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Rohan Shah

Comparative Analysis of Type 2 Diabetes Pathophysiology Across Multiple Ethnicities

By

Rohan Shah
Master of Public Health

Hubert Department of Global Health

Lisa Staimez, PhD, MPH
Assistant Professor, Hubert Department of Global Health
Rollins School of Public Health
Emory University
Committee Chair

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By

Rohan Shah
Bachelor of Science in Clinical Neuroscience
Virginia Polytechnic Institute and State University
2019

Thesis Committee Chair: Lisa Staimez, PhD, MPH
Assistant Professor, Hubert Department of Global Health
Rollins School of Public Health
Emory University

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Abstract

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By Rohan Shah

Purpose: Type 2 diabetes is a complex chronic disease that develops under different conditions of risk globally. Heterogeneity in diabetes pathophysiology will be examined by comparing several high-risk populations across a wide spectrum of BMI and by examining the relative contributions of insulin resistance and β-cell function on diabetes pathophysiology across these populations, with particular emphasis on African and Asian Indian populations.
Methods: Participants were from four different cohorts without known diabetes: Asian Indian (n=1750), African-born blacks living in America (African immigrants, n=523), Mixed ancestry South African (n=1112), and African Americans (n=185). All participants had a 75g oral glucose tolerance test, with glucose and insulin measured at 0 and 120 minutes, and glucose and insulin at 30 minutes was additionally measured in Asian Indians, African immigrants, and African Americans. Participants were classified on glycemic status based on the American Diabetes Association criteria cutpoints. Key measures of insulin resistance (HOMA-IR: ([$insulin_{t0}$ x $glucose_{t0}$]/ 22.5)) and β-cell function (insulinogenic index: ([($insulin_{t30}$ - $insulin_{t0}$) / ($glucose_{t30}$ - $glucose_{t0}$)]) were calculated and compared between ethnicities by ANOVA and logistic regression.
Results: SA-Mixed ancestry were the oldest (mean 45.6 ± SD 13.8, Asian Indians: 38.9 ± 10.8 years; African immigrants 38.5 ± 10.3 years; African Americans 34.5 ± 7.8 years). African Americans had the highest BMI (mean 34.5 ± SD 7.8 kg/m^2; SA-Mixed ancestry 28.6 ± 8.2; African immigrants 27.7 ± 4.5; Asian Indians 25.8 ± 4.9). Fasting glucose adjusted for age, sex, and BMI was highest in Asian Indians (mean 101.2 mg/dL ± SE 0.6; African immigrants 92.3 ± 1.1; SA-Mixed ancestry 89.9 ± 0.7; African Americans 86.6 ± 1.8). Adjusting for age, sex, and BMI, Asian Indians were the most insulin resistant (HOMA-IR 2.3 ± SE 0.1; SA-Mixed ancestry 2.1 ± 0.1; African immigrants 1.6 ± 0.1; African Americans 1.6 ± 0.2) and had the poorest insulin secretion (Insulinogenic Index 0.8 pmol/mmol ± SE 1.0; African immigrants: 1.4 ± 1.0; African Americans: 1.4 ± 1.1). Among prediabetes subtypes Asian Indians had predominately impaired fasting glucose (iIFG: Asian Indians 17.3%; SA-Mixed ancestry 6.2%; African immigrants 4.8%; African Americans 2.7%), whereas African subgroups had predominately impaired glucose tolerance (iIGT: African immigrants 20.7%; African Americans 20.5%; SA-Mixed ancestry 9.8%; Asian Indians 3.2%) .The odds of prediabetes versus normoglycemia after adjusting for age, sex, and BMI was lowest in African immigrants (OR insulinogenic index: 0.36, 95% CI: 0.26, 0.49; Asian Indians 0.49, 95% CI: 0.42, 0.57; African Americans 0.45, 95% CI: 0.27, 0.74).
Conclusion: In the early natural history of disease, heterogenous pathways of disease development seem to be present among the four populations. Asian Indians have poor insulin secretion, as do African immigrants, but the pathways leading to impairments in insulin secretion may vary across mechanisms related to glucose tolerance rather than maintenance of basal glucose. The compensation for hyperglycemia may be greater in SA-Mixed ancestry who had varying levels of insulin resistance compared to the other populations. African Americans appear to have improved β-cell function even in the presence of insulin resistance.

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Introduction

Globally, diabetes mellitus (DM) is a public health pandemic as the burden continues to rise causing a large impact on the daily lives of many individuals and communities. It is estimated that 537 million individuals ages 20 – 79 are living with diabetes as of 2021, a meteoric rise from an estimated 151 million individuals in 2000 (International Diabetes Federation, 2021). Additionally, 80% of diabetes cases are in low- and middle-income countries (International Diabetes Federation, 2021). Diabetes continues to be a population-level problem across multiple regions around the world. The countries with the highest prevalence of diabetes include China, India, Pakistan, United States, and Indonesia (International Diabetes Federation, 2021). Epidemiologic trends indicate growth in the prevalence amongst island nations in the Pacific Ocean and Southeast Asian countries over the past 20 years (Khan et al., 2020). Additionally, Africa has the highest percentage of individuals with undiagnosed diabetes, with lack of reliable of data making it difficult to estimate the overall prevalence (International Diabetes Federation, 2021).

Type 2 diabetes accounts for about 90% of all diabetes cases worldwide (Kotwas et al., 2021). The global burden of disease (GBD) is measured in disability-adjusted life-years (DALYs) which quantify the relative magnitude of healthy life that is lost associated with a specific injury or disease (Salomon, 2014). In 2017 the DALYs for type 2 diabetes were 751 per 100,000, which was seventh highest among all causes tracked (Khan et al., 2020). There are several risk factors associated with type 2 diabetes including family history of diabetes, high body mass index (BMI), limited physical activity, smoking, and poor diet (Wu et al., 2014). Type 2 diabetes is a chronic condition where the body has abnormal high levels of glucose in the blood. The pancreas contains islet beta β-cell function which are responsible for the production

and release of hormonal insulin. When the body detects higher levels of glucose, insulin is released in response with the goal of keeping glucose levels at the proper physiological state (Galicia-Garcia et al., 2020). However, the beta cells can have impaired function when blood glucose levels creep up into high concentrations, as occurs in prediabetes and type 2 diabetes. Dysglycemia is caused by two factors: poor insulin sensitivity (i.e., insulin resistance) and poor insulin secretion (i.e., β-cell dysfunction).

Insulin resistance can be defined as the decreased ability of cells in the liver, fat, and muscles to respond to insulin, decreasing the body's ability to uptake glucose (Galicia-Garica et al., 2020). The development of insulin resistance can be a precursor to developing type 2 diabetes over time. In patients with type 2 diabetes, a prolonged hyperglycemic state can lead to the pancreas being unable to produce enough insulin to overcome the weak response of the cells (Galicia-Garica et al., 2020). Obesity, physical inactivity, and older age are risk factors for diabetes that are associated with insulin resistance (Amati et al., 2009). Insulin resistance is present in the early phase of diabetes leading to impaired glucose tolerance among patients (Goldstein, 2002). Poor insulin sensitivity due to insulin resistance is just one factor affecting dysglycemia.

The other factor relating to type 2 diabetes development is poor insulin secretion. In β-cell dysfunction insulin secretion is impaired, and a hyperglycemic state over time can lead to impaired β-cells. Due to the very narrow physiological range healthy of blood glucose concentration, any impairment in the pathway over a prolonged period can greatly affect β-cell function and worsen the state of hyperglycemia in the body. The loss of β-cell mass due to β-cell dysfunction, functional defects, or both play a role in the pathway leading to Type 2 diabetes (Cho et al., 2010). A previous study of European patients found a reduction of 39% in average

β-cell mass among patients with type 2 diabetes compared to matched controls (Rahier et al., 2008). Another study concluded that β-cell mass decreased in patients with type 2 diabetes due to apoptosis (Butler et al., 2003). If β-cells are unable to compensate for the loss of mass and apoptosis β-cell dysfunction continues (Cerf, 2013). While β-cell dysfunction can be a long-term process, with many patients not exhibiting or recognizing symptoms as the disease progresses, it plays a large role in type 2 diabetes development (Cerf, 2013).

The traditional paradigm for the development of Type 2 diabetes has been recognized as a combination between environment, lifestyle, and genetic factors (Murea et al., 2012). The paradigm follows the two-step model which states a shift from normal to impaired glucose tolerance is caused mainly by insulin resistance, while the shift from impaired glucose tolerance to type 2 diabetes is driven by β-cell dysfunction (Saad et al., 1991). The conventional thinking is to maintain normoglycemia, the body increases insulin production due to insulin resistance. Over time, the β-cells in the pancreas are strained and not able to produce enough insulin to overcome the insulin resistance leading to the development of type 2 diabetes long-term (DeFronzo et al., 1992). This stepwise process characterizes type 2 diabetes development in one approach, but recent research indicates a potential shift in the model.

While this traditional paradigm has been the conventional thinking, there has recently been a shift to examining if heterogeneity is present in the development of diabetes. Heterogeneity in disease pathways relates to which pathway (insulin resistance or β-cell dysfunction) is the dominant pathway in disease development (Tumoi et al., 2014). This challenges the traditional paradigm as β-cell dysfunction may have a larger primary role in diabetes development, especially in the early phase of disease (Gerich, 2003). The variations in mechanisms are connected to certain individuals who present with unique phenotypes, which

may not be captured by the traditional paradigm (Ahlqvist, 2018). Understanding the heterogeneity in disease development and progression, especially among non-traditional phenotypes may help to better understand diagnosis and treatment for different groups.

Most prior research has focused on individuals who are obese, physically inactive, and live sedentary lifestyles or those with a familial history of type 2 diabetes (Olokoba et al., 2012). A previous study found that the risk of type 2 diabetes was doubled in patients with higher abdominal obesity (Freemantle et al., 2008). Another study of patients in the United States found a strong and independent association between BMI and risk of type 2 diabetes (Ganz et al., 2014). While the increased risk for type 2 diabetes in individuals with higher BMI is known, there is an assumption that those with low BMI are at low risk. In contrast, Asian Indians, who normally exhibit a thin BMI phenotype, have a high prevalence of diabetes (Staimez et al., 2019). When evaluating diverse populations, conventional factors like BMI do not account for the high burden of disease in some countries (Dagenais, 2016). Additionally, recent studies amongst multi-ethnic normal weight populations suggest a large prevalence of cardiometabolic abnormalities among various populations, indicating a need to investigate further among groups, especially different ethnic groups, who may screen normal under conventional risk factors (Gujral et al., 2017). There is a paucity of research across minority populations or wide BMI spectrum to better understand the risk for those with specific phenotypes.

In Asian Indians a high prevalence of type 2 diabetes is seen compared to other ethnic groups despite being having a thin BMI phenotype (Staimez et al., 2019). Asian Indians also have been found to have high basal insulin levels without obesity and adverse fat distribution seen as primary drivers, indicating there may be other factors related to insulin resistance among the group (Mohan et al., 1986; Dowse et al., 1993). In younger South Asian men with relatively

low insulin resistance, a study found poor insulin secretion as a driver to diabetes development (Narayan et al., 2021). Analysis of data for Asian Indians suggests poor insulin secretion, especially in the early phase of disease as a significant pathway of disease development (Staimez et al., 2019). While findings in disease development Asian Indians are well characterized there are other groups that needs further research, including populations of African descent, who have a higher prevalence of type 2 diabetes compared to European and white populations (Marshall, 2004; Rodriguez et al., 2017; Goedecke et al., 2020).

Among those with African descent there are several different populations: Native Africans currently residing in Africa, African-born Blacks who are now living in the United States, and African Americans born in the United States. Previous studies in African born Blacks living in United States found β-cell failure as a primary driver in abnormal glucose tolerance (Ishimwe et al., 2021). In a subset of native Africans over three years there was an increase in worsening glucose tolerance among the cohort of mixed ancestry South Africans (Matsha et al., 2012). Analysis of participants with impaired fasting glucose comparing Ghanaians in Ghana versus migrant Ghanaians found insulin resistance as a major driver compared to β-cell dysfunction (Meeks et al., 2017). The differences in results from the various studies highlight the need for further investigation into the disease development among populations of African descent.

Measures such as glucose tolerance, plasma insulin, and anthropometric measures can be used to compare degrees of insulin resistance and β-cell dysfunction. This study seeks to explore the relative degree of insulin resistance and β-cell dysfunction contributes to the pathophysiology of diabetes among various African populations, compared to the Asian Indian population which have well characterized β-cell function.

Literature Review

Traditional Paradigm of Type 2 Diabetes

There are several key organs involved in the mechanism of type 2 diabetes development, including but not limited to, the pancreas, liver, muscles, brain, and kidneys (DeFronzo, 2009). The traditional paradigm of type 2 diabetes development suggests that individuals have genes or risk factors which make their tissues more prone to insulin resistance. In response β-cell produce insulin to meet the demand for glucose lowering. However, over time exhaustion of β β-cells can lead them to fail, and individuals are unable to produce enough insulin to reduce glucose levels leading to the development of type 2 diabetes (DeFronzo et al., 1992). A previous study of Pima Indians proposes two models in the development of disease: insulin resistance in the transition from normal glucose tolerance to impaired glucose tolerance and β-cell dysfunction in the transition from impaired glucose tolerance to diabetes (Saad et al., 1991). More recent studies have postulated similar models for type 2 diabetes disease development. Insulin resistance in the liver leads to an overproduction of glucose and insulin resistance in the muscles leads to impaired glucose uptake, causing a state of increased glucose. As β-cells become unable to produce enough insulin to compensate for the insulin resistance, β-cell dysfunction occurs leading to a rise in fasting plasma glucose and the onset of recognizable type 2 diabetes (Defronzo 2009, Galicia-Garcia et al. 2020).

Genetic differences present between ethnic groups contribute to the variation in the shift from normal glucose tolerance (NGT) to impaired glucose tolerance (IGT) to type 2 diabetes (Abdul-Ghani et al., 2007), as well as the shift from NGT to impaired fasting glucose to type 2 diabetes (Staimez et al., 2013). Insulin resistance occurs in greater than 85% of all patients with Type 2 diabetes, coupled with progressive β-cell dysfunction which drives the shift from NGT to

Type 2 diabetes (Del Prato et al., 2009). Previous cross-sectional studies have found that on average patients with IGT have higher rates of obesity and increased insulin resistance compared to patients with NGT (Weyer et al., 1999). Additionally, environment and lifestyle factors are widely recognized as contributing to the traditional paradigm of Type 2 diabetes development (Galicia-Garcia et al., 2020). While the traditional paradigm of Type 2 diabetes has been largely studied, there is increasing evidence that multiple paradigms can explain disease development.

Heterogeneity in Type 2 Diabetes

Heterogeneity of disease development requires a new way of examining and treating disease processes that recognize diversity across human populations, resulting from a different set of biological and environmental factors that impact the development of this complex chronic disease. Biological, social, environmental, genetic, lifestyle, and clinical factors all play a role in insulin resistance and ß-cell dysfunction contribute to the development of Type 2 diabetes (Redondo et al., 2020). However, there is still a more research needed on the social, environmental, and genetic factors in the disease development of type 2 diabetes and associations with different ethnic populations (Ali et al., 2016).

Studies comparing a diverse set of populations have suggested heterogenous pathways are present in the development of Type 2 diabetes. Those with diabetes have different characteristics than can affect disease development. One study compared the physiologic response in a large sample of Pima Indians in the United States (n=865) and Asian Indians from Chennai, India (n=2374) both groups with a high prevalence of type 2 diabetes and who are phenotypically different. Pima Indians generally have higher amounts of obesity and insulin resistance among their population, while Asian Indians generally have a lower BMI indicating a more lean/thin phenotype. Poor insulin secretion was found in Asian Indians while high insulin

resistance was found in Pima Indians indicating differences in mechanisms of disease for each group in the early course of diabetes (Staimez et al., 2019). A recent study found in young non-obese South Asian men a higher incidence of diabetes compared to Pima Indian men. In obese South Asians the incidence of diabetes was like Pima Indians. These findings suggest differences in diabetes development among Asian Indians and Pima Indians, despite high incidence of diabetes among the groups (Narayan et al., 2021).

In African populations, there is limited data available examining various phenotypes and heterogeneity in disease manifestation. The continent of Africa is considered to have the highest genetic heterogeneity, with environmental and clinical exposures that are not found in other areas (Kibirigie et al., 2019). Previous studies in Northern Ethiopia found a lower mean age and median BMI among patients with diabetes which does not fit the conventional wisdom of older and obese patients (Gill et al., 2011). Another study identified a high prevalence of insulin resistance and reduced insulin secretion among a small group of Nigerians with type 2 diabetes compared to controls. While these results may be seen as significant, most patients were obese and the sample was not representative (Oli et al., 2009). A study of non-obese participants native to Ghana found patients with impaired fasting glucose and type 2 diabetes associated with insulin resistance and beta cell dysfunction. Due to the cross-sectional nature of the study, researchers were unable to identify predictors of impaired fasting glucose and type 2 diabetes among the population (Amoah et al., 2002). These studies focused on single populations within Africa, but each showed different mechanisms for disease development of type 2 diabetes that should be studied further.

In African Americans, there is also conflicting and limited data available to understand the variations in the pathways of disease development in type 2 diabetes. A study comparing

African American and White women found that African Americans had lower insulin sensitivity independent of obesity, fat distribution, or inflammation (Hyatt et al., 2009). Another study comparing non-Hispanic Whites, African Americans, South Asian, and East Asian participants found similar levels of insulin resistance in Whites and African Americans, and higher levels of insulin resistance among the Asian populations after adjusting for BMI (Raygor et al., 2020). The discrepancies in understanding the level of insulin resistance driving disease development may be due to differences in methodology of studies, or alternatively may be due to the inherent differences in pathways leading to diabetes. Understanding the differences in disease development in African Americans compared to other ethnic groups can help to provide a better foundation for mechanistic targets for future research, targets that may eventually impact tailored guidelines for diabetes prevention, diagnosis, and treatment, instead of relying on the current standard guidelines used for all individuals that do not account for important population differences in risk factors or disease pathogenesis.

Current Findings in Asian Indians

Type 2 diabetes continues to be a large global health issue in India, which has the second largest population with about 74.2 million individuals with diagnosed diabetes (International Diabetes Federation, 2021). This is a significant increase from 10 years prior, when an estimated 61.3 million individuals had diagnosed diabetes in India (International Diabetes Federation, 2011). Asian Indians may have some inherent levels of type 2 diabetes risk irrespective of country of residence. Comparisons of Asian Indians to various populations in other countries have shown that Asian Indians have a higher risk of diabetes. For example, a study of Asian Indians who had immigrated to the United States who were randomly selected from seven different urban sites. They found a prevalence rate of type 2 diabetes of 17.4%. The prevalence

was much higher than the comparison data from the American Diabetes Association and Centers for Disease Control for non-Hispanic whites (7.8%) and non-Hispanic blacks (13%) (Misra et al., 2009). Another population-based study in California known as the Mediators of Atherosclerosis in South Asians Living in America (MASALA) study, found an even higher prevalence rate of diabetes (29%) among Asian Indians participants (Kanaya et al., 2010). The prevalence type 2 diabetes among Asian Indians living in Chennai, India (25.2%) was also higher compared to non-Hispanic Whites (13.1%), non-Hispanic blacks (15.1%), and Hispanics (16.2%) participants from the National Health and Nutrition Examination Survey (NHANES) in the United States (Gujral et al., 2016). The high prevalence of diabetes among Asian Indians, despite location indicates there may be a specific phenotype associated with the ethnicity making it more prone to developing type 2 diabetes.

Along with overall prevalence, Asian Indians have been seen to have high prevalence on type 2 diabetes at lower BMI. Asian Indians are "thin-fat" with greater body fat composition, but lower muscle mass compared to Caucasians or Africans (Joshi, 2012). A review by Gujral et al. (2013) found that when defined by BMI, Asian Indians have lower rates of obesity, but a higher amount of central obesity defined by large waist circumferences and waist to hip ratios. One study compared Asian Indian participants from Chennai, India and MASALA study participants from the United States found a higher prevalence of diabetes amongst normal BMI participants from Chennai, who were Asian Indians living in India, despite lower overall BMI and waist circumference measurements than MASALA participants living in the United States (Gujral et al., 2015). Another study compared Asian Indians from the Chennai, India, and non-Hispanic whites from NHANES and found a higher prevalence of diabetes in Asian Indians in both

underweight and normal weight groups indicating there are possible ethnic differences in the population make up of type 2 diabetes (Gujral et al., 2018).

There is growing evidence among Asian Indians that β-cell dysfunction is involved in the early natural history of type 2 diabetes development, in addition to insulin resistance, even in low BMI and younger age groups. One study suggested that β-cell dysfunction in Asian Indians could have an independent effect on the pathogenesis of type 2 diabetes, a potential indication of innate susceptibility among this group (Gujral et al., 2014). Results from a study with Asian Indian participants with mild dysglycemia from Chennai, India suggested that β-cell dysfunction could be a driving factor in developing Type 2 diabetes (Staimez et al., 2013). Another study focusing on Asian Indians with onset of Type 2 diabetes compared to those with prediabetes at 25 years old or younger matched for age and sex, found that β-cell dysfunction was more strongly associated with type 2 diabetes (Mohan et al., 2013) compared to insulin resistance. Further research is warranted, especially in Asian Indians of across a range of ages of BMI to better understand the development of Type 2 diabetes amongst the population.

Current Findings in Africans & African Americans

African populations are heterogenous in nature, each with a unique set of characteristics that can affect type 2 diabetes development. High quality data on native born Africans currently residing in Africa is difficult to obtain, even as the prevalence of prediabetes and diabetes is expected to grow significantly in this group over the next 20 years. The differences in regions, lifestyles, disease prevalence, ethnic variations and environmental factors among Africans makes it a complex group to characterize. By contrast, there is more known about the prevalence of type 2 diabetes among African Americans within the United States. Data from NHANES from 1999 to 2010 indicated almost a doubling of the prevalence of type 2 diabetes from 7.9% to 14.1% in

African Americans (Ferdinand et al., 2015). More recent data from the Centers for Disease Control (CDC) showed an age-adjusted prevalence of 12.7% in non-Hispanic blacks (Golden et al., 2019). While not as high as Asian Indians, the prevalence is higher than non-Hispanic whites. One study indicated that African Americans are known to have higher BMI and worse cardiometabolic health compared to whites in the United States (Brancati et al., 2000). The high prevalence of prediabetes and diabetes and the factors surrounding disease development in African Americans are important to understand the proper thresholds for treatment. African immigrants in the United States are those who were born in Africa and have thus immigrated to the United States. A previous study from the Africans in America cohort, found a prevalence of newly diagnosed type 2 diabetes at 7% among participants (Ishimwe et al., 2021). A study outside the United States, based in the United Kingdom, found the prevalence of type 2 diabetes was three times higher in West African immigrants than in the general population (Alloh et al., 2021). African immigrants are unique as they may be benefitting from the healthy immigrant effect or there may be a loss of the effect over time (O'Conner et al., 2014). Due to the wide range of prevalence and unique presentation of each group there is a need to further study similarities and differences in type 2 diabetes disease development.

Africans living in Africa

There is a significant burden of type 2 diabetes within Africa, but lack of reliable data and information. Only about 30% of Africans are aware diabetic status, making it difficult to assess the overall prevalence of type 2 diabetes within Africa (Pheiffer et al., 2021). Despite the difficulty assessing the overall prevalence, the prevalence of type 2 diabetes in Africa is predicated to have the largest relative increase by 2045. Several studies have attempted to estimate the prevalence of diabetes, many through systematic reviews. A study of the

International Diabetes Federation Africa Region estimated a prevalence of 4.9% in 2013, however there is variance among low-income and high-income countries (Peer et al., 2014). In Africans aged 55 and older, a systematic review with data from 2000 - 2015 found an overall prevalence of 13.7% (Werfalli et al., 2016). Another systemic review focused on the prevalence of type 2 diabetes in South Africa, one of the largest countries within Africa, found a pooled prevalence of 15.2% (Pheiffer et al., 2021). The wide range of prevalence, especially among specific countries or groups highlights the need to better understand differences in disease development among Africans.

Previous studies have focused on specific populations within sub-Saharan Africa to evaluate the disease pathway for diabetes. The Research of Obesity & Diabetes among African Migrants (RODAM) study followed Ghanaians ages 25 – 70 years old living in Ghana (rural and urban), Amsterdam, Berlin, and London. They found higher BMI in the urban populations compared to rural Ghana and a large portion of the population had impaired fasting glucose (IFG) (Agyemang et al., 2016). A study focused on Africans in South Africa, suggested that Black Africans present with low insulin sensitivity and with hyperinsulinemia due to increased insulin secretion and lower insulin clearance (Goedecke & Olsson, 2020). Therefore, these studies show that some in the population may be more susceptible to the IFG form of prediabetes and low insulin sensitivity may be a primary factor in the disease development among Africans with specific phenotypes.

African Americans in the United States

In the United States the prevalence of type 2 diabetes among African Americans is about 13%, the second highest after Native Americans (Ng, 2013). Previous research in African Americans has largely focused on comparisons to white populations. A previous study of African

Americans and Caucasians found a 1.5 – 2.4-fold increase in the risk for developing type 2 diabetes among African Americans compared to Caucasians (Brancati et al., 2000). In a representative sample of individuals ages 25 – 70 from NHANES a study found non-Hispanic blacks had higher BMI and subscapular-to-triceps skinfold ratio, putting them at a greater risk for developing diabetes over the 16-year period compared to Caucasians (Lipton et al., 1993). When evaluating anthropometric data African Americans tend to have a higher overall BMI compared to Caucasians (Brancati et al., 2000). A follow-up study to Lipton et al. found that African Americans were at higher risk for type 2 diabetes across the BMI spectrum compared to Caucasians, but especially at low BMI (Resnick et al., 1998).

Genetic factors may also play a role as observed in an analysis of African American participants and African ancestry from the Atherosclerosis Risk in Communities (ARIC) Study, the Jackson Heart Study, and Multiethnic Cohort (MEC) study. Using an admixture genetic analysis, researchers found a significant association between type 2 diabetes and African American participants with greater African ancestry indicating genetic factors could possibly play a role, along with non-genetic factors (Cheng et al., 2012).

African immigrants in the United States

African immigrants have a unique set of characteristics including ethnic variations and environmental differences which may affect the pathway of disease development in type 2 diabetes. A study of the Africans in America cohort (n=486), which includes Africans who have immigrated to the United States, found the prevalence of newly diagnosed type 2 diabetes to be 7% among participants (Ishimwe et al., 2021). Previous studies in this population have also focused on the prevalence and pathways for abnormal glucose tolerance. In a U.S.-based study, only 1/3rd of Africans with abnormal glucose tolerance (Abnl-GT) tests were associated

primarily with insulin resistance. In contrast, participants with abnormal glucose associated primarily with β-cell dysfunction had a lower prevalence of obesity and less central obesity (Ishimwe et al., 2021; Goff et al., 2013). In the upcoming years there is projected to be a large increase in the prevalence of abnormal glucose tolerance within Africa across all BMI spectra (Hobabagabo et al., 2020).

Previous studies comparing the health of African immigrants to African Americans have postulated a "healthy immigrant" effect (Venters et al., 2009). While this has been shown in some areas such as infectious disease, there is conflicting data about the presence of the effect in metabolic health. A study focusing on the cardiometabolic health of African Immigrant men versus African American men suggested that despite lower BMI, the cardiometabolic health of African immigrants was worse and they had higher levels of glucose overall (O'Connor et al., 2014). As migration continues, it will be important to understand how disease development may differ based on ethnic variations and different environmental conditions of immigration.

With the projected rise in prevalence amongst African and African American populations it is important to understand the mechanisms to developing type 2 diabetes. Importantly, we need a wide spectrum of understudied ethnicities with high prevalence of diabetes to understand the variation that exists in pathways to diabetes. As a first step, study population characteristics in the pathophysiology of diabetes could expose variation in the relative contributions of β-cell function and insulin resistance in diabetes development that can later be studied across laboratory and clinical sciences for the development of new prevention strategies, something sorely lacking now given the common one-size-fits-all approach for risk stratification and clinical management.

Objective of Study

While it is becoming increasingly recognized there is heterogeneity within the disease development of type 2 diabetes, research is needed to compare a variety of populations globally that develop high levels of diabetes under different conditions of risk. This study will look at a wide spectrum of BMI and across four cohorts which have not been compared together in the past. The main objective of this study is to examine the relative contributions of insulin resistance and beta cell failure on diabetes pathophysiology across populations, with particular emphasis on African and Asian Indian populations. The study will include the following African groups: Africans that immigrated to the United States, African Americans in the United States, and mixed-ancestry South Africans in Africa, and these groups will be compared to Asian Indians, a population that has been previously found to have large impairments in β-cell function in the early natural history of diabetes.

Methods

Study Population

Study participants for this analysis originated from four different cohorts. Descriptions of the cohorts are provided below.

(1) Asian Indian (n=1750) participants from the Centre for cArdiometabolic Risk Reduction in South-Asia Surveillance Study (CARRS) were adults 20 or older in 2011, permanent residents of the household and non-pregnant. A representative sample and multi-stage cluster sampling was used to select urban and semi-urban (about 5 million) residents from Chennai, India. Ethical approval for human subjects' research for CARRS-Chennai was obtained from the ethics committees at Madras Diabetes Research Foundation (MDRF) and Emory University (Nair et al., 2012).

(2) African-born blacks living in America (n=523) from the Africans in America cohort included participants living in metropolitan Washington, DC who were born in sub-Saharan Africa with two black parents who were also born in sub-Saharan Africa and self-identified as healthy. Participants were recruited through newspaper ads, recruitment flyers, referrals, and community events. Those who successfully completed the telephone screening interview, then completed two screening visits at the National Institute of Health (NIH) Clinical Center. The study was approved by the National Institute of Diabetes and Digestive Kidney Diseases (NIDDK) Institutional Review Board (Kabakambira et al. 2018, Hobabagabo et al. 2020).

(3) Mixed ancestry South African (n=1112) participants from the Belville South cohort who were recruited between January 2008 and March 2009 in Belville-South, a northern suburb of Cape Town, South Africa. Mixed ancestry was defined as individuals who have Khoisan, white, black, and Malay heritage. Participants were selected through multistage stratified random sampling and information about the study was provided through newspaper ads, flyers, and radio ads. Participants who agreed to participate were visited by the recruitment team the night before their clinic visits and were reminded of the survey procedures. The study was approved by the Faculty of Health and Wellness Sciences Ethics Committee of the Cape Peninsula University of Technology (Matsha et al., 2012).

(4) African American (n=185) participants from the Triglyceride and Cardiovascular Risk in African Americans (TARA) study were recruited by the NIH in Bethesda, Maryland. Recruitment was done through flyers in Washington, D.C., and postings on the NIH website. Participants were African American with two parents who were also African American without the presence of liver or kidney disease and women were premenopausal and not receiving exogenous estrogen. The study was approved by the Institutional Review Board of National

Institute of Diabetes and Digestive and Kidney Diseases (Sumner et al., 2005). Informed consent was obtained from all participants. For the present analysis, participants across any of the cohorts were included if they were between the ages 20-70 with recorded heights, weights, and with an oral glucose tolerance test measuring glucose and insulin at time zero and time 120 minutes after glucose bolus. Participants were excluded from the analysis if they had self-reported previous diagnosis of diabetes, were pregnant, or were currently taking medications for diabetes.

Study Procedures

Asian Indian participants underwent recruitment, data collection, and specimen collection through three visits to their home. They were surveyed about demographics such as age and sex and anthropometric data such as height, weight, and waist circumference were collected. Height was measured using a portable stadiometer (SECA Model 213, SecaGmbh Co, Hamburg, Germany), weight was recorded after the removal of shoes, and waist circumference was measured at the smallest horizontal girth between the costal margins and the iliac crests. A standard 75-g oral glucose tolerance test (OGTT) was performed after an overnight fast of at least 8 hours with plasma glucose and insulin sampled at 0, 30, and 120 minutes. Plasma glucose concentration was measured using the hexokinase method. Serum insulin concentration was estimated using two different samples by electrochemiluminescence (COBAS E 411, Roche Diagnostics, Mannheim, Germany). Glucose and insulin measurement from the CARRS laboratory (Madras Diabetes Research Foundation Laboratory) were validated against U.S.-based Northwest Lipid Metabolism and Research Laboratories (NWRL). For glucose, a high concordance of glucose with values ranging from 3.8 to 10.1 mmol/L ($n = 20$, $y = 1.03x – 1.8$) was found with a correlation (r) of 0.996 and % bias range of 0.5 to 5.5%. For insulin, two batches of samples from India were examined. The first group of samples had an insulin

concentration range of 24.0 to 1,902.0 pmol/L (n = 29, y = 0.9x – 3.90), r of 0.945 and % bias range of 1.1 to 25%. The second group of samples had an insulin concentration range of 43.2 to 2,574.0 pmol/L (n = 30, y = 1.04x + 0.2), r of 0.997 and % bias range of 0.1% to 18.0% (Staimez et al., 2019).

African-born Blacks living in America (African immigrants) underwent two clinical visits for data and specimen collection. The first visit consisted of the collection of demographic data and anthropometric measures including height, weight, and waist circumference. Height was measured using a wall stadiometer with the average of three readings recorded (Seca 242; Seca Corp., Hanover, MD), weight measured using a calibrated scale (Scale-Tronix 5702; Carol Stream, Illinois), and waist circumference measured at two different spots using a stretch-resistant tape with the participant standing feet hip width apart and weight evenly distributed from (1) the superior border of the iliac crest and (2) the midpoint between the iliac crest and lowest palpable rib, at the end of expiration with the average of three recordings recorded. A standard 75-g OGTT (Trutol 75; Custom Laboratories, Baltimore, Maryland) was performed after an overnight fast of 12 hours with plasma glucose and serum insulin (Roche Cobas 6000 analyzer, Roche Diagnostics) measured at -15, 0, 30, 60, and 120 minutes (Kabakambira et al., 2018).

Mixed ancestry South African (SA-Mixed ancestry) participants completed a standardized interview where demographic information such as age and sex were collected, and a physical examination where anthropometric measures such as height, weight, and waist circumference were collected. All anthropometric measures were collected three times and the average was recorded. Height was measured using a stadiometer, weight measured using a Sunbeam EB710 digital bathroom scale, and waist circumference measured at the level of the

narrowest part of the torso when looking at the anterior view using a non-elastic tape. A 75-g OGTT was performed after an overnight fast with plasma glucose measured by the enzymatic hexokinase method (Cobas 6000, Roche Diagnostics) and insulin measured by a microparticle enzyme immunoassay (Axsym, Abbot) at 0 and 120 minutes (Masha et al., 2013).

African American participants provided demographic information such as age and sex and anthropometric measures such as height, weight, and waist circumference. Height was measured using a stadiometer (to nearest 0.1 cm), weight was measured (to nearest 0.1 kg) using a platform scale, and waist circumference was measured (to nearest 0.1 cm) around the abdomen at the iliac crest using a non-stretching tape with the average of three measurements being recorded. A standard 75-g OGTT (Trutol 75; Custom Laboratories, Baltimore, Maryland) was performed after an overnight fast of 12 hours with measurements taken at time 0, 30, and 120 minutes. An insulin-modified frequently sampled intravenous glucose tolerance test (MinMOD Millenium v6.02, Los Angeles, California) was performed after an overnight fast of 12 hours with glucose measured through the glucose oxidase method (Yellow Springs Instrument, Yellow Springs, Ohio) and insulin measured through double antibody chemiluminescent sandwich assays (Diagnostic Products, Los Angeles, California) at several times including 0, 30, 60, and 120 minutes (Sumner et al., 2008).

Key Variables

Participants were classified on glycemic status based on the American Diabetes Association criteria with (1) normal glucose tolerance (NGT) with fasting plasma glucose (FPG) <100 mg/dl or two-hour plasma glucose (2hPG) <140 mg/dl (2) isolated impaired fasting glucose (iIFG) with FPG 100-125 mg/dl and 2hPG <140 mg/dl (3) isolated impaired glucose tolerance (iIGT) with FPG <100 mg/dl and 2hPG 140-199 mg/dl (4) impaired fasting glucose and

impaired glucose tolerance (IFG + IGT) with FPG 100-125 mg/dl and 2hPG 140-199 mg/dl and (5) type 2 diabetes with FPG ≥ 126 mg/dl and/or 2hPG ≥ 200 mg/dl (American Diabetes Association, 2022). BMI was calculated as kg/m^2 and groups were defined as (1) normal weight (BMI < 25.0 kg/m^2), and (2) overweight (25.0 ≤ BMI). Participants were also classified based on glucose tolerance and insulin resistance status into groups based on glycemic status and the upper quartile of HOMA-IR, respectively. Glycemic status was classified into two variables: normal glucose tolerance (NGT) like above, and abnormal glucose tolerance (iIFG, iIGT, IFG + IGT, type 2 diabetes). The four groups were defined as: (1) normal glucose tolerance-reference (NGT-ref) with HOMA-IR < 75^{th} percentile, (2) normal glucose tolerance-insulin resistance (NGT-IR) with HOMA-IR > 75^{th} percentile, (3) abnormal glucose tolerance-insulin resistance (Abnl-GT-IR) with HOMA-IR >75^{th} percentile, and (4) abnormal glucose tolerance-β-cell failure (Abnl-GT-B-Cell-Failure) with HOMA-IR < 75^{th} percentile.

The primary measure of insulin resistance was HOMA-IR, while the primary measure of β-cell function was the insulinogenic index. HOMA-IR was calculated using ([$insulin_{t0}$ x $glucose_{t0}$]/ 22.5). The insulinogenic index in the early phase was calculated as ([($insulin_{t30}$ - $insulin_{t0}$) / ($glucose_{t30}$ - $glucose_{t0}$)]. Participants with insulinogenic index values of zero or negative values were excluded from the present analysis. Secondary measures of β-cell function included HOMA-B and the early oral disposition index. HOMA-B was measured as ([20 x $insulin_{t0}$]/[$glucose_{t0}$ – 3.5]) and early oral disposition index was calculated using [($insulin_{t30}$ - $insulin_{t0}$) / ($glucose_{t30}$ - $glucose_{t0}$)](1/$insulin_{t0}$).

Statistical Analysis

The present analysis was conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina). Age, BMI, and waist circumference were examined as continuous variables. BMI was

also examined as a categorial variable with adjustments for age and sex. Continuous variables were compared using analysis of variance (ANOVA) and categorical data were compared using Chi-square tests. Metabolic characteristics between ethnic groups were compared using two-sided T-tests and ANOVA. Variables not normally distributed were log-transformed to meet the assumptions for linear regression. For HOMA-IR and HOMA-B cutoffs for the 25^{th} and 75^{th} percentile for each ethnicity were determined. Insulin resistance was defined as HOMA-IR above cohort-specific 75^{th} percentile, while β-cell failure was defined as hyperglycemia without insulin resistance. To compare baseline anthropometric and cardiometabolic data, general linear regression models were fit. To examine the relative contribution of insulin resistance and insulin secretion, HOMA-IR and the insulinogenic index were standardized and fit with multivariate multinominal (i.e., polytomous) logistic models. The odds of prediabetes and odds of diabetes were examined for every standardized unit increase in HOMA-IR and the insulinogenic index and compared between ethnicities.

Results

Overall, there were 3570 participants used in this analysis (Asian Indians: 1750, African immigrants: 523, SA-Mixed ancestry: 1112, African Americans: 185). SA-Mixed ancestry participants were the oldest and had the highest percentage of females (mean age 45.6 years, SD 13.8; 73.2% females) compared to Asian Indians (mean age 38.9 years, SD 10.8; 64.5% females), African immigrants (mean age 38.5 years, SD 10.3; 36.1% females), African Americans (mean age 34.5 years, SD 7.8; 60% females). African Americans were the most overweight (mean BMI 34.5 kg/m^2, SD 7.8) followed by SA-Mixed ancestry (mean BMI 28.6 kg/m^2, SD 8.2), African immigrants (mean BMI 27.7 kg/m^2, SD 4.5), and Asian Indians (mean BMI 25.8 kg/m^2, SD 4.9). The prevalence on newly diagnosed type 2 diabetes ($p=0.0070$) was

highest in Asian Indians (8.1%), followed by African immigrants (6.9%), and SA-Mixed ancestry (6.4%), and much lower in African Americans (1.6%). Prediabetes ($p<0.0001$) was highest among African immigrants (31.4%), African Americans (27.0%), Asian Indians (25.6%) and lowest among SA-Mixed ancestry (21.0%). The distribution of prediabetes subtypes varied across ethnicities. Asian Indians had predominately iIFG, whereas African subgroups had predominately iIGT (iIFG: Asian Indians 17.3%; SA-Mixed ancestry 6.2%; African immigrants 4.8%; African Americans 2.7%). For iIGT: African immigrants 20.7%; African Americans 20.5%; SA-Mixed ancestry 9.8%; and Asian Indians 3.2%. The prevalence of IFG+IGT was not significantly different across groups, ranging in prevalence from 4% to 6% across groups.

TABLE 1. Participant Characteristics across four ethnicities

Characteristic	Asian Indians (n=1750)		African immigrants (n=523)		SA-Mixed ancestry (n=1112)		African Americans (n=185)		Total (n=3570)
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p-value
Age (years)	38.9	10.8	38.5	10.3	45.6	13.8	34.5	7.8	<.0001
BMI (kg/m^2)	25.8	4.9	27.7	4.5	28.6	8.2	30.4	7.5	<.0001
Female, n (%)	1128 (64.5)		189 (36.1)		814 (73.2)		111 (60.0)		<.0001
NGT, n (%)	1160 (66.3)		323 (61.8)		808 (72.7)		132 (71.4)		<.0001
IFG, n (%)	302 (17.3)		25 (4.8)		69 (6.2)		5 (2.7)		<.0001
IGT, n (%)	56 (3.2)		108 (20.7)		109 (9.8)		38 (20.5)		<.0001
IFG + IGT, n (%)	90 (5.1)		31 (5.9)		55 (5.0)		7 (3.8)		0.6936
Newly Diagnosed type 2 diabetes, n (%)	142 (8.1)		36 (6.9)		71 (6.4)		3 (1.6)		0.0070

Table 2 shows metabolic measures with adjustment for age, sex, and BMI. Asian Indians had the highest mean fasting plasma glucose (101.2 mg/dL), while African immigrants had the highest mean 2-hour plasma glucose (134.6 mg/dL). Asian Indians were the most insulin resistant (HOMA-IR 2.3, SE: 0.1) followed by SA-Mixed ancestry (HOMA-IR 2.1, SE: 0.1) and African immigrants (HOMA-IR 1.6, SE: 0.1) and African Americans (HOMA-IR 1.6, SE: 0.2).

Insulin levels at 30 minutes of OGTT and insulinogenic index was highest in African immigrants (76.1 uIU/mL; 1.4 pmol/mmol) and African Americans (75.5 uIU/mL; 1.4 pmol/mmol) and lowest in Asian Indians (60.0 uIU/mL; 0.8 pmol/mmol).

Participants were stratified by glycemic status groups adjusting for age, sex, and BMI within ethnicities as shown in Tables 3A-E (African Americans results are unavailable for IFG, IFG+IGT, and type 2 diabetes due to low sample sizes). Among the NGT Asian Indians had the highest fasting glucose (89.6 mg/dL), most insulin resistance (HOMA-IR 1.8, SE: 0.0), and least β-cell function (Insulinogenic Index 1.1 pmol/mmol, SE: 1.0). African immigrants and African Americans had similar fasting glucose (88.1 mg/dL and 84.5 mg/dL, respectively), levels of insulin resistance (HOMA-IR 1.3, SE: 0.1 for both), and β-cell function (Insulinogenic Index 1.5 pmol/mmol, SE: 1.1 for both). In iIFG African immigrants had the highest 2-hour glucose (121.5 mg/dL, SE: 3.7) followed by SA-Mixed ancestry (105.1 mg/dL, SE: 2.3) and Asian Indians (105.1 mg/dL, SE: 1.1). SA-Mixed ancestry (HOMA-IR 3.8, SE: 0.3) had the highest insulin resistance ($p<0.0001$) compared to Asian Indians (HOMA-IR 2.5, SE: 0.1) and African immigrants (HOMA-IR 1.9, SE: 0.5). Among iIGT fasting glucose ($p=0.0045$) was similar in Asian Indians (91 mg/dL, SE: 0.9), African immigrants (90.9 mg/dL, SE: 0.7), and SA-Mixed ancestry (89.7 mg/dL, SE: 0.7) and lowest in African Americans (86.8 mg/dL, SE: 1.2). Insulin resistance was greatest and beta-cell function was lowest in Asian Indians (HOMA-IR 2.5, SE: 0.2; 0.7 pmol/mmol, SE: 1.1). Among the IFG+IGT group insulin resistance was highest among SA-Mixed ancestry (HOMA-IR 3.4, SE: 0.3) and β-cell function was lowest in Asian Indians (0.4 pmol/mmol, SE: 1.1). In the newly diagnosed type 2 diabetes group insulin resistance was highest in SA-Mixed ancestry (HOMA-IR 7.7). Asian Indians had the lowest β-cell function (Insulinogenic Index 0.3 pmol/mmol) compared to African immigrants (Insulinogenic Index 0.5

pmol/mmol). Figure 1 shows mean fasting glucose levels across glycemic status groups for each ethnicity. For all ethnicities, no significant difference was seen in mean fasting glucose between the normoglycemia group and iIGT group. For Asian Indians, African immigrants, and SA-Mixed ancestry a significant difference ($p \leq 0.001$) was seen between the NGT and newly diagnosed type 2 diabetes groups within each ethnicity.

TABLE 2. Metabolic Characteristics across four ethnicities adjusted for age, sex, and BMI

Characteristic	Asian Indians (n=1750)		African immigrants (n=523)		SA-Mixed ancestry (n=1112)		African Americans (n=185)		Total (n=3570)
	LS Mean	SE	LS Mean	SE	LS Mean	SE	LS Mean	SE	p-value
Waist Circumference (cm)	86.5	0.2	88.6	0.3	87.1	0.2	91.6	0.5	<.0001
Fasting Glucose (mg/dL)	101.2	0.6	92.3	1.1	89.9	0.7	86.6	1.8	<.0001
30 min Glucose (mg/dL)	159.3	1.1	135.4	1.9			127.6	3.3	<.0001
2-hour Glucose (mg/dL)	119.5	1.3	134.6	2.4	110.6	1.6	123.7	3.9	<.0001
Fasting Insulin (uIU/mL)	9.0	0.2	7.0	0.3	8.5	0.2	7.2	0.5	<.0001
30 min Insulin (uIU/mL)	60.0	1.1	76.1	2.1			75.5	3.5	<.0001
2-hour Insulin (uIU/mL)	53.7	1.2	72.0	2.2	48.8	1.5	67.2	3.6	<.0001
HOMA-IR ((uIU/mL*mmol)/L^2)	2.3	0.1	1.6	0.1	2.1	0.1	1.6	0.2	<.0001
HOMA-B (uIU/mL)/(mmol/L)	99.9	6.5	87.3	12.1	131.8	8.3	118.3	20.1	<.0001
Insulinogenic Index (pmol/mmol) *	0.8	1.0	1.4	1.0			1.4	1.1	<.0001
Oral Disposition Index (l/mmol) *	0.1	1.0	0.2	1.0			0.2	1.1	<.0001

*Geometric means and geometric standard errors provided.

TABLES 3A-E. Metabolic Characteristics across glycemic status groups adjusted for age, sex, and BMI

(A) NORMOGLYCEMIA

Characteristic	Asian Indians (n=1160)		African immigrants (n=323)		SA-Mixed ancestry (n=808)		African Americans (n=132)		Total (n=2423)
	LS Mean	SE	LS Mean	SE	LS Mean	SE	LS Mean	SE	p-value
Waist Circumference (cm)	84.1	0.2	85.6	0.4	84.3	0.3	88.7	0.6	<.0001
Fasting Glucose (mg/dL)	89.6	0.2	88.1	0.4	84.0	0.2	84.5	0.6	<.0001
30 min Glucose (mg/dL)	138.0	0.8	128.3	1.4			124.1	2.2	<.0001
2-hour Glucose (mg/dL)	93.8	0.6	111.9	1.1	93.9	0.7	108.6	1.7	<.0001
Fasting Insulin (uIU/mL)	8.0	0.1	5.9	0.3	7.2	0.2	6.3	0.4	<.0001
30 min Insulin (uIU/mL)	61.2	1.4	77.8	2.7			73.1	4.2	<.0001
2-hour Insulin (uIU/mL)	46.7	1.1	54.8	2.2	41.0	1.4	46.4	3.4	<.0001
HOMA-IR ((uIU/mL*mmol)/L^2)	1.8	0.0	1.3	0.1	1.5	0.0	1.3	0.1	<.0001
HOMA-B (uIU/mL)/(mmol/L)	113.8	9.4	83.3	17.9	135.8	11.4	115.7	27.7	0.0033
Insulinogenic Index (pmol/mmol) *	1.1	1.0	1.5	1.1			1.5	1.1	<.0001
Oral Disposition Index (l/mmol) *	0.2	1.0	0.3	1.1			0.3	1.1	<.0001

*Geometric means and geometric standard errors provided.

(B) IMPAIRED FASTING GLUCOSE

Characteristic	Asian Indians (n=302)		African immigrants (n=25)		SA-Mixed ancestry (n=69)		African Americans (n=5) ~		Total (n=401)
	LS Mean	SE	LS Mean	SE	LS Mean	SE	LS Mean	SE	p
Waist Circumference (cm)	88.4	0.4	91.1	1.5	91.5	0.9			<.0001
Fasting Glucose (mg/dL)	105.7	0.3	102.6	1.1	106.4	0.7			0.0006
30 min Glucose (mg/dL)	168.7	1.7	151.6	6.0					<.0001
2-hour Glucose (mg/dL)	105.1	1.1	121.5	3.7	105.6	2.3			<.0001
Fasting Insulin (uIU/mL)	9.5	0.5	7.7	1.6	14.4	1.0			<.0001
30 min Insulin (uIU/mL)	58.6	2.1	88.8	7.3					<.0001
2-hour Insulin (uIU/mL)	53.6	2.3	63.7	8.2	48.2	5.1			<.0001
HOMA-IR ((uIU/mL*mmol)/L^2)	2.5	0.1	1.9	0.5	3.8	0.3			<.0001
HOMA-B (uIU/mL)/(mmol/L)	80.2	3.6	71.3	12.5	116.5	7.8			<.0001
Insulinogenic Index (pmol/mmol) *	0.8	1.1	1.5	1.2					0.0008
Oral Disposition Index (l/mmol) *	0.1	1.1	0.2	1.2					<.0001

*Geometric means and geometric standard errors provided.

~IFG analysis not shown for African Americans due to low sample size.

(C) IMPAIRED GLUCOSE TOLERANCE

Characteristic	Asian Indians (n=56)		African immigrants (n=108)		SA-Mixed ancestry (n=109)		African Americans (n=38)		Total (n=311)
	LS Mean	SE	LS Mean	SE	LS Mean	SE	LS Mean	SE	p-value
Waist Circumference (cm)	91.9	0.8	94.3	0.6	92.7	0.7	97.4	1.0	<.0001
Fasting Glucose (mg/dL)	91.0	0.9	90.9	0.7	89.7	0.7	86.8	1.2	0.0045
30 min Glucose (mg/dL)	167.8	3.3	139.9	2.3			145.4	4.2	<.0001
2-hour Glucose (mg/dL)	160.5	2.2	157.1	1.7	161.1	1.8	154.9	2.8	0.0905
Fasting Insulin (uIU/mL)	11.2	0.7	8.1	0.5	9.5	0.6	6.9	0.9	<.0001
30 min Insulin (uIU/mL)	66.0	7.6	80.0	5.3			73.7	9.8	0.4695
2-hour Insulin (uIU/mL)	96.7	11.1	106.8	8.3	105.7	8.9	110.4	14.0	<.0001
HOMA-IR ((uIU/mL*mmol)/L^2)	2.5	0.2	1.8	0.1	2.1	0.1	1.5	0.2	<.0001
HOMA-B (uIU/mL)/(mmol/L)	109.6	28.8	114.1	21.5	141.4	23.0	94.6	36.2	0.0001
Insulinogenic Index (pmol/mmol) *	0.7	1.1	1.2	1.1			0.9	1.1	<.0001
Oral Disposition Index (l/mmol) *	0.1	1.1	0.2	1.1			0.1	1.1	<.0001

*Geometric means and geometric standard errors provided.

(D) IFG + IGT

Characteristic	Asian Indians (n=90)		African immigrants (n=31)		SA-Mixed ancestry (n=55)		African Americans (n=7) ~		Total (n=183)
	LS Mean	SE	LS Mean	SE	LS Mean	SE	LS Mean	SE	p-value
Waist Circumference (cm)	92.6	0.9	95.4	1.6	96.3	1.2			<.0001
Fasting Glucose (mg/dL)	111.0	0.7	106.2	1.3	108.8	1.0			0.0289
30 min Glucose (mg/dL)	200.3	2.6	160.9	4.8					<.0001
2-hour Glucose (mg/dL)	163.1	1.8	159.5	3.2	161.9	2.4			0.0631
Fasting Insulin (uIU/mL)	11.1	0.7	9.6	1.3	12.5	1.0			0.0008
30 min Insulin (uIU/mL)	63.6	4.8	62.3	8.7					0.5539
2-hour Insulin (uIU/mL)	79.4	6.0	98.7	10.9	82.5	8.0			0.1555
HOMA-IR ((uIU/mL*mmol)/L^2)	3.1	0.2	2.5	0.4	3.4	0.3			0.0018
HOMA-B (uIU/mL)/(mmol/L)	84.4	5.2	80.3	9.4	97.6	7.0			0.0003
Insulinogenic Index (pmol/mmol) *	0.4	1.1	0.9	1.1					<.0001
Oral Disposition Index (l/mmol) *	0.0	1.1	0.1	1.1					<.0001

*Geometric means and geometric standard errors provided.

~IFG + IGT analysis not shown for African Americans due to low sample size.

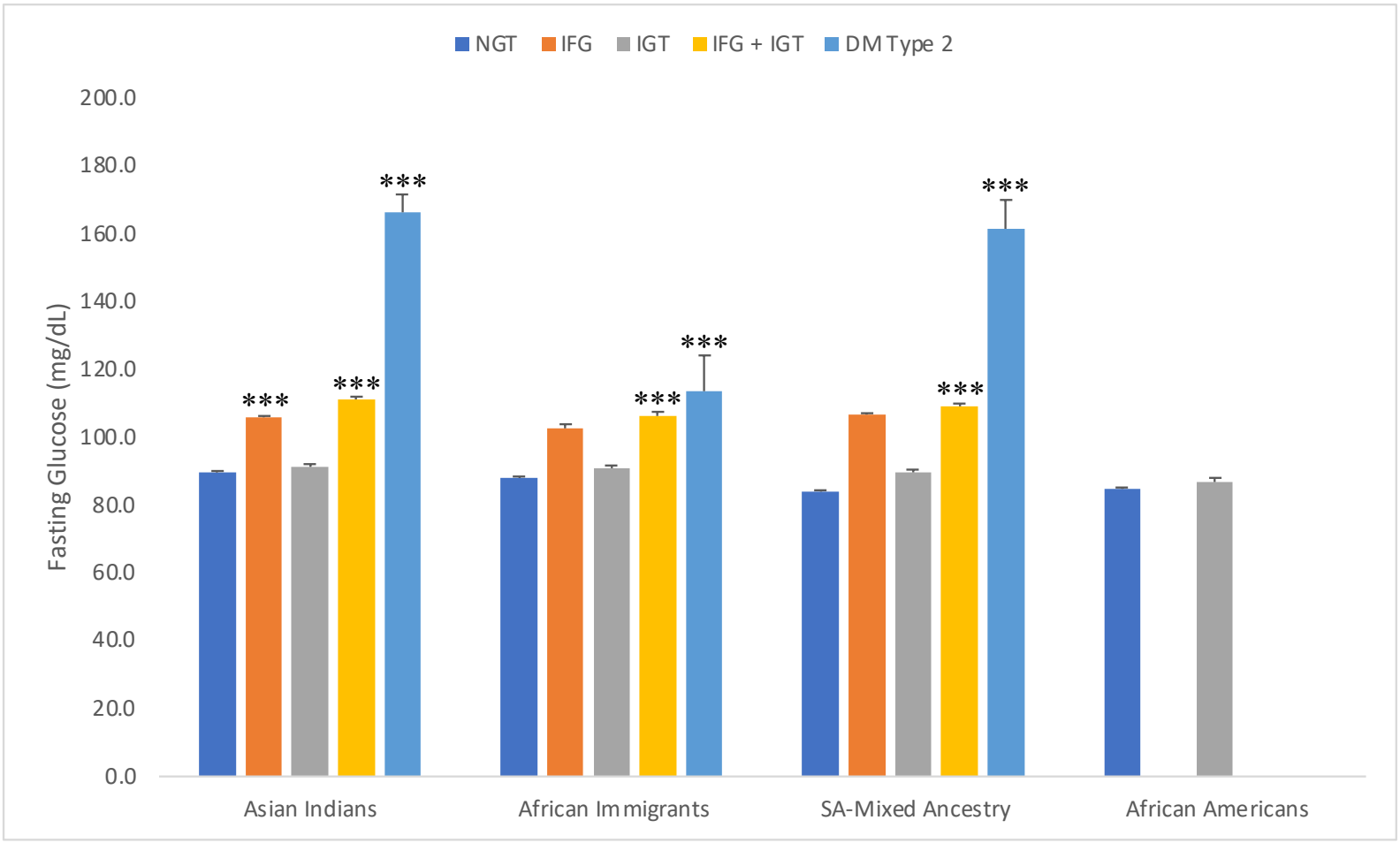
(E) NEWLY DIAGNOSED TYPE 2 DIABETES

Characteristic	Asian Indians (n=142)		African immigrants (n=36)		SA-Mixed ancestry (n=71)		African Americans (n=3) ~		Total (n=252)
	LS Mean	SE	LS Mean	SE	LS Mean	SE	LS Mean	SE	p-value
Waist Circumference (cm)	93.0	0.6	97.1	1.1	96.6	0.9			<.0001
Fasting Glucose (mg/dL)	166.3	5.2	113.6	10.3	161.5	8.2			0.0005
30 min Glucose (mg/dL)	269.9	5.7	185.5	11.9					<.0001
2-hour Glucose (mg/dL)	275.5	7.7	250.3	15.2	275.3	12.1			0.4693
Fasting Insulin (uIU/mL)	11.7	1.7	10.9	3.4	16.7	2.7			0.0563
30 min Insulin (uIU/mL)	47.6	2.5	48.1	5.2					0.4142
2-hour Insulin (uIU/mL)	67.1	4.7	103.1	9.3	51.2	7.4			0.0005
HOMA-IR ((uIU/mL*mmol)/L^2)	4.7	1.0	3.0	1.9	7.7	1.5			0.1413
HOMA-B (uIU/mL)/(mmol/L)	53.2	4.8	88.5	9.5	68.1	7.5			<.0001
Insulinogenic Index (pmol/mmol) *	0.3	1.1	0.5	1.2					0.0166
Oral Disposition Index (l/mmol) *	0.0	1.1	0.1	1.2					0.0012

*Geometric means and geometric standard errors provided.

~Newly diagnosed type 2 diabetes analysis not shown for African Americans due to low sample size.

FIGURE 1. Variation of mean fasting glucose within each ethnicity across glycemic groups, adjusted for age, sex, and BMI.



Asterisks denote differences within each ethnicity compared to the NGT group adjusted for age, sex, and BMI. *p≤0.05, **p≤0.01, ***p≤0.001. IFG, IFG+IGT, and DM Type 2 not shown for African Americans due to low sample size.

Table 4 compares characteristics adjusted for age and sex across BMI strata for each ethnicity. In the normal weight category mean BMI was similar across ethnicities ranging from 21 kg/m^2 (SA-Mixed ancestry) to 22.9 kg/m^2 (African immigrants). Asian Indians continued to have the highest fasting glucose (95.0 mg/dL, SE: 0.7), the most insulin resistance (HOMA-IR 1.7, SE: 0.0), and lowest β-cell function (Insulinogenic Index 1.0 pmol/mmol, SE: 1.0). HOMA-IR was similar across the three African populations (African immigrants: 1.1, SE: 0.1; SA-Mixed ancestry 1.1, SE: 0.1; African Americans 1.2, SE: 0.2; $p<0.0001$). In the overweight category mean BMI was similar among Asian Indians (29.4 kg/m^2) and African immigrants (30.6 kg/m^2) and among SA-Mixed ancestry (33 kg/m^2) and African Americans (33.6 kg/m^2). Despite the lowest mean BMI among the group, Asian Indians had the highest fasting glucose (104.6 mg/dL, SE: 0.9), lowest 30-minute insulin (63.1 uIU/mL, SE: 1.7), and least amount of β-cell function (Insulinogenic Index 0.8 pmol/mmol, SE: 1.0). SA-Mixed ancestry had the highest amount of insulin resistance (HOMA-IR 3.0, SE: 0.2). β-cell function was higher in African immigrants among the overweight group (Insulinogenic Index 1.4 pmol/mmol, SE: 1.0) compared to the normal weight group (Insulinogenic index 1.1 pmol/mmol, SE: 1.1) and the same among African Americans (Insulinogenic Index 1.3 pmol/mmol, SE: 1.1 for both).

TABLE 4. Metabolic Characteristics across BMI strata adjusted for age, and sex

	NORMAL WEIGHT (BMI < 25.0 KG/M^2)								
Characteristic	Asian Indians (n=810)		African immigrants (n=148)		SA-Mixed ancestry (n=441)		African Americans (n=46)		Total (n=1445)
	LS Mean	SE	LS Mean	SE	LS Mean	SE	LS Mean	SE	p
BMI (kg/m^2)	21.7	0.1	22.9	0.2	21.0	0.1	22.4	0.3	<.0001
Waist Circumference (cm)	76.1	0.3	79.1	0.7	74.3	0.4	80.3	1.2	<.0001
Fasting Glucose (mg/dL)	95.0	0.7	89.3	1.8	84.5	1.0	84.6	3.2	<.0001
30 min Glucose (mg/dL)	145.6	1.5	137.5	3.6			131.1	6.5	<.0001
2-hour Glucose (mg/dL)	105.4	1.6	126.8	3.8	96.9	2.2	113.9	6.8	<.0001
Fasting Insulin (uIU/mL)	7.1	0.1	4.7	0.3	5.1	0.2	5.7	0.6	<.0001
30 min Insulin (uIU/mL)	53.7	1.3	62.9	3.1			70.3	5.6	0.0001
2-hour Insulin (uIU/mL)	43.6	1.2	55.5	2.8	27.4	1.6	49.7	5.0	<.0001
HOMA-IR ((uIU/mL*mmol)/L^2)	1.7	0.04	1.1	0.1	1.1	0.1	1.2	0.2	<.0001
HOMA-B (uIU/mL)/(mmol/L)	93.4	13.03	58.3	30.9	132.5	17.8	114.3	55.0	0.0308
Insulinogenic Index (pmol/mmol) *	1.0	1.0	1.1	1.1			1.3	1.1	<.0001
Oral Disposition Index (l/mmol) *	0.1	1.0	0.3	1.1			0.3	1.2	<.0001

*Geometric means and geometric standard errors provided.

Characteristic	OVERWEIGHT (BMI >= 25.0 KG/M^2)								
	Asian Indians (n=940)		African immigrants (n=375)		SA-Mixed ancestry (n=671)		African Americans (n=139)		Total (n=2125)
	LS Mean	SE	LS Mean	SE	LS Mean	SE	LS Mean	SE	p
BMI (kg/m^2)	29.4	0.2	30.6	0.3	33.0	0.2	33.6	0.4	<.0001
Waist Circumference (cm)	90.6	0.4	94.9	0.6	99.0	0.4	103.9	0.9	<.0001
Fasting Glucose (mg/dL)	104.6	0.9	94.5	1.4	94.8	1.1	90.8	2.2	<.0001
30 min Glucose (mg/dL)	168.1	1.4	138.1	2.3			136.1	3.6	<.0001
2-hour Glucose (mg/dL)	127.0	1.9	140.6	3.1	122.4	2.3	136.0	4.9	<.0001
Fasting Insulin (uIU/mL)	9.5	0.3	8.3	0.5	11.6	0.4	9.4	0.8	<.0001
30 min Insulin (uIU/mL)	63.1	1.7	84.2	2.8			84.6	4.4	<.0001
2-hour Insulin (uIU/mL)	56.3	1.9	81.7	3.1	67.5	2.3	83.5	4.9	<.0001
HOMA-IR ((uIU/mL*mmol)/L^2)	2.5	0.14	2.0	0.2	3.0	0.2	2.2	0.4	0.0018
HOMA-B (uIU/mL)/(mmol/L)	99.3	5.50	108.0	9.1	130.7	6.9	138.4	14.3	<.0001
Insulinogenic Index (pmol/mmol) *	0.8	1.0	1.4	1.0			1.3	1.1	<.0001
Oral Disposition Index (l/mmol) *	0.1	1.0	0.2	1.1			0.2	1.1	<.0001

*Geometric means and geometric standard errors provided.

To examine the presence of beta cell failure with and without low insulin sensitivity, participants were categorized with NGT or Abnl-GT to evaluate within each ethnicity and across glucose tolerance groups. Among those with Abnl-GT, individuals were separated based on whether individuals who had worse β-cell function (lowest quartile) and the upper three quartiles of insulin resistance (i.e., lower three quartiles of HOMA-IR). Appendix Tables 1A-D shows glucose tolerance groups by ethnicity and adjusted for age, sex, and BMI. Like previous findings, fasting glucose was highest and 30-minute insulin was lowest among Asian Indians in all four groups. In the two insulin resistance groups, HOMA-IR was highest in the SA-Mixed ancestry. Appendix Figures 1A-E show mean values of multiple characteristics (fasting glucose, 30-min insulin, HOMA-IR, HOMA-B, and insulinogenic index) among the different groups by ethnicity. Fasting glucose and HOMA-IR were highest in the Abnl-GT-IR groups for each ethnicity and were significantly different than the NGT-Ref group ($p<0.0001$) for each ethnicity. Insulin at 30 minutes of OGTT, HOMA-B, and the Insulinogenic Index were largest in the NGT-IR groups for Asian Indians, African immigrants, and African Americans ($p<0.01$).

Appendix Tables 2A-C focuses on the relative contributions of insulin resistance and β-cell function to glycemic status (normoglycemia, prediabetes, type 2 diabetes) by ethnicity. Odds ratios for African Americans in the diabetes group were not included in the analysis due to low sample size (n=3). Generally, result appeared similar across ethnicities, with odds ratios and 95% confidence intervals (CI) overlapping. However, for African immigrants and the prediabetes outcome, associations of the insulinogenic index and prediabetes appeared somewhat stronger, with odds ratios lowest compared to other ethnicities and after adjustment for age, sex, and BMI. For every unit increase in the standardized insulinogenic index, the odds ratio of prediabetes versus normoglycemia was lowest in African immigrants (OR insulinogenic index: 0.36, 95%

CI: 0.26, 0.49) compared to Asian Indians (OR insulinogenic index: 0.49, 95% CI: 0.42, 0.57) or African Americans (OR insulinogenic Index: 0.45, 95% CI: 0.27, 0.74), even after adjusting for age, sex, and BMI. For standardized HOMA-IR, odds ratios were similar for African immigrants and Asian Indians across models.

Discussion

This study compared four different ethnic populations who are at high-risk for type 2 diabetes and compared the relative contributions of insulin resistance and β-cell function on diabetes pathophysiology. Among prediabetes subtypes Asian Indians had predominantly impairments to fasting glucose, while African immigrants and African Americans had predominant impairments to glucose tolerance. SA-Mixed ancestry exhibited iIGT greater than iIFG, but not to the same extent as the other African populations. Among NGT and iIGT Asian Indians had the highest insulin resistance, while SA-Mixed ancestry had the highest insulin resistance among iIFG, IFG+IGT, and newly diagnosed type 2 diabetes. When comparing the African populations, the African immigrants and African Americans seem to be the most similar regarding insulin resistance and β-cell function, while the SA-Mixed ancestry group had higher levels of insulin resistance compared to the other African groups. These findings suggest there may be differences in the development of type 2 diabetes early in development of type 2 diabetes across ethnic populations. Therefore, key findings from this study include: (1) the relative contributions of β-cell function and insulin resistance are very similar across ethnic groups for the odds of diabetes (2) more variation exists for the relative contributions of β-cell function and insulin resistance on the development of prediabetes, particularly for β-cell function (3) African immigrants may be more prone to iIGT for every unit reduction in β-cell function and (4) Asian Indians may be more prone to iIFG for every unit reduction in β-cell function.

Previous studies of Asian Indians hypothesize a phenotype with impaired insulin secretion and suggest that the conversion from iIFG to diabetes can occur even with small increases in insulin resistance (Staimez et al., 2019). Our findings replicate these findings as fasting glucose was consistently highest in this group regardless of glycemic or glucose tolerance status. Another study noted that at mild levels of dysglycemia, insulin secretion in Asian Indians is reduced (Staimez et al., 2013). A study by Mohan et al. (2013) found that in young Asian Indians β-cell failure has a stronger association than insulin resistance in type 2 diabetes. In our study insulin secretion, as measured by the insulinogenic index, in Asian Indians was consistently lower than all three African populations. Like the study by Narayan et al. (2021) the findings suggest that problems in insulin secretion may play a primary role in early-stage type 2 diabetes development among Asian Indians as opposed to primarily insulin resistance as previously suggested (Dhawan et al., 1994; Raji et al., 2001; Misra et al., 2003).

African immigrants and African Americans seem to be the most similar among the four groups despite differences in BMI. African immigrants and African Americans exhibited similar levels of insulin resistance and β-cell function overall. Both populations had similar percentages in the NGT-Ref and NGT-IR groups, while there were more African immigrants in the Abnl-GT-β-cell failure group and more African Americans in the Abnl-GT-IR group. For both ethnicities HOMA-IR was significantly different in the Abnl-GT groups. This indicates that β-cell failure without insulin resistance may play a significant role in both populations. Previous studies have found that β-cell failure may be a more common primary factor in abnormal glucose tolerance in Africans as opposed to insulin resistance (Ishimwe et al., 2021). Previously African immigrants have been described as having the “healthy immigrant effect” suggesting that they were healthier than African Americans (O’Connor et al., 2014). In contrast, African immigrants in this analysis,

were less obese, had similar levels of insulin resistance and β-cell function to African Americans than SA-Mixed ancestry, suggesting duration of the healthy immigrant effect, if present in African immigrants, may be finite. When comparing insulin resistance and diabetes prevalence, a high age-adjusted prevalence of diabetes appears among African Americans (18%) compared to South Asians (13%), yet HOMA-IR levels were significantly higher in South Asians (Kanaya et al., 2014). Thus, insulin resistant African American populations may be more successful at compensation for persistent hyperglycemia compared to Asian Indians in diabetes development.

SA-Mixed ancestry had the highest levels of insulin resistance among iIFG, IFG+IGT, and newly diagnosed type 2 diabetes compared to the three other groups. Other studies have reported elevated insulin resistance among sub-Saharan Africans. A study of Ghanaians found that insulin resistance among iIFG accounted for the geographical differences among native Ghanaians and Ghanaian migrants. Additionally, BMI and waist circumference were associated with insulin resistance (Meeks et al., 2017). The SA-Mixed ancestry group may be different than other populations due to the mixed ancestry nature of the population and lack of studies focused on the role the mixed ancestry heritage. The three African populations were distinct, and SA-Mixed ancestry did not follow the trends of the African immigrants and African Americans. While problems in insulin secretion among Asian Indians seems to be a significant phenotype, insulin resistance and primary β-cell failure among Abnl-GT participants in the African populations seems to be a major driver despite the differences in the populations.

This study has several strengths. First, the study uses samples of three different African cohorts who are at high-risk for type 2 diabetes which have not been compared in the past. We also included a population known *a priori* for impairments to β-cell function under low BMI levels as an additional comparator. The inclusion of participants across glycemic groups, allow

us to assess the full spectrum of glycemia, and those with diabetes were newly classified, without confounding by factors such as medication use. All glycemic categories were determined using OGTT data, which are more rigorous and informative than random glucose values or fasting blood measures alone.

Limitations of this study include its cross-sectional design, limiting the ability to infer temporality or causality. Three different insulin assays were used across the four cohorts and observations may be due to differences in assay performance. There were also large differences in sample sizes and prevalence of type 2 diabetes among the four cohorts. While three cohorts had fasting, 30-minute, and 2-hour measures for glucose and insulin, 30-minute measures for SA-Mixed ancestry were not available making it not possible to compare the main measure of β-cell function (insulinogenic index). To overcome some of these limitations, standardized variables within each ethnicity were used in the polytomous logistic regression models. The results of the present analysis cannot be generalized to all African populations or African immigrants due to limitations in participant selection, including convenience sampling across two of the cohorts analyzed.

Conclusion

This study suggests that there are heterogenous pathways across the development of type 2 diabetes and the contributions of insulin resistance and β-cell function may vary among various ethnic populations. Specifically, contributions of insulin resistance and β-cell function were similar in the odds of diabetes, while there was increased variation in the relative contribution of insulin resistance and β-cell function in the odds of prediabetes across ethnic groups. Additionally, for every unit reduction in the insulinogenic index, Asian Indians had more prediabetes that was predominately iIFG, while African immigrants had more prediabetes that

was predominately iIGT. Asian Indians had pronounced impairments in insulin secretion and are unable to compensate even small increases in insulin resistance, especially in the early phase of disease. African immigrants and African Americans had insulin resistance but also seem to be able to compensate with higher levels of insulin secretion compared to Asian Indians. SA-Mixed ancestry participants had high levels of insulin resistance in specific strata but there was not a consistent pattern driving disease development.

While causality cannot be determined from this study, there are several important implications of these results. First, there is pronounced ethnic heterogeneity in the early natural history of diabetes. Future studies will need to examine the molecular mechanisms driving these physiologic phenotypes. Next, this study provides evidence that precision medicine will need to address risk stratification in ways that are beyond current clinical practices, such as the role of overweight BMI or the lack thereof in stratifying risk. Next, populations, including those of African origin are not homogenous, and true progress in medicine will require refinements to screening, early diagnosis, and treatment that acknowledge. An improved understanding of how diabetes may develop differently across global populations may improve approaches to screening, diagnosis, and treatment.

Public Health Implications

Our study suggests that different ethnicities have variation in early disease processes leading to prediabetes, and it is important to understand the differences, especially given the projected to increase among Asian Indian, African, and African American populations (International Diabetes Federation, 2021). Future epidemiologic research characterizing prediabetes subtypes globally, including how race/ethnicity, age, sex, environmental conditions, genetics, and other factors impact risk of these subtypes could lead to advances in the areas of

clinical care and precision public health, defined as appropriate public health interventions delivered to populations at the right time of need (Khoury et al., 2016), including prevention strategies in weight loss, monitoring and screening, and even medication effectiveness.

This study contributes to the evidence demonstrating the importance of evaluating participants based on a wide range of BMI spectra and not focusing solely on overweight and obese populations. Even within normal weight there were participants with prediabetes and diabetes, especially among Asian Indians, demonstrating limitations of this traditional risk factor for type 2 diabetes among Asian Indians. While obesity correlates strongly with the pathophysiology of insulin resistance, insulin resistance is less commonly measured in the clinic. Thus, for individuals who have high risk, there is a need for additional biomarkers, beyond blood glucose and HbA1c, that may indicate early-stage progression towards diabetes and impairments to pancreatic beta cell function. This highlights the need for further research to understand disease mechanisms and, further, to identify markers or tools that can stratify diabetes risk or more effectively treat individuals for specific subtypes of metabolic dysregulation in diabetes development.

Finally, this study focused on four populations that have been previously understudied in diabetes pathophysiology. Studying these populations is important because they reside in regions that are growing epicenters of diabetes development. For example, Africans in Africa are projected to have the largest increase in prevalence of type 2 diabetes by 2045 (International Diabetes Federation, 2021). This study provides evidence for how African populations are heterogeneous in diabetes development, further supporting the need to include diverse populations in research. By coupling evidence from epidemiologic research with evidence in basic science, future research will be better positioned to develop new, more effective targets for

prevention and treatment. Taking an approach of pluralism in global diabetes research, including who is included at the table of discovery, will enable more rapid development of precision medicine for all, and not just some.

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Appendix

APPENDIX TABLES 1A-D. Metabolic Characteristics across glucose tolerance groups adjusted for age, sex, and BMI

(A) NORMAL GLUCOSE TOLERANCE-REFERENCE

Characteristic	Asian Indians (n=993)		African immigrants (n=269)		SA-Mixed ancestry (n=682)		African Americans (n=109)		Total (n=2053)
	LS Mean	SE	LS Mean	SE	LS Mean	SE	LS Mean	SE	p-value
Waist Circumference (cm)	82.5	0.2	83.8	0.4	82.4	0.3	86.7	0.7	<.0001
Fasting Glucose (mg/dL)	89.0	0.2	87.7	0.4	83.4	0.3	83.7	0.7	<.0001
30 min Glucose (mg/dL)	136.4	0.81	127.73	1.6			124.5	2.4	<.0001
2-hour Glucose (mg/dL)	92.7	0.6	110.9	1.2	92.2	0.8	108.4	1.9	<.0001
Fasting Insulin (uIU/mL)	6.5	0.1	4.5	0.1	5.3	0.1	5.5	0.2	<.0001
30 min Insulin (uIU/mL)	52.1	1.1	65.8	2.1			65.3	3.3	<.0001
2-hour Insulin (uIU/mL)	38.3	0.9	44.5	1.7	32.3	1.1	45.7	2.6	<.0001
HOMA-IR ((uIU/mL*mmol)/L^2)	1.4	0.0	1.0	0.0	1.1	0.0	1.1	0.0	<.0001
HOMA-B (uIU/mL)/(mmol/L)	94.2	9.7	58.7	19.0	133.2	11.9	108.0	29.3	0.0039
Insulinogenic Index (pmol/mmol) *	1.0	1.0	1.4	1.1			1.3	1.1	<.0001
Oral Disposition Index (l/mmol) *	0.2	1.0	0.4	1.1			0.3	1.1	<.0001

*Geometric means and geometric standard errors provided.

(B) NORMAL GLUCOSE TOLERANCE-INSULIN RESISTANCE

Characteristic	Asian Indians (n=167)		African immigrants (n=54)		SA-Mixed ancestry (n=126)		African Americans (n=23)		Total (n=370)
	LS Mean	SE	LS Mean	SE	LS Mean	SE	LS Mean	SE	p-value
Waist Circumference (cm)	92.5	0.7	95.9	1.2	95.8	0.8	100.5	1.8	<.0001
Fasting Glucose (mg/dL)	92.4	0.6	90.4	0.9	87.7	0.6	89.9	1.5	<.0001
30 min Glucose (mg/dL)	146.8	1.97	132.25	3.4			126.3	5.6	0.0005
2-hour Glucose (mg/dL)	98.9	1.5	117.7	2.6	104.1	1.8	111.8	4.0	<.0001
Fasting Insulin (uIU/mL)	15.4	0.5	14.3	0.9	18.5	0.6	13.6	1.4	0.0002
30 min Insulin (uIU/mL)	108.1	6.0	150.3	10.4			134.2	17.1	0.0039
2-hour Insulin (uIU/mL)	90.2	4.9	114.8	8.3	90.6	5.8	65.7	13.0	0.001
HOMA-IR ((uIU/mL*mmol)/L^2)	3.5	0.1	3.2	0.2	3.9	0.1	3.0	0.3	0.0016
HOMA-B (uIU/mL)/(mmol/L)	240.5	29.3	228.9	49.3	123.6	34.2	168.2	76.7	0.0055
Insulinogenic Index (pmol/mmol) *	1.6	1.1	2.9	1.1			2.8	1.2	<.0001
Oral Disposition Index (l/mmol) *	0.1	1.1	0.2	1.1			0.2	1.2	<.0001

*Geometric means and geometric standard errors provided.

(C) ABNORMAL GLUCOSE TOLERANCE-INSULIN RESISTANCE

Characteristic	Asian Indians (n=270)		African immigrants (n=77)		SA-Mixed ancestry (n=152)		African Americans (n=24)		Total (n=523)
	LS Mean	SE	LS Mean	SE	LS Mean	SE	LS Mean	SE	p-value
Waist Circumference (cm)	95.0	0.5	100.1	0.8	99.2	0.6	104.1	1.5	<.0001
Fasting Glucose (mg/dL)	137.4	3.1	106.6	5.7	126.1	4.3	106.0	10.3	<.0001
30 min Glucose (mg/dL)	224.4	4.0	162.1	7.6			164.2	14.4	<.0001
2-hour Glucose (mg/dL)	198.7	5.9	187.1	10.8	184.9	8.1	179.3	19.5	<.0001
Fasting Insulin (uIU/mL)	13.7	0.9	14.0	1.7	20.8	1.3	16.3	3.1	0.0001
30 min Insulin (uIU/mL)	67.0	3.0	97.3	5.7			117.6	10.8	<.0001
2-hour Insulin (uIU/mL)	78.7	4.9	136.1	8.9	99.5	6.7	173.7	16.0	<.0001
HOMA-IR ((uIU/mL*mmol)/L^2)	4.5	0.5	3.7	0.9	6.8	0.7	4.3	1.6	0.0476
HOMA-B (uIU/mL)/(mmol/L)	94.2	7.0	135.3	12.8	163.9	9.6	167.1	23.1	<.0001
Insulinogenic Index (pmol/mmol) *	0.5	1.1	1.3	1.1			1.6	1.2	<.0001
Oral Disposition Index (l/mmol) *	0.04	1.1	0.1	1.1			0.1	1.2	<.0001

*Geometric means and geometric standard errors provided.

(D) ABNORMAL GLUCOSE TOLERANCE-BETA-CELL-FAILURE

Characteristic	Asian Indians (n=320)		African immigrants (n=123)		SA-Mixed ancestry (n=152)		African Americans (n=29)		Total (n=624)
	LS Mean	SE	LS Mean	SE	LS Mean	SE	LS Mean	SE	p-value
Waist Circumference (cm)	87.5	0.4	89.6	0.6	89.2	0.6	94.6	1.3	<.0001
Fasting Glucose (mg/dL)	105.4	0.7	94.2	1.1	98.6	1.1	87.6	2.3	<.0001
30 min Glucose (mg/dL)	176.0	1.8	143.7	3.0			140.7	6.1	<.0001
2-hour Glucose (mg/dL)	130.5	2.3	158.5	3.9	156.8	3.7	157.8	7.7	<.0001
Fasting Insulin (uIU/mL)	7.1	0.1	5.6	0.2	5.5	0.2	6.8	0.4	<.0001
30 min Insulin (uIU/mL)	48.1	2.0	58.8	3.2			64.1	6.6	0.0248
2-hour Insulin (uIU/mL)	49.4	2.2	78.4	3.7	54.0	3.5	87.0	7.3	<.0001
HOMA-IR ((uIU/mL*mmol)/L^2)	1.9	0.0	1.3	0.0	1.3	0.0	1.5	0.1	<.0001
HOMA-B (uIU/mL)/(mmol/L)	56.4	7.3	75.8	12.1	63.1	11.5	108.3	24.1	0.0338
Insulinogenic Index (pmol/mmol) *	0.6	1.1	0.9	1.1			0.9	1.2	<.0001
Oral Disposition Index (l/mmol) *	0.1	1.1	0.2	1.1			0.1	1.2	<.0001

*Geometric means and geometric standard errors provided.

APPENDIX TABLES 2A-C. Relative contributions of insulin resistance and β-cell failure across glycemic status across three ethnicities

(A) ASIAN INDIANS

		Normoglycemia	**Prediabetes**		**Diabetes**	
Model	Variable	OR	OR	p-value	OR	p-value
1	Insulinogenic Index	1	0.58 (0.51, 0.66)	<.0001	0.16 (0.12, 0.21)	<.0001
2	Insulinogenic Index	1	0.47 (0.41, 0.54)	<.0001	0.09 (0.06, 0.13)	<.0001
2	HOMA-IR	1	3.32 (2.8, 3.94)	<.0001	10.53 (7.95, 13.94)	<.0001
3	Insulinogenic Index	1	0.49 (0.42, 0.57)	<.0001	0.09 (0.07, 0.14)	<.0001
3	HOMA-IR	1	3.30 (2.77, 3.92)	<.0001	10.48 (7.89, 13.91)	<.0001
4	Insulinogenic Index	1	0.48 (0.42, 0.56)	<.0001	0.09 (0.06, 0.13)	<.0001
4	HOMA-IR	1	3.32 (2.78, 3.95)	<.0001	10.66 (8.01, 14.19)	<.0001
5	Insulinogenic Index	1	0.49 (0.42, 0.57)	<.0001	0.09 (0.07, 0.14)	<.0001
5	HOMA-IR	1	2.97 (2.48, 3.55)	<.0001	9.50 (7.09, 12.71)	<.0001

Odds ratios (OR) are expressed per 1 standard deviation (SD) unit for each variable standardized within each ethnicity for each outcome relative to the normoglycemia group (OR=1). Model 1 contains insulinogenic index independently. Model 2 contains insulinogenic index and HOMA-IR. Model 3 adjusts for age. Mode 4 adjusts for age and sex. Model 5 adjusts for age, sex, and BMI.

(B) AFRICAN IMMIGRANTS

		Normoglycemia	**Prediabetes**		**Diabetes**	
Model	Variable	OR	OR	p-value	OR	p-value
1	Insulinogenic Index	1	0.66 (0.53, 0.82)	<.0001	0.18 (0.11, 0.29)	<.0001
2	Insulinogenic Index	1	0.35 (0.26, 0.48)	<.0001	0.05 (0.03, 0.11)	<.0001
2	HOMA-IR	1	3.68 (2.63, 5.15)	<.0001	10.84 (6.33, 18.55)	<.0001
3	Insulinogenic Index	1	0.35 (0.26, 0.49)	<.0001	0.05 (0.03, 0.11)	<.0001
3	HOMA-IR	1	3.75 (2.65, 5.32)	<.0001	10.95 (6.34, 18.90)	<.0001
4	Insulinogenic Index	1	0.36 (0.26, 0.49)	<.0001	0.05 (0.03, 0.11)	<.0001
4	HOMA-IR	1	3.80 (2.68, 5.39)	<.0001	11.04 (6.39, 19.09)	<.0001
5	Insulinogenic Index	1	0.36 (0.26, 0.49)	<.0001	0.05 (0.03, 0.11)	<.0001
5	HOMA-IR	1	3.57 (2.48, 5.14)	<.0001	9.64 (5.42, 17.13)	<.0001

Odds ratios (OR) are expressed per 1 standard deviation (SD) unit for each variable standardized within each ethnicity for each outcome relative to the normoglycemia group (OR=1). Model 1 contains insulinogenic index independently. Model 2 contains insulinogenic index and HOMA-IR. Model 3 adjusts for age. Mode 4 adjusts for age and sex. Model 5 adjusts for age, sex, and BMI.

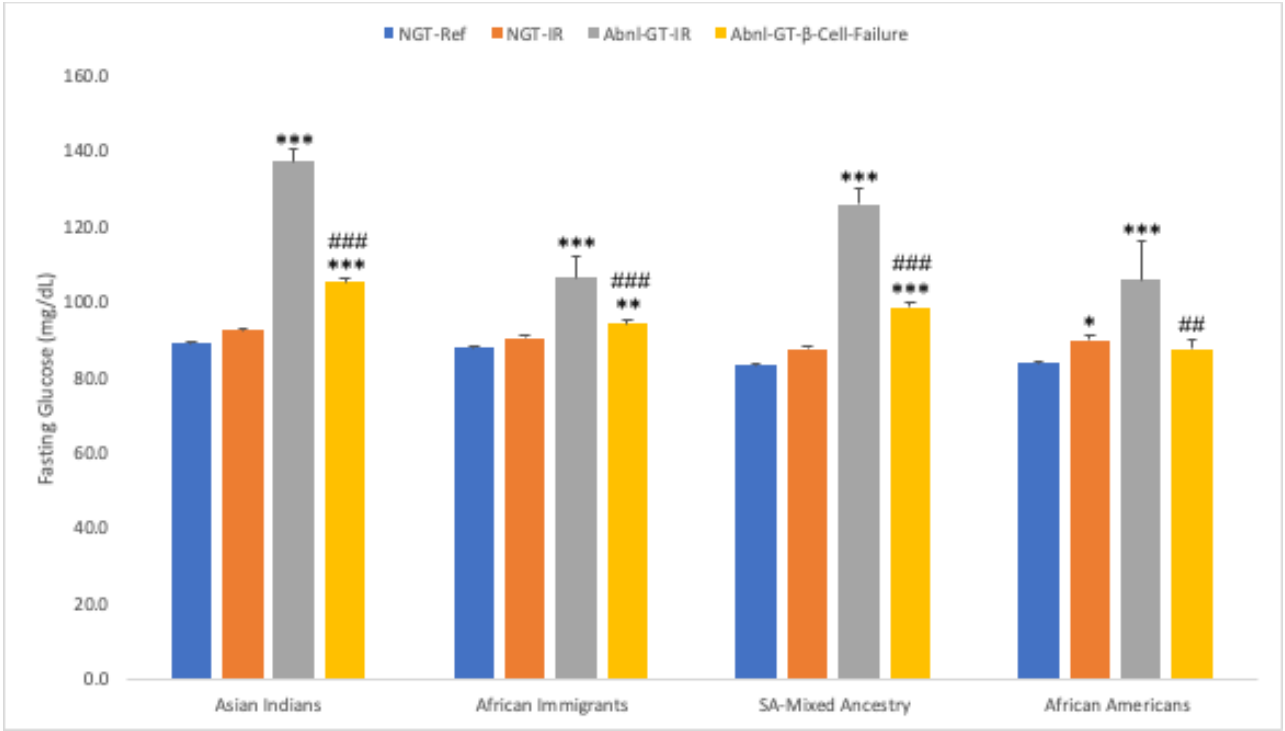
(C) AFRICAN AMERICANS

		Normoglycemia	**Prediabetes**		**Diabetes ~**	
Model	Variable	OR	OR	p-value	OR	p-value
1	Insulinogenic Index	1	0.79 (0.57, 1.11)	0.1735		
2	Insulinogenic Index	1	0.42 (0.26, 0.68)	0.0005		
2	HOMA-IR	1	4.38 (2.52, 7.63)	<.0001		
3	Insulinogenic Index	1	0.45 (0.27, 0.74)	0.0018		
3	HOMA-IR	1	4.05 (2.33, 7.04)	<.0001		
4	Insulinogenic Index	1	0.43 (0.26, 0.72)	0.0014		
4	HOMA-IR	1	4.12 (2.36, 7.20)	<.0001		
5	Insulinogenic Index	1	0.45 (0.27, 0.74)	0.002		
5	HOMA-IR	1	2.89 (1.57, 5.34)	0.0007		

Odds ratios (OR) are expressed per 1 standard deviation (SD) unit for each variable standardized within each ethnicity for each outcome relative to the normoglycemia group (OR=1). Model 1 contains insulinogenic index independently. Model 2 contains insulinogenic index and HOMA-IR. Model 3 adjusts for age. Mode 4 adjusts for age and sex. Model 5 adjusts for age, sex, and BMI. ~Odds ratios for the diabetes group not shown for African Americans due to low sample size.

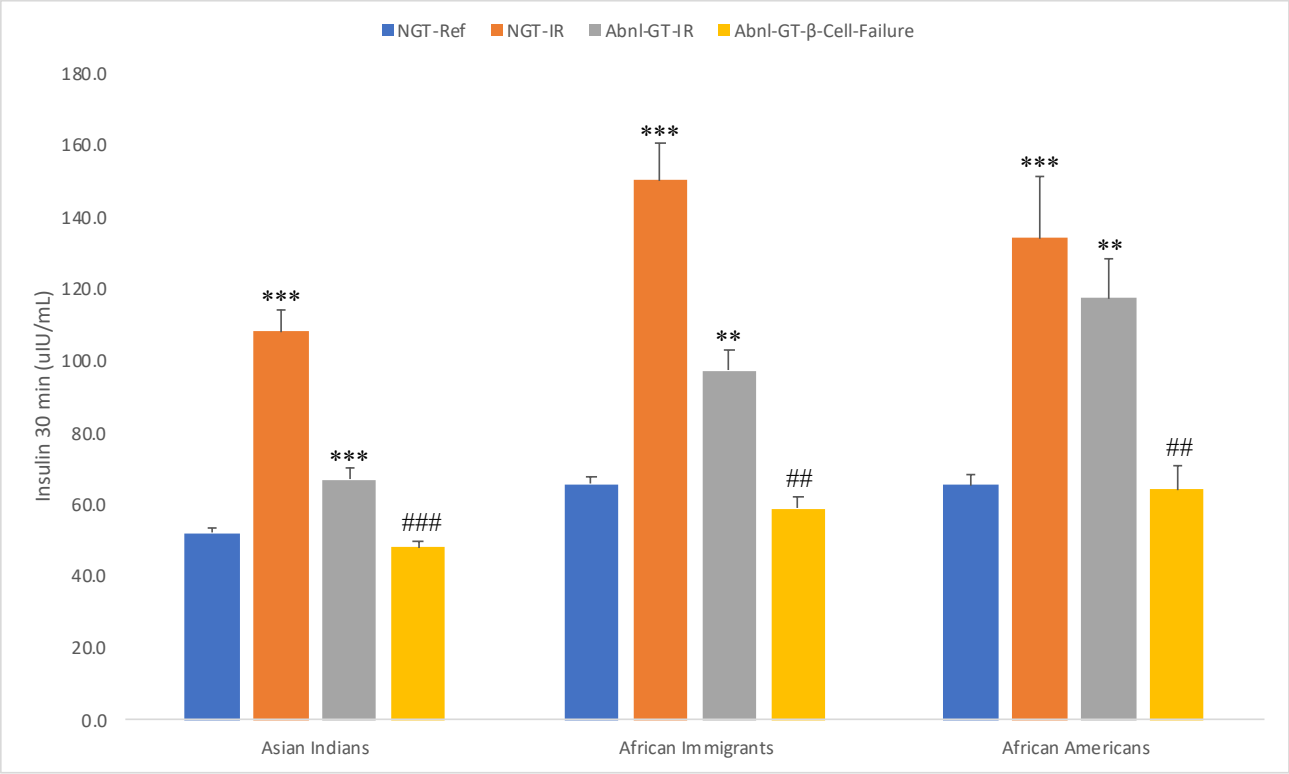
APPENDIX FIGURES 1A-E. Variation of measures within each ethnicity across glucose tolerance groups, adjusted for age, sex, and BMI. The glucose tolerance groups include normal glucose tolerance-reference (NGT-Ref), NGT-insulin resistant (NGT-IR), abnormal glucose tolerance-insulin resistance (Abnl-GT-IR), and Abnl-GT-beta-cell-failure (Abnl-GT-β-Cell-Failure).

(A) Mean Fasting Glucose within each ethnicity across glucose tolerance groups, adjusted for age, sex, and BMI



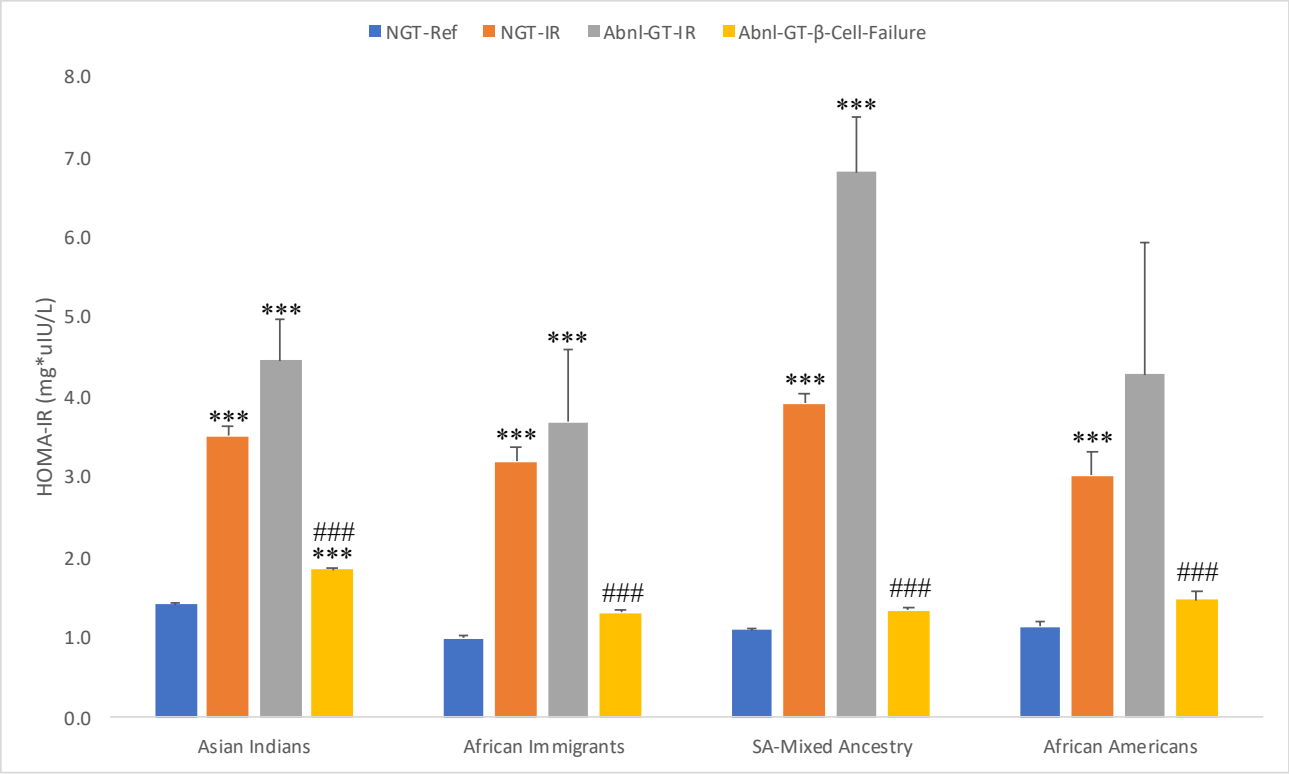
Asterisks denote differences within each ethnicity adjusted for age, sex, and BMI compared to the NGT-Ref group. *p≤0.05, **p≤0.01, ***p≤0.001. Hashtags are for differences between the two groups with Abnl-GT. # p≤0.05, ## p≤0.01, ### p≤0.001.

(B) 30-minute Insulin within each ethnicity across glucose tolerance groups, adjusted for age, sex, and BMI



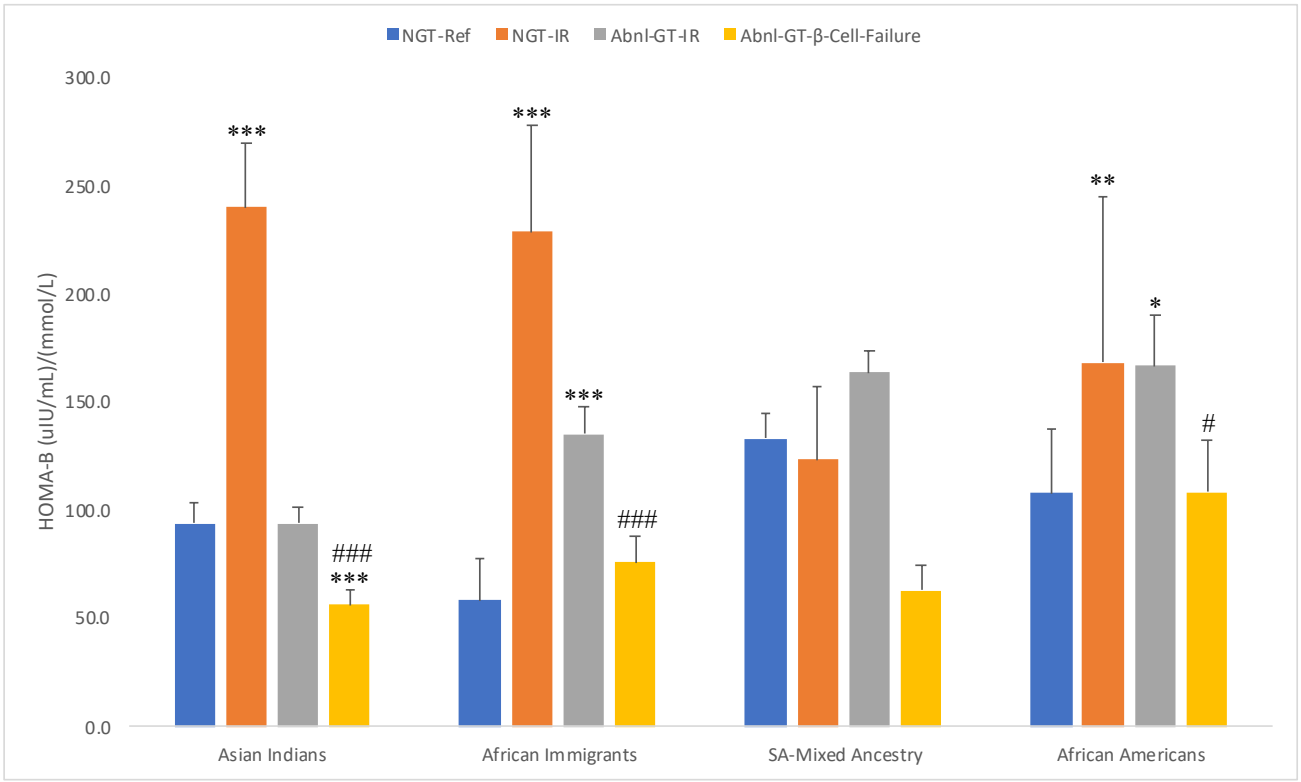
SA-Mixed ancestry are not represented due to lack of 30-minute OGTT measurements. Asterisks denote differences within each ethnicity adjusted for age, sex, and BMI compared to the NGT-Ref group. *p≤0.05, **p≤0.01, ***p≤0.001. Hashtags are for differences between the two groups with Abnl-GT. # p≤0.05, ## p≤0.01, ### p≤0.001.

(C) HOMA-IR within each ethnicity across glucose tolerance groups, adjusted for age, sex, and BMI



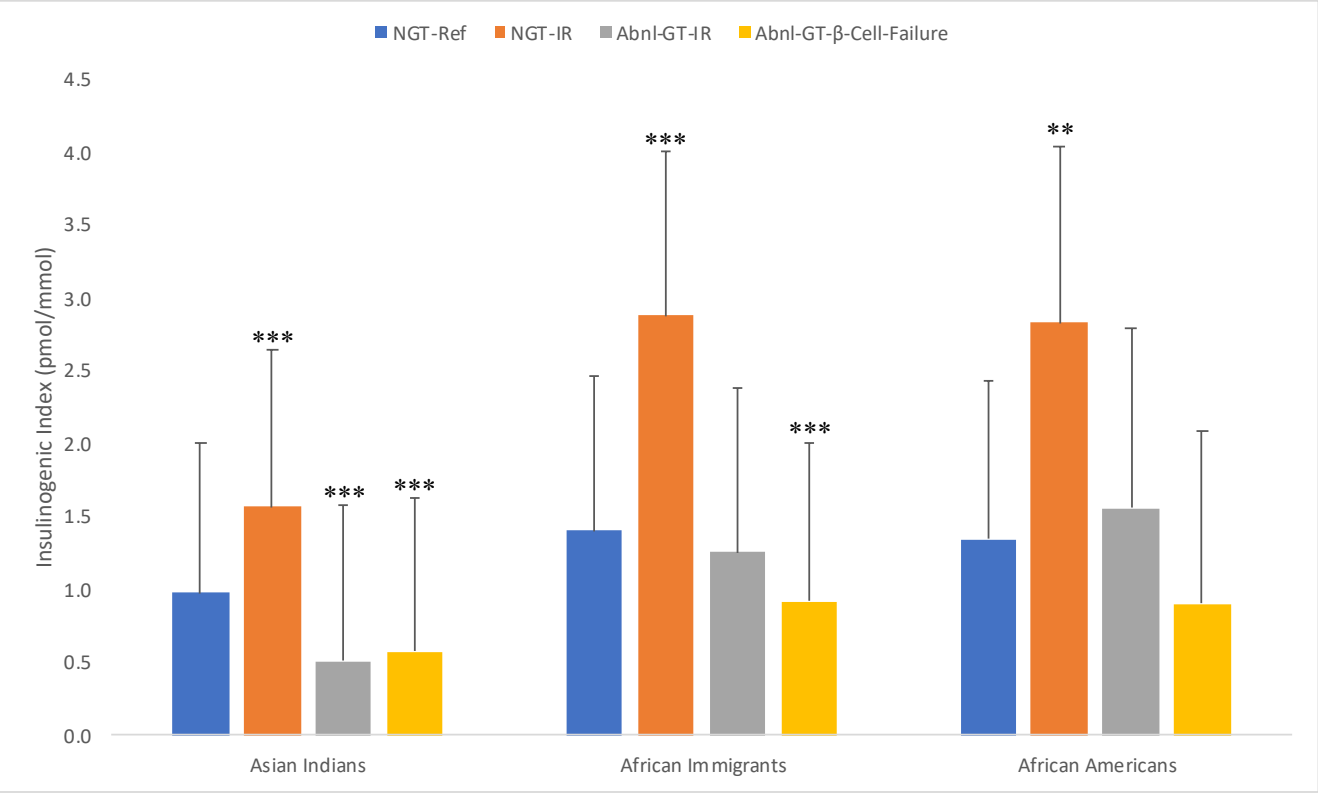
Asterisks denote differences within each ethnicity adjusted for age, sex, and BMI compared to the NGT-Ref group. *p≤0.05, **p≤0.01, ***p≤0.001. Hashtags are for differences between the two groups with Abnl-GT. # p≤0.05, ## p≤0.01, ### p≤0.001.

(D) HOMA-B within each ethnicity across glucose tolerance groups, adjusted for age, sex, and BMI



Asterisks denote differences within each ethnicity adjusted for age, sex, and BMI compared to the NGT-Ref group. *p≤0.05, **p≤0.01, ***p≤0.001. Hashtags are for differences between the two groups with Abnl-GT. # p≤0.05, ## p≤0.01, ### p≤0.001.

(E) Insulinogenic Index within each ethnicity across glucose tolerance groups, adjusted for age, sex, and BMI



SA-Mixed ancestry are not represented due to lack of 30-minute OGTT measurements. Asterisks denote differences within each ethnicity adjusted for age, sex, and BMI compared to the NGT-Ref group. *p≤0.05, **p≤0.01, ***p≤0.001. Hashtags are for differences between the two groups with Abnl-GT. # p≤0.05, ## p≤0.01, ### p≤0.001.