

# Phenotypic characterization of nonautoimmune diabetes in adult Ugandans with low body mass index

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*Ther Adv Endocrinol Metab*

2024, Vol. 15: 1–9

DOI: 10.1177/  
20420188241252314

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## Abstract

**Background:** Type 2 diabetes is common in relatively lean individuals in sub-Saharan Africa. It is unclear whether phenotypic differences exist between underweight and normal-weight African patients with type 2 diabetes. This study compared specific characteristics between underweight (body mass index <18.5 kg/m<sup>2</sup>) and normal-weight (body mass index of 18.5–24.9 kg/m<sup>2</sup>) adult Ugandans with new-onset nonautoimmune diabetes.

**Methods:** We collected the demographic, clinical, anthropometric, and metabolic characteristics of 160 participants with nonobese new-onset type 2 diabetes (defined as diabetes diagnosed <3 months, body mass index <25 kg/m<sup>2</sup>, and absence of islet-cell autoimmunity). These participants were categorized as underweight and normal weight, and their phenotypic characteristics were compared.

**Results:** Of the 160 participants with nonobese new-onset type 2 diabetes, 18 participants (11.3%) were underweight. Compared with those with normal weight, underweight participants presented with less co-existing hypertension (5.6% versus 28.2%,  $p=0.04$ ) and lower median visceral fat levels [2 (1–3) versus 6 (4–7),  $p<0.001$ ], as assessed by bioimpedance analysis. Pathophysiologically, they presented with a lower median 120-min post-glucose load C-peptide level [0.29 (0.13–0.58) versus 0.82 (0.39–1.50) nmol/l,  $p=0.04$ ] and a higher prevalence of insulin deficiency [66.7% versus 31.4%,  $p=0.003$ ].

**Conclusion:** This study demonstrates that nonautoimmune diabetes occurs in underweight individuals in sub-Saharan Africa and is characterized by the absence of visceral adiposity, reduced late-phase insulin secretion, and greater insulin deficiency. These findings necessitate further studies to inform how the prevention, identification, and management of diabetes in such individuals can be individualized.

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## Plain language summary

### Type 2 diabetes in underweight Ugandans

In this study that investigated how type 2 diabetes presents in adult Ugandans with normal body mass index, about one in ten were underweight. Type 2 diabetes in these individuals was characterized by a low prevalence of hypertension, lower body fat levels, and features of reduced insulin production by the pancreas.

**Keywords:** atypical diabetes phenotypes, low BMI type 2 diabetes, sub-Saharan Africa

Received: 12 October 2023; revised manuscript accepted: 10 April 2024.

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## Introduction

In addition to a high background prevalence of communicable diseases like malaria, tuberculosis, and HIV, sub-Saharan Africa (SSA) is currently experiencing a steadily increasing burden of type 2 diabetes (T2D), posing significant challenges to the weak and underdeveloped healthcare systems in the region.<sup>1,2</sup>

Besides its classical presentation in obese individuals, T2D has been widely described in nonobese adult individuals in SSA.<sup>3–7</sup> The mechanisms for this atypical presentation are unknown, but it has been linked to certain genetic polymorphisms and environmental exposures such as early-life (*in utero* and/or early childhood) malnutrition and tropical infections like malaria. These factors induce epigenetic changes that could affect the growth and, ultimately, function of the pancreas.<sup>8–10</sup>

Nonobese T2D constitutes a spectrum of underweight (body mass index or BMI <18.5 kg/m<sup>2</sup>) and normal-weight (BMI 18.5–24.9 kg/m<sup>2</sup>) individuals with T2D. The majority of studies that have characterized T2D in underweight and normal-weight adult patients have been conducted in Asian Indian populations, where differences have been observed.<sup>11–16</sup> Few comparative studies have been conducted in sub-Saharan African populations. Such studies would be fundamental in identifying the frequency of diabetes in underweight patients, and whether it represents a distinct cluster with its phenotypic characteristics. This would guide appropriate preventive and therapeutic approaches for this atypical diabetes subtype in SSA.

As a substudy of the Uganda Diabetes Phenotype (UDIP) study, we compared specific demographic, clinical, anthropometric, and metabolic characteristics of underweight (BMI of <18.5 kg/m<sup>2</sup>) and normal-weight (BMI of 18.5–24.9 kg/m<sup>2</sup>) adult Ugandans with recently diagnosed diabetes and confirmed islet-cell autoantibody negative status. We aimed to establish if the underweight participants exhibited some distinct phenotypic features.

## Materials and methods

### *Study setting and participants*

This substudy that was cross-sectional in design was part of the larger UDIP study that

investigated how diabetes manifested in adult Ugandan patients. The study participants were recruited from the adult diabetes outpatient clinics of seven public and mission private not-for-profit tertiary hospitals in Central and Southwestern Uganda between February 2019 and October 2020.

The participants were nonobese (based on the traditional World Health Organization BMI cut-off of <25 kg/m<sup>2</sup>), with a recent diagnosis of diabetes (diagnosis made within 3 months), and without evidence of islet-cell autoimmunity. The latter was defined as the presence of concentrations of antibodies to glutamic acid decarboxylase-65 (GADA), tyrosine phosphatase (IA-2A), and zinc transporter 8 (ZnT8-A) of ≤34, ≤58, and ≤67.7 U/ml, respectively. These diagnostic cut-off points for islet-cell autoimmunity were derived from a general population cohort of 600 adult rural Ugandans without diabetes, and they represented the 97.5th percentile (corresponding to a 97.5% specificity). All participants presenting to the tertiary hospitals with acute severe hyperglycemia and metabolic decompensation were recruited later in the study following proper correction of the acute metabolic state following the standard treatment protocols in the respective hospitals where they presented. Pregnant women with recently diagnosed diabetes were excluded from the study.

### *Assessment of the phenotypic characteristics of interest*

Relevant information on the demographic (age, sex, and residence) and clinical characteristics (presence of serum and/or urine ketosis on admission, self-reported history of hypertension, and diabetes therapies initiated at the time of diagnosis of diabetes) was collected from all participants. This was followed by resting blood pressure (BP) and anthropometric measurement and the documentation of the systolic and diastolic BP, weight, height, waist circumference (WC), hip circumference (HC), BMI, waist:hip circumference ratio (WHR), and waist:height ratio (WHR). Bioimpedance analysis (BIA) using an OMRON BF511 body composition monitor (Omron® Healthcare, Tokyo, Japan) was used to indirectly assess the total body and visceral fat levels. The BIA method assesses body composition (body fat and muscle mass) based on the resistance to a high-frequency, low-amplitude alternating

electric current.<sup>17</sup> Because we lack local or African-specific cut-offs for total body and visceral fat, we used the manufacturer's recommended cut-offs. A total body fat percentage of <34% and <22% in the female and male participants, respectively, was considered normal, while participants with visceral fat levels  $\leq 9$  were considered normal.

A fasting venous blood sample was drawn for the measurement of blood glucose (FBG), glycated hemoglobin (HbA1c), lipid profile, insulin, C-peptide, serum creatinine [for the estimation of glomerular filtration rate (e-GFR) using the Chronic Kidney Disease Epidemiology formula], and three islet autoantibodies (GADA, IA-2A, and ZnT8-A). All participants were then subjected to a 75-g oral glucose tolerance test (OGTT) for measurement of the 30- and 120-min glucose, insulin, and C-peptide concentrations and calculation of the oral insulinogenic index (IGI), as an additional surrogate marker of pancreatic beta-cell secretory function. Insulin resistance (homeostatic model assessment 2-insulin resistance, HOMA2-IR) and the pancreatic beta-cell function (homeostatic model assessment 2-beta-cell function, HOMA2-%B), as additional surrogate markers of insulin resistance and pancreatic beta-cell function, respectively, were calculated using the online homeostatic model assessment-2 (HOMA2) calculator by the Diabetes Trial Unit of the University of Oxford, Oxford, UK.<sup>18</sup>

All participants provided a spot mid-stream urine sample for the measurement of urine albumin-creatinine ratio (UACR) using the Siemens Healthcare Clinitek<sup>®</sup> microalbumin reagent test strips and a point-of-care Clinitek<sup>®</sup> status analyzer.

All the above metabolic tests were carried out at the Medical Research Council/Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine Uganda Research Unit, Entebbe Uganda.

#### *Definition of study outcomes*

Underweight and normal-weight participants were defined as participants with a BMI of <18.5 kg/m<sup>2</sup> and 18.5–24.9 kg/m<sup>2</sup>, respectively. A fasting C-peptide concentration of <0.25 nmol/l was used to define the presence of insulin deficiency.<sup>19</sup>

#### *Statistical analysis*

Percentages and medians with their corresponding interquartile range (IQR) were used to describe the categorical and continuous variables, respectively. The demographic, clinical, anthropometric, and metabolic characteristics of the participants with BMI of <18.5 kg/m<sup>2</sup> and 18.5–24.9 kg/m<sup>2</sup> were analyzed using the Chi-test for categorical data and the Kruskal–Wallis test for continuous data, respectively. A *p* value of <0.05 was considered statistically significant. All analyses were performed using STATA statistical software version 15 (StataCorp, Texas, USA).

## **Results**

#### *Baseline characteristics of all study participants*

The demographic, clinical, anthropometric, and metabolic characteristics of all study participants and the underweight and normal-weight participants are summarized in Table 1.

The median (IQR) age at diagnosis, BMI, HbA1c, and fasting C-peptide for all the participants were 48 years (37–58), 22.2 kg/m<sup>2</sup> (20.3–23.5), 99 mmol/mol (58–121), and 0.33 nmol/l (0.20–0.53), respectively. About 61% of the participants were male.

Of the 160 participants with nonobese new-onset nonautoimmune diabetes, 18 were underweight (11.3%, 95% CI 6.8–17.2).

#### *Demographic, clinical, anthropometric, and metabolic characterization of the underweight and normal-weight participants with new-onset nonautoimmune diabetes*

Compared with those with normal weight, underweight participants presented with less co-existing hypertension (5.6% *versus* 28.2%, *p*=0.04) and lower resting BP levels on clinical examination [systolic BP-108 (102–124) *versus* 125 (112–134) mmHg, *p*=0.005, and diastolic BP-75 (71–81) *versus* 81 (74–87) mmHg, *p*=0.04].

Regarding the markers of adiposity, compared with normal-weight participants, underweight participants had markedly lower median levels of total body fat [13.5 (8.0–18.0)% *versus* 23.3 (16.6–32.3)%, *p*=0.03], visceral fat [2 (1–3) *versus* 6 (4–7), *p*<0.001], and WHtR [0.45

**Table 1.** Sociodemographic, clinical, anthropometric, and metabolic characteristics of all study participants and underweight and normal-weight participants with nonautoimmune diabetes.

Characteristics	All study participants (n = 160)	Underweight participants (n = 18, 11.3%)	Normal-weight participants (n = 142, 88.7%)	p Value
Sociodemographic and clinical				
Age, years	48 [37–58]	49 [34–58]	47 [37–58]	0.86
Sex				
Males	97 (60.6)	12 (66.7)	85 (59.9)	0.58
Residence				
Rural	39 (24.5)	7 (38.9)	32 (22.7)	0.31
Presence of urine and/or serum ketones	34 (39.1)	4 (40.0)	30 (39.0)	0.69
Treatment used				
Initiated on insulin therapy	68 (42.5)	9 (50.0)	59 (41.6)	0.49
Co-existing hypertension	41 (25.6)	1 (5.6)	40 (28.2)	0.04
Systolic blood pressure, mmHg	123 (109–133)	108 (102–124)	125 (112–134)	0.005
Diastolic blood pressure, mmHg	80 (74–87)	75 (71–81)	81 (74–87)	0.04
Anthropometry				
Markers of adiposity				
Weight, kg	58.2 (52.2–65.0)	45.9 (42.3–47.4)	59.8 (54.7–65.5)	<0.001
Height, cm	163.1 (158.0–168.6)	164.1 (160.5–166.0)	163.0 (157.9–169.0)	0.69
Body mass index, kg/m <sup>2</sup>	22.2 (20.3–23.5)	17.2 (16.0–17.8)	22.6 (20.9–23.7)	<0.001
Waist circumference, cm	83 (77–90)	74.5 (71.5–78.5)	84.0 (79.0–90.0)	<0.001
Hip circumference, cm	93.5 (88.0–98.0)	83.0 (81.0–86.5)	94.0 (90.0–98.0)	<0.001
Waist:hip circumference ratio	0.90 (0.85–0.95)	0.91 (0.84–0.95)	0.90 (0.85–0.95)	0.73
Waist:height ratio	0.51 (0.48–0.55)	0.45 (0.44–0.48)	0.52 (0.48–0.55)	<0.001
Total body fat, %	22.5 (16.1–31.6)	13.5 (8.0–18.0)	23.3 (16.6–32.3)	0.03
Visceral fat level	5 (4–7)	2 (1–3)	6 (4–7)	<0.001
Metabolic				
Markers of glycemia				
HbA1c, mmol/mol	99 (58–121)	120 (80–140)	96 (56–119)	0.45
HbA1c, %	11.1 (7.4–13.2)	13.1 (9.4–15.0)	10.9 (7.2–13.0)	0.45
Fasting blood glucose, mmol/l	9.1 (5.8–14.5)	14.6 (12.4–20.6)	8.8 (5.8–13.6)	0.001
30-Min blood glucose, mmol/l (post-OGTT)	13.5 (9.9–20.0)	19.9 (12.4–24.5)	13.2 (9.9–19.0)	0.001
120-Min blood glucose, mmol/l (post-OGTT)	18.8 (14–25.2)	26.3 (16.5–31.1)	18.0 (13.6–24.2)	0.008

(Continued)

**Table 1.** (Continued)

Characteristics	All study participants (n = 160)	Underweight participants (n = 18, 11.3%)	Normal-weight participants (n = 142, 88.7%)	p Value
Markers of pancreatic beta-cell function				
Fasting serum insulin, pmol/l	29.2 (14.6–44.4)	21.5 (13.2–33.3)	29.9 (14.6–50.7)	0.44
30-Min serum insulin, pmol/l (post-OGTT)	52.1 (21.5–100.0)	41.0 (19.4–56.9)	54.2 (21.2–109.4)	0.67
120-Min serum insulin, pmol/l (post-OGTT)	61.8 (29.9–123.6)	29.9 (15.3–61.8)	77.1 (36.8–144.4)	0.08
Fasting serum C-peptide, nmol/l	0.33 (0.20–0.53)	0.22 (0.13–0.31)	0.35 (0.21–0.56)	0.09
Fasting serum C-peptide, <0.25 nmol/l	56 (35.4)	12 (66.7)	44 (31.4)	0.003
30-Min C-peptide, nmol/l (post-OGTT)	0.50 (0.23–0.83)	0.29 (0.15–0.59)	0.51 (0.28–0.84)	0.18
120-Min serum C-peptide, nmol/l (post-OGTT)	0.70 (0.33–1.36)	0.29 (0.13–0.58)	0.82 (0.39–1.50)	0.04
Oral insulinogenic index, pmol/mmol	0.8 (0.3–2.5)	0.24 (0.06–0.68)	0.99 (0.36–2.68)	0.19
HOMA2-%B	33.3 (15.5–75.8)	9.5 (8.4–73.4)	34.7 (17.1–77.1)	0.28
HOMA2-IR	0.89 (0.65–1.58)	0.76 (0.63–1.03)	0.94 (0.65–1.65)	0.70
Markers of diabetic nephropathy				
Estimated glomerular filtration rate, ml/min/1.73 m <sup>2</sup>	126.9 (107.6–139.2)	135.3 (127.4–147.6)	124.9 (105.6–136.6)	0.17
Urine albumin creatinine ratio, mg/g	2.27 (1.14–3.41)	2.27 (1.13–6.82)	2.27 (1.14–3.41)	1.00
The categorical and continuous variables are presented as percentages and median (interquartile ranges), respectively. HbA1c, glycated hemoglobin, HOMA2-%B, homeostatic model assessment 2-beta-cell function; HOMA2-IR, homeostatic model assessment 2-insulin resistance; OGTT, oral glucose tolerance test.				

(0.44–0.48) *versus* 0.52 (0.48–0.55),  $p < 0.001$ ]. No differences in height were noted between both groups [164.1 (160.5–166.0) *versus* 163.0 (157.9–169.0) cm,  $p = 0.69$ ].

Underweight participants were more acutely hyperglycemic at presentation with higher median FBG [14.6 (12.4–20.6) *versus* 8.8 (5.8–13.6) mmol/l,  $p = 0.001$ ] and post-OGTT 120-min glucose concentrations [26.3 (16.5–31.1) *versus* 18.0 (13.6–24.2) mmol/l,  $p = 0.008$ ]. No statistically significant difference was noted in the HbA1c level between both groups [120 (80–140) *versus* 96 (56–119) mmol/mol,  $p = 0.45$ ].

Pathophysiologically, underweight participants had a lower median post-OGTT 120-min C-peptide level [0.29 (0.13–0.58) *versus* 0.82 (0.39–1.50) nmol/l,  $p = 0.04$ ] and a higher prevalence of insulin deficiency (66.7% *versus* 31.4%,  $p = 0.003$ ).

No statistically significant differences were observed with the additional markers of pancreatic beta-cell function [oral IGI-0.24 (0.06–0.68) *versus* 0.99 (0.36–2.68),  $p = 0.19$  and HOMA2-%B- 9.5 (8.4–73.4) *versus* 34.7 (17.1–77.1),  $p = 0.28$ ] and the HOMA2-IR [0.76 (0.63–1.03) *versus* 0.94 (0.65–1.65),  $p = 0.70$ ] between both groups.

Regarding the markers of diabetic nephropathy, there were no differences in the e-GFR [135.3 (127.4–147.6) *versus* 124.9 (105.6–136.6) ml/min/1.73 m<sup>2</sup>,  $p = 0.17$ ] and UACR [2.27 (1.13–6.82) *versus* 2.27 (1.14–3.41) mg/g,  $p = 1.00$ ].

## Discussion

In our study, we have shown that about 1 in 10 adult Ugandan patients with a BMI <25 kg/m<sup>2</sup> and recently diagnosed T2D was underweight in body size. Nonautoimmune diabetes in this

atypical patient subgroup is associated with less co-existing hypertension, absence of visceral adiposity, significant acute hyperglycemia, and biochemical evidence of insulin deficiency.

Other studies, notably those conducted in Asian Indian populations,<sup>11–13,15</sup> have also shown that nonautoimmune diabetes in underweight individuals is not associated with increased visceral adiposity or other markers of adiposity.<sup>11</sup> These observations indicate that excessive fat deposition and insulin resistance are not a feature of diabetes in the underweight population. Indeed, both our data and the study by Lontchi-Yimagou *et al.*<sup>11</sup> in India demonstrate that this form of diabetes is associated with a significant reduction in pancreatic beta-cell function and a high prevalence of insulin deficiency. This may explain the presentation of severe acute hyperglycemia. However, we cannot rule out that the severe hyperglycemia itself, through glucotoxicity, may also partly explain the higher frequency of insulin deficiency and lower pancreatic beta-cell functional status that we observed in our underweight patients, although this was minimized by only selecting participants whose acute hyperglycemic episodes were appropriately treated and who were metabolically stable.

In addition, it is also possible that the severe hyperglycemia or poorly controlled diabetes may explain the low BMI in these individuals. It is important to note that, despite the severe hyperglycemia noted in the underweight participants, there were no differences in the markers of diabetic nephropathy between the underweight and normal-weight participants.

The underlying cause of pancreatic beta-cell secretory dysfunction in underweight patients with nonautoimmune diabetes is not known but may relate to close interactions between environmental exposures, including those occurring early in life, and genetic influences. For example, a history of malnutrition early in life (*in utero* and/or in early childhood) is associated with reduced pancreatic beta-cell insulin secretion and increased risk of diabetes.<sup>20–23</sup>

Genetic factors may also play a role in the pathophysiology of diabetes in underweight individuals. Polymorphisms of some genes, such as the transcription factor-7 like 2 gene (*TCF7L2*), a genetic defect of ATP-sensitive potassium

channel Kir6.2 (*KCNJ11*), and genes associated with impaired beta-cell development, proliferation, or neogenesis have been associated with defective beta-cell insulin secretion.<sup>24–26</sup> Some of these, including those affecting *TCF7L2* and *KCNJ11* genes, have been reported in sub-Saharan African populations.<sup>27–29</sup> A novel gene for T2D called *ZRANB3* (encoding zinc finger RANBP2-type containing 3) that directly increases apoptosis and results in a reduced pancreatic beta-cell mass has also been described in a large adult sub-Saharan African population.<sup>30</sup>

T2D is a heterogeneous disorder and a diagnosis of exclusion. Its presentation in underweight individuals may represent an extreme end of the spectrum. The striking atypical features are low BMI, absence of visceral adiposity, and insulinopenia.

Recent studies that have used data-driven cluster analysis based on six clinical variables to identify specific diabetes subgroups in adult populations with diabetes have also described an insulin-deficient cluster of T2D, termed severe insulin-deficient diabetes (SIDD).<sup>31–36</sup> The only study that has used the data-driven cluster analysis in an adult African population was conducted on Ghanaians with adult-onset diabetes. The SIDD cluster was identified in 6.5% of the participants.<sup>36</sup> Participants in this cluster had anthropometric and metabolic features classically distinct from what we observed in our underweight participants. The BMI, body fat percentage, and fasting insulin concentrations of the Ghanaian participants with SIDD were significantly higher at  $29.0 \pm 7.2$  kg/m<sup>2</sup>,  $29.7 \pm 9.7\%$ , and  $38.19$  (24.31–65.28) pmol/l, respectively.<sup>36</sup>

In another study that used cluster analysis in an adult Indian population with newly diagnosed T2D, the mean (SD) BMI and fasting C-peptide concentration of the participants with SIDD were also significantly higher at  $24.9$  (3.5) kg/m<sup>2</sup> and  $0.8$  (0.3) nmol/l, respectively,<sup>31</sup> compared with our population or the study by Lontchi-Yimagou *et al.*<sup>11</sup> in India. This supports the notion that nonautoimmune diabetes in underweight adult patients might represent a diabetes subtype distinct from T2D.

#### Strengths and limitations

Some strengths of our study include the fact that we only included adult participants with a recent

diagnosis of diabetes (a diagnosis made in the preceding 3 months), reducing the potential confounding effect of long-standing diabetes on the key investigated phenotypic characteristics like BMI and markers of pancreatic beta-cell function. We also performed several laboratory tests to comprehensively understand the metabolic profile of this atypical patient population with nonautoimmune diabetes.

Despite these strengths, the study had some limitations. In particular, since we mainly recruited participants from tertiary hospitals located in central Uganda, we may not be able to generalize these findings to the entire Ugandan population. The sample size of the study was small and this limited the power of certain comparisons. We did not evaluate the pancreatic beta-cell function and total body and visceral adiposity using more sensitive approaches like euglycemic-hyperinsulinemic clamps and dual-energy X-ray absorptiometry or magnetic resonance imaging, respectively.

While we were able to exclude patients with autoimmune diabetes, we did not perform specific tests to exclude other subtypes of nonautoimmune diabetes like fibrocalculous pancreatic diabetes, monogenic diabetes, and lipodystrophy syndromes.

We did not calculate a sample size for this substudy.

## Conclusion

Our study adds to the increasing body of literature demonstrating that nonautoimmune diabetes in underweight individuals is prevalent in low- and middle-income countries. This condition may have a distinct pathophysiology and may also require more targeted management. Further studies are urgently needed to address these clinical questions to fully understand this atypical diabetes phenotype and optimize patient outcomes.

## Declarations

### *Ethics approval and consent to participate*

This study was approved by the Research Ethics Committee of Uganda Virus Research Centre, Entebbe Uganda (GC/127/18/05/650) and the Uganda National Council of Science and Technology (HS 2431). Administrative approval

was also obtained from all participating study sites. All enrolled study participants provided written informed consent to participate in the study. For participants who could not read and write, a thumbprint was used to express informed consent in addition to written informed consent offered by an impartial witness representing the illiterate participant. All study methods were carried out in accordance with relevant guidelines and regulations as stipulated in the Declaration of Helsinki.

### *Consent for publication*

Not applicable.

### *Author contributions*

**Davis Kibirige:** Conceptualization; Data curation; Investigation; Methodology; Project administration; Validation; Writing – original draft.

**Isaac Sekitoleko:** Data curation; Formal analysis; Methodology; Writing – review & editing.

**William Lumu:** Data curation; Investigation; Methodology; Project administration; Validation; Writing – review & editing.

**Nihal Thomas:** Conceptualization; Methodology; Validation; Writing – original draft.

**Meredith Hawkins:** Conceptualization; Methodology; Visualization; Writing – original draft.

**Angus G. Jones:** Conceptualization; Data curation; Funding acquisition; Investigation; Resources; Supervision; Writing – review & editing.

**Andrew T. Hattersley:** Conceptualization; Funding acquisition; Investigation; Resources; Supervision; Writing – review & editing.

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**Moffat J. Nyirenda:** Conceptualization; Data curation; Funding acquisition; Investigation; Project administration; Resources; Supervision; Writing – review & editing.

### *Acknowledgements*

We are grateful to the entire Uganda Diabetes Phenotype study research team, the staff of the Clinical Chemistry Unit of the Clinical Diagnostics Laboratory Services at the Medical Research Council/Uganda Virus Research

Institute and London School of Hygiene and Tropical Medicine Uganda Research Unit, Entebbe, Uganda, and all the study participants who consented to join the study.

#### Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement (Project Reference: MC\_UP\_1204/16), and National Institute for Health Research (NIHR) (17/63/131). The study sponsors were not involved in the study's design, data collection, analysis, and interpretation, and the report's writing.

#### Competing interests

The authors declare that there is no conflict of interest.

#### Availability of data and materials

The dataset used for this study is available as Supplemental File 1.

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#### Supplemental material

Supplemental material for this article is available online.

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