Concordance between fasting plasma glucose and HbA1c in the diagnosis of diabetes in black South African adults: a cross-sectional study

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ABSTRACT

Objectives We investigated concordance between haemoglobin A1c (HbA1c)-defined diabetes and fasting plasma glucose (FPG)-defined diabetes in a black South African population with a high prevalence of obesity. Design Cross-sectional study. Setting Rural South African population-based cohort. Participants 765 black individuals aged 40–70 years and with no history of diabetes. Primary and secondary outcome measures The primary outcome measure was discordance between HbA1c-defined diabetes and FPG-defined diabetes. Secondary outcome measures were differences in anthropometric characteristics, fat distribution and insulin resistance (measured using Homeostatic Model Assessment of Insulin Resistance (HOMA-IR)) between those with concordant and discordant HbA1c/FPG classifications and predictors of HbA1c variance.

Results The prevalence of HbA1c-defined diabetes was four times the prevalence of FPG-defined diabetes (17.5% vs 4.2%). Classification was discordant in 15.7% of participants, with 111 individuals (14.5%) having HbA1c-only diabetes (kappa 0.23; 95% CI 0.14 to 0.31). Median body mass index, waist and hip circumference, waist-to-hip ratio, subcutaneous adipose tissue and HOMA-IR in participants with HbA1c-only diabetes were similar to those in participants who were normoglycaemic by both biomarkers and significantly lower than in participants with diabetes by both biomarkers (p<0.05). HOMA-IR and fat distribution explained additional HbA1c variance beyond glucose and age only in women.

Conclusions Concordance was poor between HbA1c and FPG in diagnosis of diabetes in black South Africans, and participants with HbA1c-only diabetes phenotypically resembled normoglycaemic participants. Further work is necessary to determine which of these parameters better predicts diabetes-related morbidities in this population and whether a population-specific HbA1c threshold is necessary.

INTRODUCTION

Sub-Saharan Africa is projected to experience a 140% increase in the prevalence of diabetes mellitus by 2045 and accurate, comparable prevalence estimates will be essential to planning and monitoring by public health authorities. The WHO guidelines for the diagnosis of diabetes, which inform the approach in many sub-Saharan African countries, include haemoglobin A1c (HbA1c) as a diagnostic criterion for diabetes. Diagnosis based on HbA1c is attractive because it provides an integrated assessment of glycaemic status over the preceding 3 months and has low analytical variability, but the extent to which this single threshold may be adopted in all sub-Saharan African populations is questionable. Existing data suggest that in individuals of African descent, HbA1c may be higher for any given degree of glycaemia than in individuals of European descent. Beyond this, there is intracontinental variation in the prevalence of conditions which may affect red blood cells such as anaemia and haemoglobinopathies. Unlike black populations from West Africa or the largely West African-descent African-American and

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Strengths and limitations of this study

► In contrast to the few previous studies of the association between fasting glucose and haemoglobin A1c in sub-Saharan African populations, this study compares adipose tissue distribution and markers of insulin resistance between individuals with diabetes defined by different biomarkers.
► This study was population based and conducted in a rural, underserved population, reflecting the majority of sub-Saharan Africa that resides in rural communities.
► Two hour glucose tolerance tests were not performed and the contribution of postprandial glucose to HbA1c variability could not be assessed.

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Afro-Caribbean populations, haemoglobinopathies such as sickle cell disease are rare in South Africa. Regional evaluation of the appropriateness of the internationally recommended HBA1c criterion within different areas of sub-Saharan Africa is, therefore, necessary.

Previous studies comparing diabetes prevalence using different biomarkers have revealed significant heterogeneity. In a meta-analysis of 96 population-based studies, HBA1c-based prevalence was lower than fasting plasma glucose (FPG)-based prevalence in 42.8% of age-sex-survey groups, higher in 41.6% and similar in 15.6%. Interpreting this result in the context of sub-Saharan Africa more broadly and South Africa in particular is difficult, however, as a single study from a mixed ancestry sub-Saharan African population was included. This study may not be representative of South African populations with less genetic admixture.

We investigated the concordance between diabetes defined by two commonly used tests, namely FPG and HBA1c, in a black South African population with high background rates of obesity and therefore at higher risk for dysglycaemia. We hypothesised that the prevalence of diabetes would differ by biomarker and performed analyses to investigate what factors, in addition to FPG, predicted HBA1c overall and in analyses stratified by sex.

METHODS

Study setting and sample

This work was nested in two studies: Health and Ageing in Africa—a Longitudinal Study in an INDEPTH community (HAALSI) and the Africa Wits-INDEPTH partnership for Genomic Studies (AWI-Gen), which jointly recruited participants from the Agincourt Health and Socio-Demographic Surveillance System (HDSS). The Agincourt HDSS comprises 450 km² and approximately 120 000 people living in 31 research villages and is located 500 km northeast of Johannesburg in rural Mpumalanga, South Africa. The HDSS is managed by the MRC/Wits Rural Public Health and Heath Transitions Research Unit (Agincourt), which annually enumerates the entire population of the HDSS to capture all vital events, that is, births, deaths and migrations, which ensures robust denominators.

Both HAALSI and AWI-Gen have been described in detail previously. In brief, 6281 individuals of the 12 875 people ≥40 years and resident in the HDSS who met eligibility criteria were randomly selected to participate in HAALSI and 5059 were enrolled in the study cohort. A random sample of 3 273 HAALSI participants, stratified by age, were invited to enrol in the AWI-Gen cohort. A total of 2486 individuals enrolled in AWI-Gen and samples for 1497 of these individuals were randomly selected for HBA1c analysis.

The sampling strategy for this analysis is shown in online supplemental figure S1. HAALSI/AWI-Gen cohort members were eligible for inclusion in this analysis if they were aged 40–70 years, reported never having been diagnosed with diabetes by a healthcare practitioner and had valid results for HBA1c, FPG and study covariates in the dataset. Individuals ≥70 years were excluded from the analysis as these individuals completed a limited study protocol and did not attend clinic visits as outlined below.

Patient and public involvement

Prior to the initiation of the HAALSI and AWI-Gen studies, an extensive process of community engagement was led by Dr Rhian Twine, head of the Agincourt Office of Public Engagement. This included meetings with the Community Advisory Group, nominated by Community Development Forums and civic and traditional leadership structures to discuss planned research activities. Feedback on the results of this study will be included in the annual feedback of study results to villagers and community leaders.

Data collection

Data collection occurred at household and clinic visits which took place between November 2014 and August 2016.

Household visits

Sociodemographic and health status data were obtained from participants during household visits as previously described. Capillary blood samples and dried blood spots were collected.

Clinic visits

Participants were subsequently evaluated at a single central facility (median 160 days between household and clinic visits) where weight, height, waist circumference (WC) and hip circumference (HC) were measured using standard procedures and visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) were measured with ultrasound as previously described. In brief, VAT was measured as the thickness of the fat pad between the peritoneum and anterior spine at end expiration and SAT as the distance between the skin and the outer edge of the linea alba. Venous blood samples were collected at the clinic visit after an overnight fast.

Sample processing

Sample collection and processing occurred at the same location, which facilitated immediate sample processing. Samples for FPG and insulin were collected in potassium oxalate/sodium fluoride and clot activator tubes, respectively, and centrifuged immediately after collection, with storage of the resulting supernatant at −80°C until analysis. Two millilitres of whole blood were collected in an EDTA tube for HBA1c determination and frozen under similar conditions until analysis.

Sample analyses

Capillary blood samples were tested for haemoglobin at point of collection (Haemocue Hb 201+analyser; Haemocue, Sweden). Whole blood was analysed for HBA1c using high-performance liquid chromatography on the
National Glycohaemoglobin Standardisation Programme-traceable Bio-Rad D-10 (Bio-Rad Laboratories, USA) with a reportable range of 3.8%–18.5% (18–179 mmol/mol) and coefficient of variation (CV) <1.3%. Plasma was analysed for glucose using colorimetric methods on the Random Plus clinical chemistry analyser (Random, UK) with a range of 0.36–35 mmol/L and CV <2.5%. Serum insulin assays were performed on the Immulite 1000 chemistry analysis system (Siemens, Germany), using a solid-phase, enzyme-labelled chemiluminescent immunoometric assay (range 2–300 μU/mL; CV <8%).

Dried blood spots were analysed for HIV serostatus using the Vironostika Uniform 11 (Biomerieux, France) screening assay. Positive tests were confirmed with Roche Elecsys (Roche, USA).

Definition of variables
Body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared. Individuals were classified as HIV positive if they reported being previously diagnosed with HIV or tested positive on screening and subsequent confirmatory tests, HIV negative if they reported previously having tested negative or tested negative on screening and indeterminate if they were unaware of their status and declined a screening test; antiretroviral therapy use was self-reported.

Individuals were classified as having diabetes by FPG criteria if FPG was ≥7.0 mmol/L and by HbA1c criteria if HbA1c was ≥6.5% (48 mmol/mol). Insulin resistance was estimated using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), calculated as fasting glucose (mmol/L) × fasting insulin (mU/mL) / 22.5.

Statistical analyses
Continuous variables were described using medians and IQR as several of our variables, including the key variables of FPG and HbA1c, were not normally distributed; categorical variables were described using percentages. Concordance between FPG and HbA1c classifications was determined using Cohen’s kappa statistic and was designated as negative by both biomarkers, HbA1c-only diabetes, FPG-only diabetes or diabetes by both biomarkers. As several of our variables were not normally distributed, the non-parametric Mann-Whitney U test was used to compare continuous variables between groups stratified by sex, while the Kruskal-Wallis test was used to compare continuous variables between groups stratified by concordance classification. Post hoc Dunn’s tests were used to compare continuous variables between concordance classification pairs if the overall test was significant. χ² and Fisher’s exact tests were used to compare categorical variables between groups.

The association between FPG (both FPG and FPG² terms were included, given the quadratic relationship between fasting glucose and HbA1c) and HbA1c was explored in age-adjusted linear regression models which were sequentially adjusted for potential confounders. Confounders were included if they were associated with HbA1c on univariate regression analysis (p<0.02) or if previous research suggested a possible relationship with HbA1c and were grouped as medical history (previous diagnosis of tuberculosis, HIV status and haemoglobin), anthropometrics (BMI, WC, HC and waist-to-hip ratio), markers of insulin resistance (HOMA-IR) and indices of fat distribution (VAT and SAT). WC, HC and waist-to-hip ratio proved to be multicollinear (variance inflation factor greater than 5) and WC and HC were then excluded from the model, leaving BMI and waist-to-hip ratio in the anthropometrics grouping. HIV status was categorised as positive, negative or indeterminate and HOMA-IR was categorised into two strata: (1) incalculable due to undetectable insulin or below the median of available HOMA-IR values and (2) above the median of available HOMA-IR values. Likelihood ratio testing was performed to evaluate the statistical significance of additional variables in the model.

Observations were excluded from the analysis if data were missing for FPG, HbA1c or any of the study covariates. Sensitivity analyses were performed for our primary outcome of concordance between FPG and HbA1c in all individuals with both FPG and HbA1c, regardless of whether covariate data were missing. We also performed a sensitivity analysis to explore the effect of antiretroviral drugs on HbA1c variability in which HIV status, categorised as HIV negative, HIV positive not taking antiretroviral therapy and HIV positive taking antiretroviral therapy, was included in the medical history confounder.

Non-normal continuous variables were log transformed prior to linear regression analyses to improve normality. Values of p<0.05 were considered statistically significant. Analyses were performed using STATA V.14.2 (StataCorp).

An abstract presenting a similar analysis of these data was accepted for presentation at the 2020 conference of the Endocrine Society and published in a supplement of the Journal of the Endocrine Society.

RESULTS
Determination of analytic sample
The determination of the analytic sample is illustrated in online supplemental figure S1. Of the 1497 individuals whose samples were randomly selected for HbA1c analysis, 100 (6.7%) reported having previously been diagnosed with diabetes and were excluded from the analytic sample. Of the remaining 1397 participants, 1121 were aged 40–70 years and of these, 954 had available data on both FPG and HbA1c. One hundred and fifty-four individuals were missing valid data on FPG, 12 were missing valid data on HbA1c and one individual was missing both.

One hundred and eighty-nine participants were excluded due to missing data for one or more covariates. The most frequently missing covariates were visceral fat, which was missing in 12% of participants and subcutaneous fat which was missing in 9% of participants. Participants excluded due to missing covariate data did not
differ from the included participants by age (p=0.172), sex (p=0.807) or median FPG (p=0.770). Median HbA 1c was slightly lower in participants who were excluded (5.4% (36 mmol/mol) vs 5.5% (37 mmol/mol); p=0.026). The baseline characteristics of individuals excluded from the study are shown in online supplemental table S1.

Seven hundred and sixty-five participants were included in the final analysis.

**Characteristics of analytical sample**

The characteristics of the sample are shown in table 1. The median age was 55 years (IQR 48–62) and, as expected given the sampling strategy, half the sample was male. Women had greater general obesity (BMI 29.6 vs 23.8 kg/m²; p<0.01) and regional obesity (WC 98 vs 87 cm, p<0.01; HC 107 vs 96 cm, p<0.01). Direct assessments of body fat distribution revealed higher SAT in women (2.2 vs 1.1 cm, p<0.01), but no statistically significant difference in VAT (6.3 vs 6.4 cm; p=0.06). Diabetes prevalence defined by HbA 1c was four times higher than by FPG (17.5% vs 4.2%), with this several-fold increase in prevalence evident in both women (20.6% vs 4.4%) and men (14.4% vs 3.9%).

**Concordance between FPG classification and HbA 1c classification**

In 84.3% of cases, glycaemic status classification by FPG and HbA 1c was the same with 81.5% of individuals being classified as normoglycaemic by both measures and 3% classified as having diabetes (table 2). Classification discordance was largely due to having diabetes by HbA 1c but normoglycaemia by FPG, with 111 individuals (14.5%) in this category. Nine (1.2%) individuals were normoglycaemic by HbA 1c but had diabetes by FPG. The overall Cohen’s kappa statistic was 0.23. Using FPG-diagnosed diabetes as the standard, HbA 1c had a sensitivity of 71.9% and specificity of 84.9%.

In women, HbA 1c and FPG classifications were concordant in 82.8% of individuals (78.9% were normoglycaemic and 3.9% were classified as having diabetes), while 16.7% of women had diabetes defined only by HbA 1c and 0.5% had diabetes defined only by FPG. Concordance was similar in men, with 83.7% having normoglycaemia by both HbA 1c and FPG and 2.1% having diabetes by both measures; HbA 1c-only diabetes was present in 12.3% of men and FPG-only diabetes in 1.8%. Kappa statistics were 0.26 and 0.18 for women and men, respectively.

Concordance between HbA 1c and FPG classifications was similar in sensitivity analyses which included all 954 participants with valid FPG and HbA 1c data (online supplemental table S2).

**Phenotypic comparison by concordance classification**

Phenotypic differences were evident between classification groups (figure 1 and online supplemental table S3). No significant differences existed between those with HbA 1c-only diabetes and normoglycaemia, but there

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**Table 1 Clinical and demographic characteristics of the study sample**

|                          | Overall (n=765) | Women (n=384) | Men (n=381) | P value (women vs men) |
|--------------------------|----------------|--------------|------------|------------------------|
| Age (years)              | 55 (48, 62)    | 55 (49, 62)  | 55 (48, 62) | 0.77                   |
| BMI (kg/m²)              | 26.2 (22.4, 31.7) | 29.6 (25.4, 34.3) | 23.8 (20.7, 27.4) | <0.01          |
| Waist circumference (cm) | 92 (82, 103)   | 98 (86, 108) | 87 (79, 97) | <0.01                  |
| Hip circumference (cm)   | 101 (93, 110)  | 107 (99, 115) | 96 (90, 102) | <0.01                  |
| Waist-to-hip ratio       | 0.91 (0.86, 0.96) | 0.91 (0.85, 0.96) | 0.91 (0.87, 0.97) | 0.29             |
| Family history of diabetes | 115 (15.0)    | 66 (17.2)    | 49 (12.9)  | 0.20                   |
| HIV positive             | 148 (19.4)     | 66 (17.2)    | 82 (21.5)  | 0.29                   |
| Haemoglobin (g/L)        | 12.9 (11.7, 14.1) | 12.3 (11.1, 13.2) | 13.7 (12.5, 14.8) | <0.01          |
| Fasting glucose (mmol/L) | 4.8 (4.4, 5.4) | 4.8 (4.4, 5.3) | 4.9 (4.4, 5.4) | 0.19             |
| HbA 1c (%)               | 5.5 (5.1, 6.2) | 5.5 (5.1, 6.3) | 5.5 (5.1, 6.1) | 0.26             |
| HbA 1c (mmol/mol)        | 37 (32, 44)    | 37 (32, 45)  | 37 (32, 43) | 0.26                   |
| Fasting insulin (μIU/mL)*| 6.3 (3.6, 11.4)| 6.3 (3.7, 11.3)| 6.2 (3.5, 11.7)| 0.82             |
| HOMA-IR*                 | 1.3 (0.8, 2.6) | 1.3 (0.8, 2.5) | 1.4 (0.8, 2.7) | 0.79             |
| Visceral fat (cm)        | 6.3 (5.0, 7.9) | 6.3 (4.7, 7.9) | 6.4 (5.2, 8.0) | 0.06             |
| Subcutaneous fat (cm)    | 1.6 (1.0, 2.3) | 2.2 (1.5, 2.8) | 1.1 (0.8, 1.6) | <0.01          |
| Diabetes (fasting glucose criteria) | 32 (4.2) | 17 (4.4) | 15 (3.9) | 0.74             |
| Diabetes (HbA 1c criteria) | 134 (17.5) | 79 (20.6) | 55 (14.4) | 0.03             |

Data are expressed as median (IQR) or n (%).

*A total of 107 women and 172 men had insulin levels below the limit of detection (<2 μIU/mL); HOMA-IR, therefore, could not be calculated.

BMI, body mass index; HbA 1c, haemoglobin A1c; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance.
In this rural black South African population with a high prevalence of obesity, concordance between FPG and HbA1c in the diagnosis of diabetes was poor. Individuals who were more closely resembled those in individuals with diabetes defined by HbA1c, alone had anthropometric measures, fat distribution and measures of insulin resistance that were significant differences between those with HbA1c-only diabetes and diabetes by both biomarkers. Sex differences were significant; those with HbA1c-only diabetes in women and diabetes by both biomarkers in men. The factors explaining HbA1c variance included FPG and age, explained 14.8% of the variance in HbA1c in women; in men, the additional factors were those with HbA1c-only diabetes and diabetes by both biomarkers. Medical history (including diabetes duration and current treatment) was also included in the model. The factors explaining FPG variance included age, sex, and BMI, explained 26.0% of the variance in FPG in women; in men, the additional factors were those with HbA1c-only diabetes and diabetes by both biomarkers. Medical history (including diabetes duration and current treatment) was also included in the model.

Table 2  Agreement in diabetes classification by fasting glucose and HbA1c in study participants

|                      | Normoglycaemia n (%) | Diabetes n (%) | Total N (%) | Kappa statistic (95% CI) |
|----------------------|----------------------|----------------|-------------|--------------------------|
| Fasting glucose (overall) |                      |                |             |                          |
| HbA1c (overall)       |                      |                |             |                          |
| Normoglycaemia       | 622 (81.3)           | 111 (14.5)     | 733 (95.8)  | 0.23 (0.14 to 0.31)      |
| Diabetes             | 9 (1.2)              | 23 (3.0)       | 32 (4.2)    |                          |
| Total                | 631 (82.5)           | 134 (17.5)     | 765 (100)   |                          |
| Fasting glucose (women) |                      |                |             |                          |
| HbA1c (women)        |                      |                |             |                          |
| Normoglycaemia       | 303 (78.9)           | 64 (16.7)      | 367 (95.6)  | 0.26 (0.15 to 0.37)      |
| Diabetes             | 2 (0.5)              | 15 (3.9)       | 17 (4.4)    |                          |
| Total                | 305 (79.4)           | 79 (20.6)      | 384 (100)   |                          |
| Fasting glucose (men) |                      |                |             |                          |
| HbA1c (men)          |                      |                |             |                          |
| Normoglycaemia       | 319 (83.7)           | 47 (12.3)      | 366 (96.0)  | 0.18 (0.05 to 0.31)      |
| Diabetes             | 7 (1.8)              | 8 (2.1)        | 15 (3.9)    |                          |
| Total                | 326 (85.6)           | 55 (14.4)      | 381 (100)   |                          |

HbA1c, haemoglobin A1c.
also evident in the degree to which insulin resistance and indices of fat distribution explained variance in HbA1c.

Our study has several strengths. We rigorously collected standardised data and used internationally standard laboratory techniques in a South African environment. While studies in similar environments are frequently restricted to more easily accessible urban, clinical populations, our work was community-based and conducted in an underserved, rural population. This is particularly important as approximately 60% of sub-Saharan Africa still lives in rural areas. We also collected extensive phenotypic data on our participants, and therefore, unlike previous studies, we were able to investigate associations between HbA1c and adipose tissue distribution and measures of

**Table 3** Analysis of the effects of sequential adjustment on HbA1c variance by sex

|                      | Women                     | Men                      |
|----------------------|---------------------------|--------------------------|
|                      | Adjusted R²  | P value of LR test | Adjusted R²  | P value of LR test |
| Base model-glucose, glucose⁵, age | 0.148               | –                        | 0.114               | –                        |
| Model 1-base model plus history of TB, HIV status, Hb | 0.154               | 0.142                   | 0.116               | 0.281                   |
| Model 2-base model plus anthropometrics (BMI, WHR) | 0.148               | 0.327                   | 0.113               | 0.437                   |
| Model 3-base model plus visceral fat, subcutaneous fat | 0.163               | 0.011                   | 0.120               | 0.083                   |
| Model 4-base model plus HOMA-IR category | 0.187               | <0.001                  | 0.112               | 0.496                   |
| Model 5-base model plus visceral fat, subcutaneous fat, HOMA-IR category | 0.198               | <0.001                  | 0.121               | 0.094                   |

BMI, body mass index; Hb, haemoglobin; HbA1c, haemoglobin A1c; HOMA-IR, Homoeostatic Model Assessment of Insulin Resistance; LR, likelihood ratio; TB, tuberculosis; WHR, waist-to-hip ratio.
insulin resistance. Our study does have limitations which merit discussion. We excluded individuals who reported a previous diagnosis of diabetes, but given limited health literacy, individuals may have been unaware of diabetes diagnoses and/or treatment and may, therefore, have been inadvertently included in our analysis. Diabetes medications, however, would affect both FPG and HbA₁c, though possibly to varying degrees. We did not perform 2-hour oral glucose tests and so could not evaluate the contribution of postprandial glucose to HbA₁c variability.

To our knowledge, only two other population-based studies have specifically investigated the relationship between laboratory-based FPG and HbA₁c in diagnosing diabetes in black sub-Saharan African individuals, although concordance was not specifically determined in these studies. While there are similarities in participant ethnicity between our work and these studies, there are key differences that distinguish our research. Hird et al found that the age-standardised prevalence of diabetes in 1190 urban Black South Africans was similar using FPG and HbA₁c (11.9% vs 13.1%), with HbA₁c having a sensitivity of 74.1% and specificity of 98.1% in detecting FPG-defined diabetes. However, participants in that study were younger than in ours, with a median age of 39.7 years. Data from a study conducted in 3645 urban and rural Malawians (median age 33 years) revealed an HbA₁c-based prevalence of 7.3% compared with an FPG-based prevalence of 1.7%. HbA₁c had a sensitivity of 78.7% and specificity of 94.0% to detect FPG-diagnosed diabetes. The high HbA₁c specificity in both of these studies relative to our study may be partly attributable to the age-dependent relationship between HbA₁c and FPG, with HbA₁c increasing in older people independent of glycaemia. A second important difference is the lower BMI (median 22.6 kg/m²) in the Malawian study, given higher BMI is also associated with higher HbA₁c independent of glycaemia. Consequently, while previous studies in black sub-Saharan African populations have suggested comparable performance characteristics between venous HbA₁c and FPG in the diagnosis of diabetes, our study suggests that this may not be the case in a key demographic at high risk of developing diabetes, namely older adults with higher BMIs. Performance characteristics of HbA₁c and FPG may, however, be different in individuals who are not overweight or obese.

While data on concordance in black sub-Saharan African populations are limited, evidence from other black populations, primarily of Western African descent, does suggest that existing HbA₁c criteria may have limited agreement. In 939 individuals in Barbados, while there was no difference in diabetes prevalence using HbA₁c or FPG (4.9% vs 3.5%), concordance was limited with a kappa statistic of 0.39. Agreement was higher than in our study, with the glycaemic status classification by FPG and HbA₁c being the same in 93.8% of cases, with a further 3.8% having diabetes by HbA₁c and normoglycaemia by FPG, and 2.3% having normoglycaemia by HbA₁c and diabetes by FPG. Adults ≥25 years were included in this study, with 42% of the sample ≤45 years. Another study suggests that existing HbA₁c criteria may more frequently classify African-Americans as having diabetes. In a US population aged 70–79 years, the prevalence of HbA₁c-diagnosed diabetes in African-Americans was 5.7% compared with a prevalence of 3.5% using FPG criteria, in contrast with a prevalence in the entire sample, including Whites, of 3.1% (HbA₁c) vs 2.7% (FPG).

Our finding that those with HbA₁c-only diabetes were more comparable to those who were normoglycaemic by both biomarkers than to those who had diabetes by both biomarkers suggests that the HbA₁c elevation is not merely indicative of worsened glucose tolerance and individuals further along the dysglycaemia continuum. Indeed, indices of insulin resistance and fat distribution which may indirectly reflect glucose tolerance explained significantly more variance in HbA₁c only in our female participants and this was still limited to 20% of the overall variance. Further, the limited degree of HbA₁c variance explained by FPG supports existing evidence that non-glycaemic factors are important contributors to HbA₁c in this population. Similar findings have been reported in other population groups, with data in Finnish men without diabetes suggesting that indices of insulin sensitivity explained little additional HbA₁c variance over the 12% explained by age, FPG and C reactive protein. Glycaemic factors, defined as preprandial glucose, post-prandial glucose and glycaemic variability calculated from continuous glucose monitoring, along with age, sex, BMI and ethnicity explained 35% of HbA₁c variance in adults without diabetes, of which half was explained by the non-glycaemic variables. The importance of non-glycaemic variables in the determination of HbA₁c is further supported by the association of non-glycaemic loci with HbA₁c but these associations require further investigation in individuals across different sub-Saharan African regions, given the extensive genetic variation on the continent.

Our study shows a high degree of discordance between venous HbA₁c and FPG in, to our knowledge, one of the first such studies in a black population in rural South Africa. Furthermore, our phenotypic data suggest that the current HbA₁c threshold overdiagnoses diabetes in this population. Our findings highlight that elevated HbA₁c may reflect factors other than hyperglycaemia and further research, including genetic studies, is necessary to understand other determinants of HbA₁c in this population. Given the anticipated increase in the prevalence of diabetes in this region, additional longitudinal work is essential to determine which of these biomarkers better predicts diabetes-related morbidities and whether population-specific HbA₁c thresholds are necessary when diagnosing diabetes in this population. In the interim, clinicians in these environments should be cautious in diagnosing diabetes based solely on an HbA₁c ≥6.5% (48 mmol/mol).
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Data availability statement Data are available in a public, open access repository. Data are available on reasonable request. The data from the HAALSI study are publicly available at the Harvard Centre for Population and Development Studies (HCPDS) programme website (www.haalsi.org). Data are also accessible through the InterUniversity Consortium for Political and Social Research (ICPSR) at the University of Michigan (www.icpsr.umich.edu) and the INDEPTH Data Repository (http://www.indepth-isare.org/index.php/catalog/113). Data from the AWI-Gen study is available on request to the AWI-Gen Data and Biospecimen Access Committee (michele.ramsay@wits.ac.za). Additional data are available on request from Alisha Wade (alisha.wade@wits.ac.za), the principal investigator of this nested study.

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