BMI, body mass index; SAS, socioeconomic status.
*$P < .05$. **$P < .01$. ***$P < .001$.

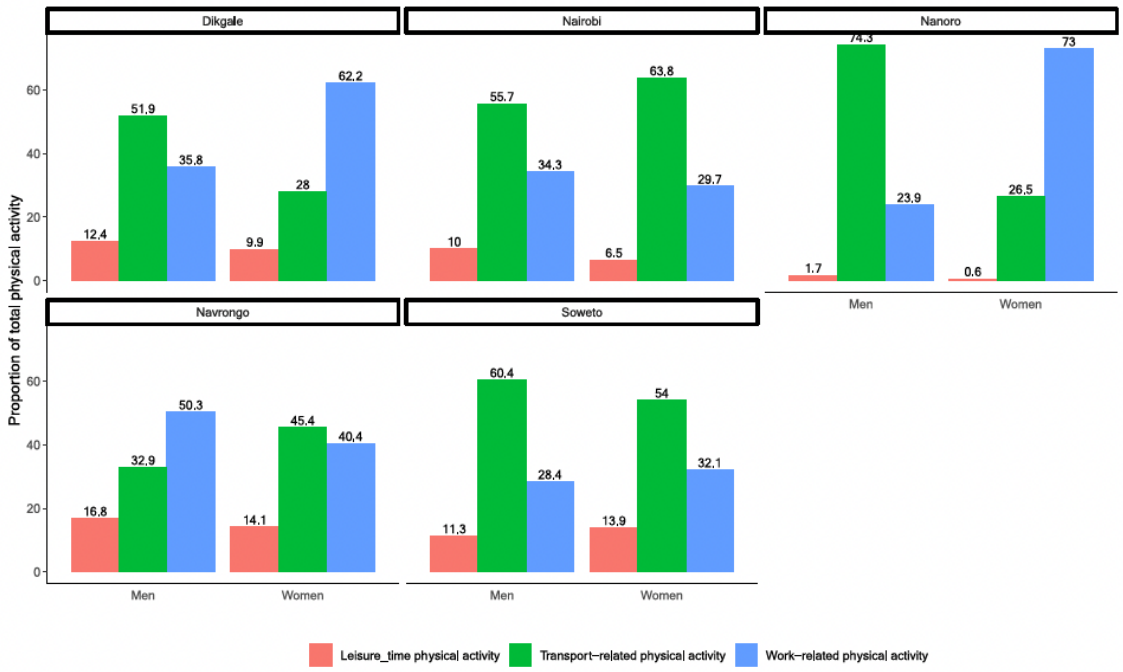

Figure 2 — The proportion of total MVPA spent on leisure, transport, and work-related physical activity among men and women in 5 study sites from 4 African countries. MVPA indicates moderate and vigorous physical activity.

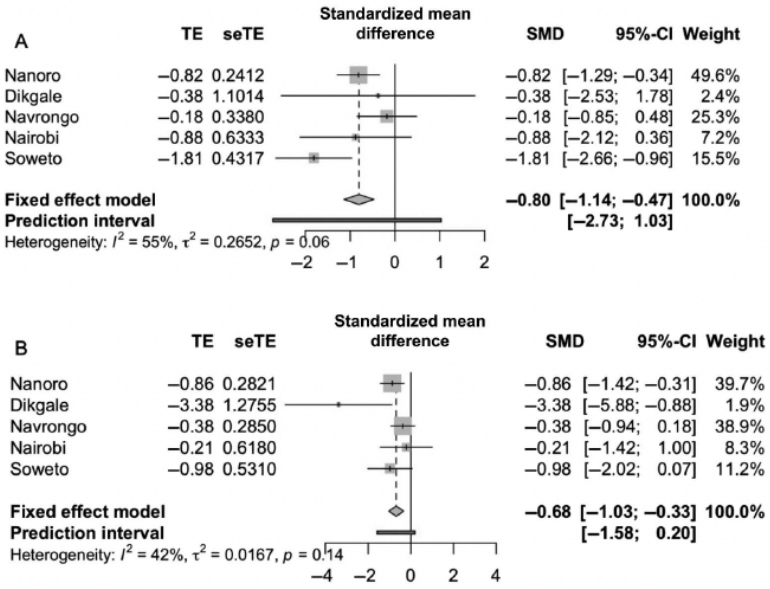

Figure 3 — Meta-analysis of the association between meeting physical activity guidelines and BMI in 6 sites in 4 African countries. (A) Site-specific meta-analysis in men and (B) site-specific meta-analysis in women. Models were adjusted for age, education, and socioeconomic status. BMI indicates body mass index; CI, confidence interval; TE, estimate; seTE, standard error of the estimate; SMD, standardized mean difference/effect size.

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Meta-Analysis of the Association Between Time Spent in Different Domains of PA With BMI in Men and Women Meeting PA Guidelines

Overall and at the different sites, among those meeting PA guidelines, there were no statistically significant associations between leisure-time PA and BMI in either men (Figure 4A) or women (Figure 4B). In the whole sample, BMI was significantly lower in men participating in moderate–high (>120 min/wk) transport-related PA (Figure 4C) and work-related (Figure 4E) PA compared with men participating in low (<12 min) PA within these domains.

In the different study sites, BMI was lower in Nanoro men who participated in moderate–high (>120 min) transport-related PA compared with their low-activity counterparts (Figure 4C). In addition, >120 minutes (moderate to high) of work-related PA in Navrongo men who met PA guidelines was associated with 0.76 kg/m^2 lower BMI compared with those who did <120 minutes (low work-related PA; Figure 4E). In Nanoro, when compared with women with <120 minutes work-related PA, women who did >120 minutes of work-related PA had 0.90 kg/m^2 lower BMI (Figure 4F) and in Nairobi women who met PA guidelines, moderate to high (>120 min) compared with low (<120 min) transport-related PA was associated with 2.34 kg/m^2 lower BMI (Figure 4D). In Nanoro, >120 minutes LTPA was associated with 2.91 kg/m^2 higher BMI compared with <120 minutes LTPA (Figure 4B) but less than 1% of the total MVPA was spent in LTPA in these women.

Discussion

Our study evaluated the association between self-reported PA and BMI in a large African cohort of middle-aged men and women from urban and rural sites in East, West, and South Africa. We found that although the prevalence of meeting PA recommendations was high (above 80%) in both men and women, it was higher in the men than the women (83.9% vs 80.5%). Time spent in work and transport-related PA contributed the most to total MVPA with leisure time PA contributing very little at the sites. Meeting PA guidelines was associated with lower BMI in the whole sample of men and women, and this was driven by men in West (Nanoro) and South Africa (Agincourt and Soweto) and women in West Africa (Nanoro) and South Africa (Dikgale). Moreover, among those meeting PA guidelines, >2 hours of work and transport-related PA were associated with lower BMI in men but not women and regional variations were observed.

The higher prevalence of men meeting PA guidelines compared with women and the majority of time spent in work (47.0%) and

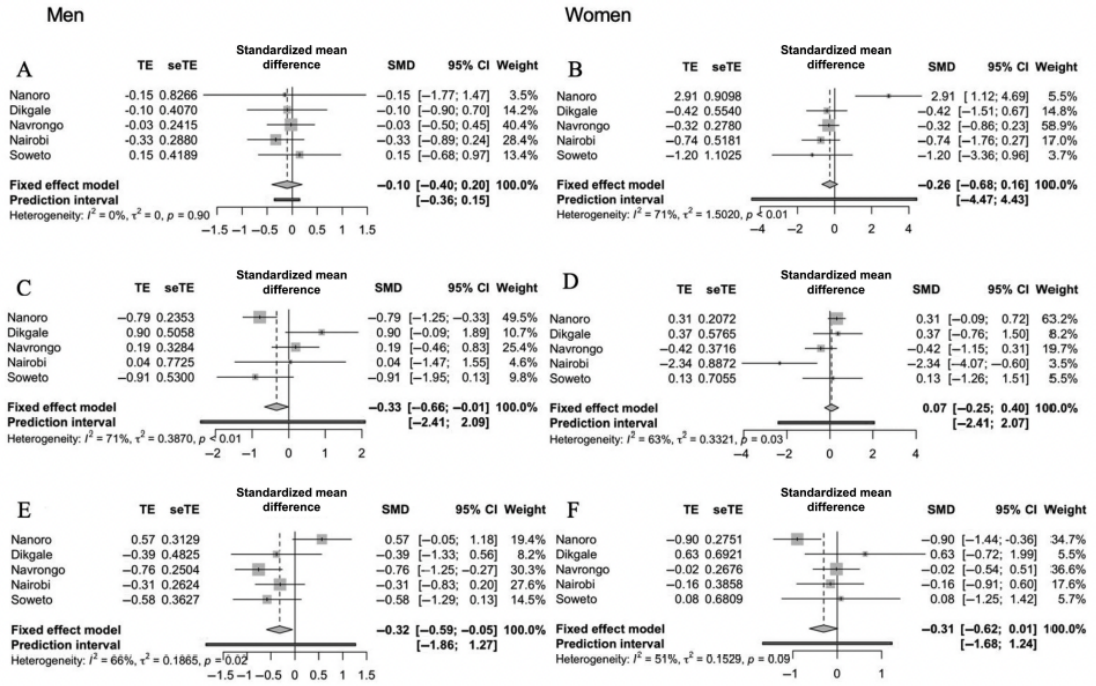

Figure 4 — Analysis of the association between domain-specific physical activity and BMI among men and women in 4 African countries. (A) Site-specific meta-analysis of leisure-related physical activity in men, (B) site-specific meta-analysis of leisure-related physical activity in women, (C) site-specific meta-analysis of transport-related physical activity in men, (D) site-specific meta-analysis of transport-related physical activity in women, (E) site-specific meta-analysis of work-related physical activity in men, and (F) site-specific meta-analysis of work-related physical activity in women. Models were adjusted for age, education, and socioeconomic status. BMI indicates body mass index; TE, estimate; seTE, standard error of the estimate.

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transport-related PA (43.5%) supports data from 22 African countries where 83.8% of men and 75.7% of women met the global World Health Organization PA guidelines, and the largest proportion of total PA was during work (48.6%) or transport (46.3%).[12] A comparison of domain-specific PA patterns in 104 countries also revealed higher work and transport-related PA in these domains in low-income compared with high-income countries.[8] Sex differences in PA participation, which were shown at all but one site in our study, have been corroborated using objectively measured PA in some of the same participants from the Soweto site.[39] Higher work and transport-related PA could arise from work in Africa typically involving manual labor. It is also possible that the transport cost may be too high for a significant proportion of the studied population. As a result, they opt to walk or use other means of nonmotorized transport, consistent with observations from an earlier study in Nairobi, where walking to work or using other nonmotorized means were the primary forms of transportation.[15,40]

We found that compared with not meeting guidelines, meeting PA guidelines were associated with 0.82 kg/m^2 lower BMI in men and 0.68 kg/m^2 lower BMI in women and site differences were also apparent. Meeting PA guidelines was associated with lower BMI only among men from 2 sites (Nanoro and Soweto) and women in 2 sites (Nanoro and Dikgale). Findings from studies in Africa have shown inconsistent results. While complying with PA guidelines of at least 150 minutes per week of MVPA was associated with lower BMI in a sample of younger Black South African women from urban Cape Town (26 [7] y old), no association was found in another study in a rural population of South African men (28.4 [17.6] y old) and women (40.1 [20.7] y old).[41,42] Therefore, these findings and observations from our study suggest that complex context-specific factors may confound the association between PA and BMI. These may include PA intensity, where PA performed at a higher intensity may be associated with lower BMI.[43] Conversely, higher BMI may be contributing to lower PA as observed in a Mendelian randomization study by Carrasquilla et al,[22] where higher MVPA was causal for lower BMI and at the same time higher BMI was causal for less PA. In addition, Kroesen and De Vos[23] found lower PA as a consequence of higher BMI.[22,23] Alternatively, depending on the stage of the epidemiologic transition, the domains contributing most to total MVPA and subsequent associations may differ.[15] For example, in our study of men and women in Soweto and Nairobi (urban sites) spent most of their time in transport-related PA while women in rural sites of Dikgale and Nanoro spent most of their time in work-related PA. Diet, obesity category, and other sociocultural, and genetic factors among participants in the different sites may also confound the association between PA and BMI.[44,45] In a study of obese and nonobese individuals, highly significant associations between PA and BMI in the obese but weak associations in nonobese individuals were apparent.[46] However, this does not seem to be the case in our study as the sites with the highest obesity prevalence do not necessarily show significant associations. Further inquiry is warranted to unpack possible reasons for these regional differences.

We also observed inverse associations between work and transport-related PA and BMI in the total sample of men but not women. Site-specific results showed inverse associations between BMI with transport-related PA in Nairobi women and men in Nanoro, where participants spent the most time in transport-related PA. These findings are corroborated in other studies where more transport-related PA has been reported in lean compared with overweight or obese men, and high use of active travel is generally associated with lower BMI.[15,47] Work-related PA was also associated with lower BMI in Navrongo men and Nanoro women in our study and these have the highest proportion of MVPA as work-related compared with the other sites. High work-related PA has been associated with lower obesity risk.[48,49]

This study was not without some limitations. First, it was a cross-sectional study of middle-aged adults; therefore, we can only report associations between PA and BMI and cannot infer causal relationships or comment on other age groups. The relationship between PA and BMI may be bidirectional, but this can only be validated by additional studies in this population. Second, we used self-reported PA measures, which are likely to result in over-reporting of PA. However, the GPAQ is helpful as a population-level PA surveillance tool as it has good validity compared with population surveillance data.[50,51] The strengths of our study include that we used a large sample size to determine the association of PA in the different domains with BMI in an African context.

Conclusions

We have demonstrated regional and sex-specific variation across 5 communities in 4 African countries in patterns of PA when assessing activity in work, travel, and leisure domains and their association with BMI. These results show that BMI varies significantly across regions and sexes, and PA alone may be insufficient to reduce BMI. There is, therefore, a need for more context-specific PA recommendations. Further inquiry into other factors not included in the study that may confound the association between PA and BMI is warranted since this was a cross-sectional study. It also remains to be determined what intensity and duration of different domains of PA offer the most significant benefits.

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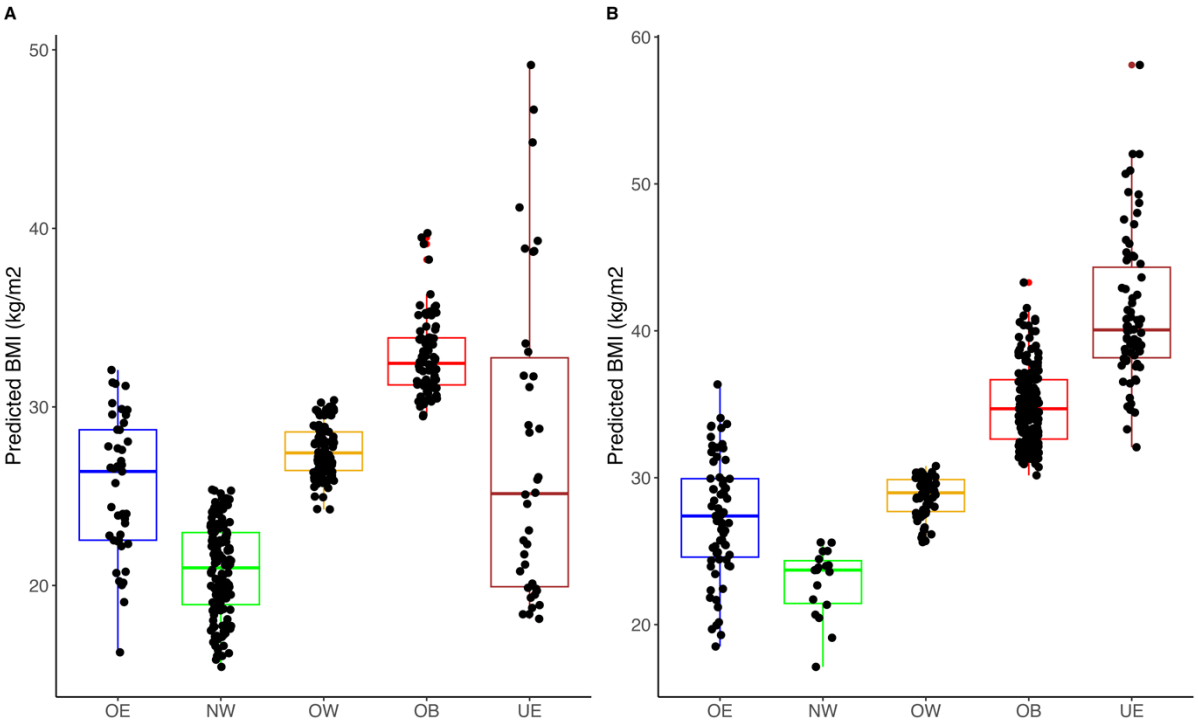
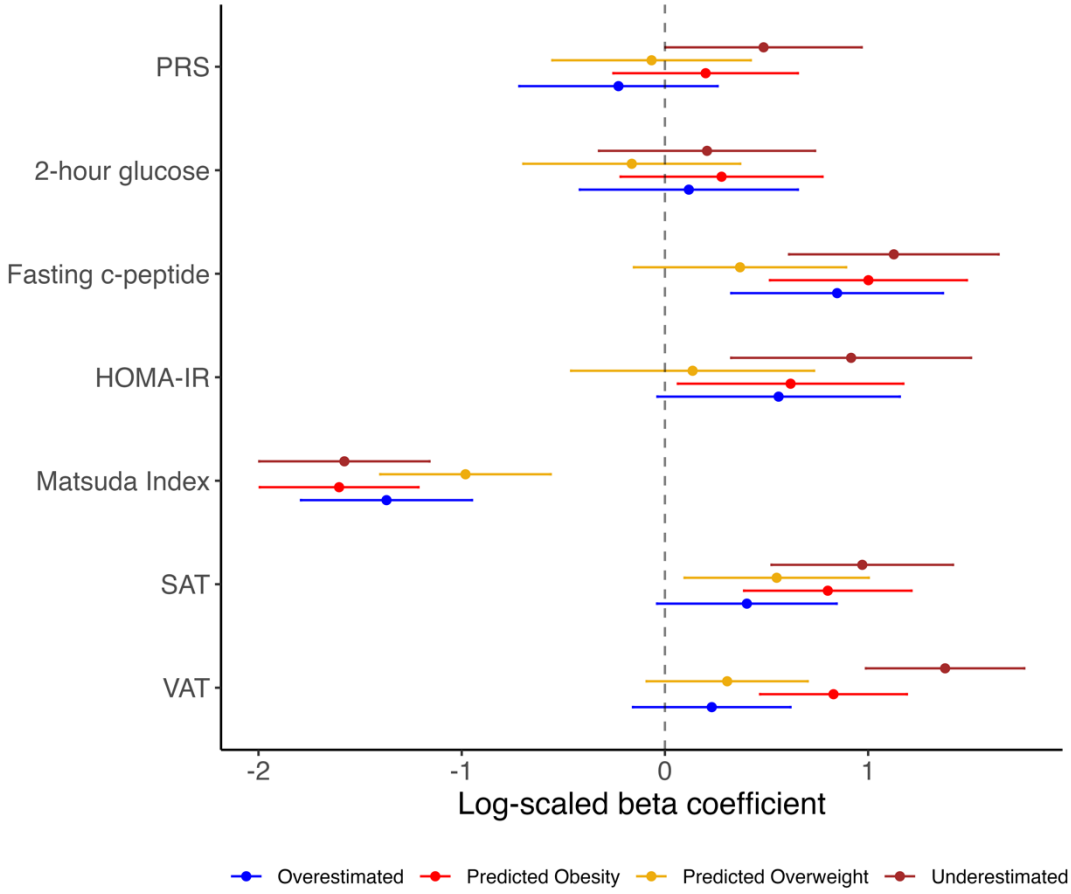
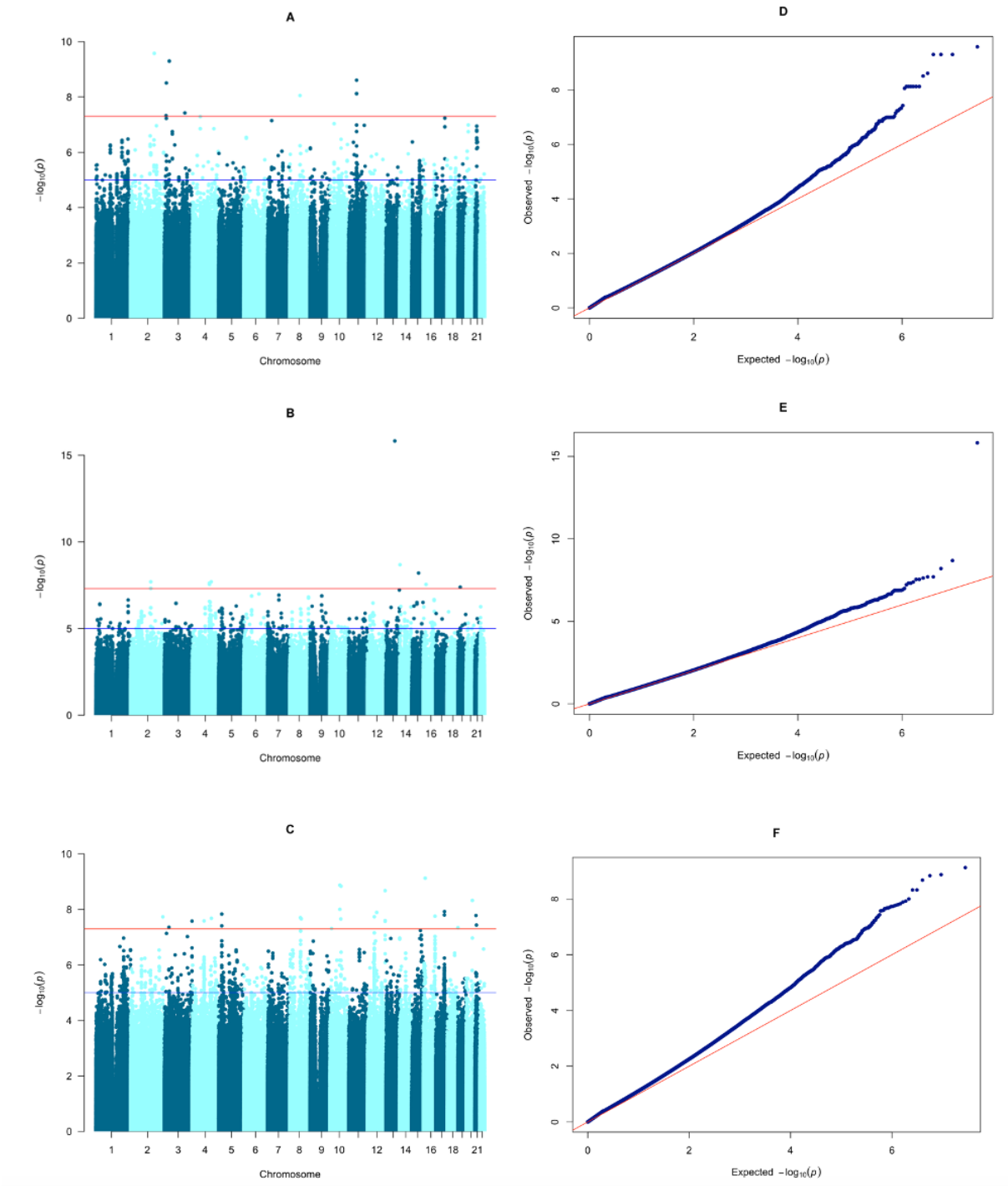
Appendix 2: Supplementary Figures



Supplementary Figure 1: Stratified analysis of the heterogeneity of BMI among adult Black men and women in Soweto, South Africa.
A. Boxplot of proteome-defined obesity classes in men. **B**. Boxplot of proteome-defined obesity classes in women. BMI was regressed on 14 proteins with age and sex as covariates. Residuals of the model were used to classify obesity into proteomic predicted BMI categories. Individuals with residuals (Actual BMI – Predicted BMI) > 1.0 kg/m^2 were classified as overestimated (OE), those with residuals < -1.0 kg/m^2 were underestimated (UE), the rest were classified according to their BMI as normal weight (NW) BMI < 25 kg/m^2), overweight (OW) (BMI 25 – 30kg/ m^2) and obese (OB) (BMI > 30 kg/m^2).



Supplementary Figure 2: Association of proteomic predicted BMI classes with glycaemic profiles, visceral adipose tissue and subcutaneous adipose tissue among in women in Soweto, South Africa.
Scaled BMI was regressed on 14 proteins with scaled age as a covariate. Residuals of the model were used to classify obesity into proteomic predicted BMI categories. Individuals with residuals (Actual BMI – Predicted BMI) > 1.0 SD were classified as overestimated (OE), those with residuals < -1.0 SD were underestimated (UE), the rest were classified according to their BMI as normal weight (NW) BMI < 25 kg/m^2), overweight (OW) (BMI 25 – 30kg/ m^2) and obese (OB) (BMI > 30 kg/m^2). Linear models were run with the proteomic-predicted BMI classes as the predictor and glycaemic profiles, visceral adipose tissue and subcutaneous adipose tissue levels as the outcome.



Supplementary Figure 3: Manhattan and qq plots showing vQTL results of BMI in three South African sites of the AWI-Gen study.
A, B, C: Manhattan plots for men, women and combined men and women respectively. D, E, F: qqplots for men, women and combined men and women respectively. Dots show the log-transformed p values of SNPs plotted against their physical positions. Horizontal lines depict the genome-wide significant (5x10e-08) and suggestive (1 x 10e-6) p value thresholds.

Appendix 3: Supplementary Tables

Supplementary Table 1: Model outputs for cross-sectional and longitudinal prs * sex interactions for BMI among adult men and women in Soweto, South Africa

Model	β	95% CI	p
Baseline (age, sex and 3 principal components used as covariates)			
PRS	1.36	0.9 1.8	1.15E-10
Sex:Men	-5.73	-8.0, -3.4	1.00E-06
PC1	-19.54	-47.8, 8.7	0.176
PC2	-25.07	-41.8, -8.4	0.003
PC3	14.63	-5.6, 34.9	0.157
Age	0.08	0.03, 0.1	0.003
PRS*Sex	-0.64	-1.2, -0.1	0.023
Longitudinal (age, sex, time to outcome and 3 principal components used as covariates)			
Sex:men	-5.37	(-7.801, -2.933)	< 0.001
PRS	1.51	(1.0, 2.0)	< 0.001
Age	0.07	(0.02, 0.1)	0.012
PC1	-26.83	(-55.7, 2.0)	0.069
PC2	-27.35	(-44.5, -10.2)	0.002
PC3	15.50	(-5.3, 36.3)	0.144
PRS*Sex	-0.69	(-1.3, -0.1)	0.029

Supplementary Table 2: Hazard ratios for severe obesity among adult men and women in Soweto, South Africa

	Hazard ratio	95% CI	P
Combined men and women (n= 1547, number of events=137)			
PRS Top 20%	2.98	1.75 - 5.07	5.33e-05
Age	0.98	0.94 - 1.02	0.306
Sex:Men	0.14	0.07 – 0.29	7.57e-08
PC1	1.60e-09	5.30e-20 – 48.30	0.100
PC2	2.94e-04	7.29e-09 – 11.84	0.133
PC3	21.46	3.57e-06 – 1.29e+08	0.700
Men (n= 806, number of events = 15)			
PRS Top 20%	1.13	0.24 – 5.37	0.878
Age	1.00	0.89 – 1.11	0.930
PC1	5.57e-23	3.92E-39 – 7.89e-07	0.007
PC2	9.48e+04	5.91E-12 – 1.52e+21	0.547
PC3	0.03	6.26E-21 – 1.19e+17	0.869
Women (n= 741, number of events= 122)			
PRS Top 20%	3.48	1.96 – 6.16	1.94e-05
Age	0.97	0.93 – 1.02	0.276
PC1	3.05E-08	1.26E-19 – 7.37e+03	0.196
PC2	3.26E-05	6.47E-10 - 1.64	0.061
PC3	59.13	3.13E-06 – 1.12e+09	0.633

*** Models were adjusted for age and 3 principal components**

Supplementary Table 3: Replication of the associations of plasma proteins with BMI in Soweto, South Africa.

The associations were observed in the Arivale cohort and validated in the TwinsUK cohort. Models were adjusted for age and sex.

	Watanabe et al., 2023			South Africa		
Variable	**β**	**SE**	**P**	**β**	**SE**	**P**
LEP	0.17	0.01	9.14e-204	3.61	0.14	< 2e-16
ADM	0.10	0.01	7.72e-74	3.85	0.54	2.83e-12
IL16	0.06	0.01	8.11e-25	2.56	0.44	6.92e-09
CD163	0.06	0.01	4.03e-23	1.00	0.42	0.016
SELE	0.06	0.01	9.18e-29	1.19	0.39	0.002
CSTB	0.05	0.01	9.73e-22	1.02	0.33	0.002
FABP4	0.14	0.01	8.12e-142	4.09	0.23	< 2e-16
LDL_recepto r	0.08	0.01	4.27e-47	1.97	0.33	3.34e-09
PON3	-0.09	0.01	8.08e-63	-2.08	0.23	<2e-16
IGFBP_1	-0.11	0.01	3.47e-102	-2.65	0.15	<2e-16
IGFBP_2	-0.09	0.01	1.75e-64	-3.44	0.22	<2e-16
SCGB3A2	-0.07	0.01	1.01e-35	-2.43	0.23	<2e-16
IL6	0.10	0.01	6.03e-77	1.31	0.25	1.35e-07
RAGE	-0.06	0.01	1.10e-24	-2.52	0.48	1.84e-07
CTSD	0.06	0.01	1.01e-29	0.25	0.41	0.536
FGF_21	0.06	0.01	3.97e-30	-0.14	0.14	0.337
TNFRSF10A	0.05	0.01	2.71e-18	-0.96	0.62	0.119
CCL3	0.05	0.01	4.86e-18	0.15	0.15	0.304

Supplementary Table 4: Model outputs for proteomic model used to derive proteomic score to predict glycaemic control and lipid profiles among adult men and women in Soweto, South Africa

Protein	β	SE	P
LEP	28.57	5.71	6.90e-07
ADM	1.84	0.17	< 2e-16
IL16	1.43	0.48	0.003
CD163	0.62	0.33	0.062
SELE	-0.09	0.33	0.777
CSTB	-0.22	0.30	0.481
FABP4	0.07	0.27	0.778
LDL_receptor	1.62	0.27	5.45e-09
PON3	-0.001	0.26	0.997
IGFBP_1	-0.36	0.18	4.59e-02
IGFBP_2	-0.77	0.18	2.23e-05
SCGB3A2	-0.64	0.26	1.23e-02
IL6	-0.62	0.19	9.25e-04
RAGE	0.61	0.19	1.34e-03

Multiple R-squared: 0.6731, Adjusted R-squared: 0.6673

Supplementary Table 5: Details of lead SNPs in vQTL analysis in adult South African men and women from three sites of the AWI-Gen study

SNP	EFFECT/OTHER ALLELE	MAF	P	Nearest gene	Functional consequence
rs111574093	T/C	0.0482902	1.85E-08	AC010149.4	None
rs62243257	C/T	0.0447668	4.39E-08	RP11-384L8.1	Intergenic vari
rs113120944	C/T	0.0671503	2.64E-08	LRCH3	Intron variant
rs434193	T/C	0.305803	2.60E-08	ARHGAP24	none
rs1135220	G/T	0.0851813	2.10E-08	PCDH18	3'-UTR
rs113100337	A/T	0.0536788	1.47E-08	CDH12	Intron variant
rs148598174	C/T	0.0406218	1.99E-08	RP11-697M17.2	Intergenic vari
rs111968788	G/A	0.0236269	2.18E-08	FABP9	Intron variant
rs3780864	A/G	0.139793	4.89E-08	NUDT5	Intron variant
rs191095294	G/A	0.0518135	1.34E-09	NPFFR1	Intergenic vari
rs1907724	G/A	0.317927	2.21E-08	KCNMA1	Intron variant
rs112127932	G/A	0.0249741	1.46E-09	RP11-90J7.3	Intron variant
rs72644851	G/A	0.178031	1.84E-08	RP11-370I10.6	Intron variant
rs527747185	T/C	0.0474611	1.28E-08	none	Intron variant
rs145685185	G/C	0.0435233	2.12E-09	RP5-916L7.1	none
rs71201219	G/A	0.5	0	RP11-521J24.1	none
rs12926383	G/A	0.0334715	7.47E-10	ERCC4	none
rs111878101	A/G	0.0242487	1.76E-08	HSBP1	none
rs576646720	G/A	0.0434197	1.59E-08	TANC2	Intron variant
rs143604086	C/T	0.0205181	1.20E-08	CSH2	none
rs181243564	T/C	0.0302591	4.55E-08	CTDP1	intronic
rs79835532	A/G	0.0615544	4.75E-09	KCNS1	3'-UTR
rs189338615	C/G	0.0249741	1.66E-08	AP000946.2	none
rs557505940	G/T	0.0289119	3.67E-08	LOC105372747	Intron variant
rs6716374	G/C	0.0730864	2.65E-10	CERS6	Intron variant
rs77545481	A/G	0.037037	4.72E-08	-	none
rs377191158	G/A	0.0328395	3.13E-09	IQSEC1	Intron variant
rs188275749	T/A	0.0009875	5.06E-10	AC018359.1	Intron variant
rs530555441	C/T	0.0197531	3.78E-08	PLSCR2	Intron variant
rs562121913	G/A	0.0335802	8.87E-09	-	-
rs3016751	G/A	0.022963	2.47E-09	LOC105369309	Intergenic vari
rs73961888	T/A	0.0173214	2.03E-08	AC079584.2	Intron variant
rs116350023	T/C	0.0342857	2.40E-08	RP11-93L9.1	Intron variant
rs34275365	C/T	0.0151786	2.02E-08	AC093875.1	Intergenic vari
rs71201219	G/A	0.666667	1.53E-16	RP11-521J24.1	-

CHR: chromosome, MAF: minor allele frequency, P: p value. The - sign depicts no data available.

Appendix 4: Declaration of Student's contribution to article and agreement of co-authors

Declaration: Student's contribution to article(s) and agreement of co-author(s)

I, Monica Muti, student number 2179043, declare that this Thesis is my own work and that I contributed adequately towards research findings published in the article stated below which is included in my Thesis.

Signature of Student ..... **Date** 16 November 2023

Name of Primary Supervisor Dr Tinashe Chikowore

Signature of Primary Supervisor ..... **Date** 28 February 2024

Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article(s) by the student as part of his/her Thesis/Dissertation/Research Report. In cases where the student is not the 1st author of a published article, the primary supervisor must explain (under comments) why the student is entitled to use the paper for his/her degree purposes.

Article 1: Title: Physical activity and its association with BMI: A cross sectional analysis in middle-aged adults

Journal name, year, volume and page numbers: J Phys Act Health 2023

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12th author	Shane A. Norris	Shane A Norris	19 Feb 2024
13th author	Tinashe Chikowore		28 Feb 2024

Comments by primary supervisor:

.....

.....

Declaration: Student's contribution to article(s) and agreement of co-author(s)

I, Monica Muti, student number 2179043, declare that this Thesis is my own work and that I contributed adequately towards research findings published in the article stated below which is included in my Thesis.

Signature of Student ..... **Date** 18 February 2024

Name of Primary Supervisor Dr Tinashe Chikowore

Signature of Primary Supervisor ..... **Date** 28 February 2024

Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article(s) by the student as part of his/her Thesis/Dissertation/Research Report. In cases where the student is not the 1st author of a published article, the primary supervisor must explain (under comments) why the student is entitled to use the paper for his/her degree purposes.

Article 2: Title: Polygenic prediction of BMI in South Africans of African Ancestry

Journal name, year, volume and page numbers: Still to be published

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Comments by primary supervisor:

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Declaration: Student's contribution to article(s) and agreement of co-author(s)

I, Monica Muti, student number 2179043, declare that this Thesis is my own work and that I contributed adequately towards research findings published in the article stated below which is included in my Thesis.

Signature of Student ..... **Date** 18 February 2024

Name of Primary Supervisor Dr Tinashe Chikowore

Signature of Primary Supervisor ..... **Date** 28 February 2024

Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article(s) by the student as part of his/her Thesis/Dissertation/Research Report. In cases where the student is not the 1st author of a published article, the primary supervisor must explain (under comments) why the student is entitled to use the paper for his/her degree purposes.

Article 3: Title: Gene-lifestyle interactions for BMI as a measure of obesity in black South Africans

Journal name, year, volume and page numbers: Still to be published

Authors	Name	Signature	Date
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6th author	Shane A. Norris		28 February 2024
7th author	Tinashe Chikowore		28 February 2024

Comments by primary supervisor:

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Appendix 5: Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Ms M Muti; Dr L Ware; Professor SA Norris

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M210166

NAME: **(Principal Investigator)**	Ms M Muti; Dr L Ware; Professor SA Norris
DEPARTMENT:	School of Clinical Medicine Department of Paediatrics and Child Health Medical School University
PROJECT TITLE:	*Relationship of diet and physical activity with genetic susceptibility to obesity: a lontitudinal analysis in adults in South Africa*
DATE CONSIDERED:	Ad hoc
DECISION:	Approved unconditionally
CONDITIONS:	Sub-study under M160604 and M170880
SUPERVISOR:	Dr T Chikowore
APPROVED BY:	CB Penny Dr CB Penny, Chairperson; HREC (Medical)
DATE OF APPROVAL:	2021/02/11

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **«Missing mail merge field»** and therefore reports and re-certification will be due in the month of **«Missing mail merge field»** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator Date