

# Non-autoimmune, insulin-deficient diabetes in children and young adults in Africa: evidence from the Young-Onset Diabetes in sub-Saharan Africa (YODA) cross-sectional study



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## Summary

**Background** Studies of type 1 diabetes in sub-Saharan Africa have suggested that the clinical phenotype might differ from phenotypes reported elsewhere. We aimed to establish whether type 1 diabetes diagnosed in children and young adults in three countries across sub-Saharan Africa is of autoimmune origin.

**Methods** In this observational, cross-sectional study, we identified participants without obesity from outpatient clinics in government and private hospitals in Cameroon, Uganda, and South Africa who were of self-reported Black African ethnicity with young-onset (age <30 years), insulin-treated, clinically diagnosed type 1 diabetes. We measured islet autoantibodies to GADA, IA-2A, and ZnT8A, and calculated a genetic risk score (GRS) for type 1 diabetes, which we compared with control populations without diabetes derived from the Uganda Genome Resource databank and other studies. Endogenous insulin secretion was assessed using plasma C-peptide. We compared findings with those for participants with self-reported Black (n=429) and White (n=2602) ancestry with type 1 diabetes from the SEARCH for Diabetes in Youth (SEARCH) study in the USA.

**Findings** Of 1072 participants identified between Aug 28, 2019, and March 31, 2022 (Cameroon and Uganda), and Oct 3, 2007, to Sept 14, 2015 (South Africa), 894 were included in our analysis (454 [50.8%] were male and 440 [49.2%] were female): 248 participants were from Cameroon, 370 from Uganda, and 276 from South Africa. Participants from sub-Saharan Africa were diagnosed with diabetes at a median age of 15 years (IQR 11–19), with a median diabetes duration of 5 years (2–10), and a BMI of 21.7 kg/m<sup>2</sup> (19.5–24.1). Only 312 (34.9%) of 894 participants were positive for islet autoantibodies; these participants had classic features of type 1 diabetes, including 225 (82.7%) of 272 with plasma C-peptide <200 pmol/L, and high type 1 diabetes GRS. Those without islet autoantibodies (582 [65.1%] of 894) had significantly lower median type 1 diabetes GRS than those with autoantibodies (9.66 [IQR 7.77–11.33] vs 11.76 [10.49–12.91]; p<0.0001), suggesting a subgroup with a non-autoimmune diabetes subtype, with clinical features and C-peptide concentrations not consistent with type 2 diabetes. Among participants diagnosed younger than 20 years, autoantibody-negative diabetes was also observed in 65 (15.1%) of 429 participants with Black ancestry in SEARCH (although less frequently than in sub-Saharan Africa [59 (55.1%) of 107]), and these participants also had a low type 1 diabetes GRS (median 10.41 [IQR 8.65–12.22] in autoantibody-negative subgroup). No such pattern was observed in White participants in SEARCH: 241 (9.3%) of 2602 were autoantibody negative and median GRS for type 1 diabetes was similar in autoantibody-negative and autoantibody-positive participants (median 13.42 [IQR 11.80–14.61] vs 13.49 [12.29–14.58]).

**Interpretation** In sub-Saharan Africa, clinically diagnosed type 1 diabetes is heterogeneous, comprising classic autoimmune type 1 diabetes and a novel, non-autoimmune, insulin-deficient diabetes subtype. There is evidence of this subtype in Black but not White individuals in the USA. Therefore, alternative causes must be considered in this group of individuals, and understanding the drivers of this subtype might offer new insights into prevention and treatment.

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## Introduction

Type 1 diabetes is a chronic condition that results from autoimmune destruction of the insulin-secreting

pancreatic  $\beta$  cells. The condition affects approximately 9 million people worldwide and is the major global cause of childhood-onset diabetes, although it can occur at any

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## Research in context

### Evidence before this study

Type 1 diabetes is an autoimmune disease that is a major cause of childhood-onset diabetes globally, but robust data on the phenotype and aetiopathogenesis of the condition in native African populations living in Africa are scarce. Findings from previous research from sub-Saharan Africa have suggested that the phenotype of type 1 diabetes might be different from the classic phenotype described in high-income settings. We conducted a systematic review focused on describing the phenotype of type 1 diabetes in sub-Saharan Africa based on searches of PubMed and African Journals Online from Jan 1, 1980, to Dec 31, 2024, with additional hand searches of the reference lists of key studies identified from the initial electronic search (appendix 2 p 14). There were no language restrictions applied. We found little robust data for the possible causes of type 1 diabetes in sub-Saharan Africa. A number of studies reported lower levels of islet autoantibodies (20–60%) than has been seen in high-income countries (70–95%). Long-term endogenous insulin secretion (as measured by C-peptide) was usually low (<200 pmol/L), especially in children. Existing data from Africa on genetic susceptibility to type 1 diabetes are scarce, but they generally show that HLA alleles associated with the disease are more common in individuals from sub-Saharan Africa with type 1 diabetes. However, these associations tend to be weaker than those observed in high-income countries, likely due to small sample sizes. No studies have reported heterogeneous causes of type 1 diabetes in sub-Saharan Africa.

### Added value of this study

This study in participants with type 1 diabetes diagnosed as children or young adults showed that clinically diagnosed

type 1 diabetes in three sub-Saharan African countries (Cameroon, Uganda, and South Africa) consists of two identifiable, distinct disease subgroups. Just over a third of participants from the sub-Saharan African cohorts had autoimmune type 1 diabetes as seen in high-income settings, with severe insulin deficiency, autoantibodies, and similar strong genetic associations. The majority (65.1%) had a non-autoimmune subtype as they did not have autoantibodies and had low genetic susceptibility to type 1 diabetes. This novel, non-autoimmune diabetes subtype observed in participants from these sub-Saharan African countries was usually accompanied by severe insulin deficiency and was not associated with the clinical or genetic features of type 2 diabetes. We also found evidence of a non-autoimmune cause of diabetes in a minority of participants of Black— but not White—ancestry, diagnosed with type 1 diabetes in the SEARCH cohort in the USA.

### Implications of all the available evidence

These findings support the existence of a non-autoimmune, insulin-deficient subtype of diabetes among children and young adults with diabetes across sub-Saharan Africa, which differs from autoimmune type 1 diabetes and type 2 diabetes. This subtype of non-autoimmune, insulin-deficient diabetes might also be present in a minority of children of African ancestry in the USA. Alternative causes should therefore be considered in this group, and identifying the underlying drivers of this atypical diabetes subtype could be crucial for advancing prevention and treatment strategies.

age.<sup>1</sup> Insights into the clinical manifestations and underlying pathogenesis of type 1 diabetes have been studied extensively. Circulating islet autoantibodies usually appear years before the clinical manifestation of the condition, and cellular-mediated  $\beta$ -cell destruction usually leads to severe endogenous insulin-deficiency.<sup>2</sup> The development of islet autoimmunity is primarily associated with HLA class II haplotypes, which have been shown to confer genetic susceptibility across different ethnicities.<sup>3</sup> The work defining aetiological processes has been predominantly conducted in populations of White European origin, with less research in other ethnic groups, particularly in resource-poor settings.<sup>4,5</sup>

In Africa, type 1 diabetes has been poorly characterised due to low availability of robust observational studies.<sup>6</sup> Evidence from existing studies suggests that type 1 diabetes in sub-Saharan Africa might have a different phenotype from that seen in other countries.<sup>6,7</sup> Studies in sub-Saharan Africa have reported lower rates of islet autoantibodies in children and young adults diagnosed with type 1 diabetes, and unusually higher levels of C-peptide, a measure of endogenous insulin secretion,

compared with other regions.<sup>7–9</sup> There are also reports of atypical forms of insulin-requiring diabetes in young people linked with malnutrition in Africa.<sup>10</sup> Together, these findings raise the question of whether differences in clinically diagnosed type 1 diabetes in sub-Saharan Africa in comparison with other populations are a result of differences in the phenotype of autoimmune type 1 diabetes, or the presence of other forms of non-autoimmune diabetes.

We therefore aimed to assess whether clinically diagnosed type 1 diabetes occurring in children and young adults from sub-Saharan Africa is of autoimmune origin, and whether the phenotype and genetic susceptibility differs from type 1 diabetes in other populations.

## Methods

### Study design and participants

In this observational, cross-sectional study (Young-Onset Diabetes in sub-Saharan Africa [YODA]), we included participants from Cameroon, Uganda, and South Africa who were of self-reported Black African ethnicity and had been clinically diagnosed with type 1 diabetes at younger

than 30 years of age and treated with insulin. Participants were identified from diabetes outpatient clinics in government and private hospitals between Aug 28, 2019, and March 31, 2022 (Yaoundé Central and Bafoussam Regional Hospitals in Cameroon, and Mulago National Referral Hospital, Masaka Regional Referral Hospital, and St Francis Hospital Nsambya in Uganda), and Oct 3, 2007, to Sept 14, 2015 (Chris Hani Baragwanath Academic, Charlotte Maxeke Johannesburg Academic, Steve Biko Academic Kalafong Hospital, Life Groenkloof, Inkosi Albert Luthuli Central, and King Edward VIII Hospitals in South Africa). Ethical approvals were granted by the National Ethics Committee for Human Health Research of the Ministry of Public Health in Cameroon (reference 2019/03/1152/CE/CNERSH/SP), Uganda National Council for Science and Technology (HS 2762), and the Human Research Ethics Committee of the University of Witwatersrand (M200174). Participants or their legal guardians provided written informed consent. This study is registered with ClinicalTrials.gov, NCT05013346.

## Procedures

Participants recruited in Cameroon and Uganda attended research visits without fasting, within 5 h of a carbohydrate-containing meal. A questionnaire was administered orally, and weight and height assessed by a trained study investigator. Sex was self-reported by the participants in the questionnaire, in which male or female options were provided. This was also confirmed when medical records were checked during the interview process. Venous blood was collected, centrifuged, and refrigerated immediately. All samples were frozen at  $-80^{\circ}\text{C}$  within 12 h of collection and transported on dry ice to the Royal Devon and Exeter Hospital, Exeter, UK, for batch analysis. We collected saliva samples in saliva pots (GeneFix Assisted DNA Saliva Collector; Isohelix, Kent, UK) for DNA extraction and analysis.

To enrich our cohort and improve geographical diversity, we included data from Black South African participants from a multicentre type 1 diabetes study conducted between 2007 and 2015,<sup>11</sup> and undertook additional analysis on stored, non-fasting blood samples to enable uniform laboratory analysis across cohorts. The original study recruited participants of any age with clinician-diagnosed type 1 diabetes, who had received insulin treatment within 1 year of diagnosis. Participants were included in our analysis if they reported Black ethnicity, were diagnosed before age 30 years, and had stored serum for autoantibody analysis.

To allow comparison of our genetic findings with those from individuals without diabetes, we included data from population controls. We used genotype array data from 4778 population controls (aged  $\geq 13$  years) without a previous diagnosis of diabetes obtained from the Uganda Genome Resource databank.<sup>12</sup> We also included array data from 77 adults (aged  $\geq 18$  years) without diabetes from Cameroon,<sup>13</sup> and 1730 Black South Africans

(aged 40–60 years) without diabetes recruited into the Africa Wits-INDEPTH partnership for Genomic Studies (AWI-Gen) population study.<sup>14</sup>

To allow comparison with individuals of similar and different ethnicities in a high-income country, we compared our findings with data from participants from the SEARCH for Diabetes in Youth (SEARCH) study in the USA. The SEARCH study is a large, multi-ethnic, prospective study of newly diagnosed, youth-onset diabetes (age  $< 20$  years).<sup>15</sup> We included 429 and 2602 participants without obesity (BMI  $< 30$  kg/m<sup>2</sup>) of Black and White ancestry, respectively, who had a clinician diagnosis of type 1 diabetes and measured islet autoantibodies.

All laboratory analyses on all cohorts recruited in Africa, except for plasma glucose and genotyping, were undertaken at the Blood Sciences Department of the Royal Devon and Exeter Hospital, Exeter, UK. Autoantibodies to glutamic acid decarboxylase (GADA), islet cell antigen-2 (IA-2A), and zinc transporter 8 (ZnT8A) were analysed using a commercial ELISA kit (RSR, Cardiff, UK) on a Dynex DS2 ELISA automated platform (Dynex, Preston, UK). Islet autoantibody positivity was defined as concentrations of GADA more than 44.8 U/mL, IA-2A more than 57.0 U/mL, or ZnT8A more than 97.6 U/mL. These thresholds represent the 97.5th percentile for 452 randomly selected Ugandan children and young adults (aged 1–30 years) without diabetes enrolled in the UK Medical Research Council–Uganda Virus Research Institute and London School of Hygiene & Tropical Medicine Uganda Research Unit General Population Cohort (Balungi PA, unpublished). We measured random plasma C-peptide concentrations by direct electrochemiluminescence immunoassay on the 601 module of the Roche Cobas 8000 automated instrument (Roche Diagnostics, Mannheim, Germany), with a minimum limit of detection at 3 pmol/L.

Genotyping was undertaken using the Infinium Global Screening Array MD Version 3 platform (Illumina, San Diego, CA, USA) at the Erasmus University Medical Centre (Rotterdam, Netherlands). We assessed genetic susceptibility to type 1 diabetes using a genetic risk score (GRS) shown to have utility across a range of ethnicities. The score was calculated based on the genome-wide association study results from 67 single nucleotide polymorphisms tagging the HLA and non-HLA loci, respectively, as described previously.<sup>16</sup> We assessed genetic susceptibility to type 2 diabetes using a previously described polygenic risk score that has shown high predictability for type 2 diabetes in populations of African ancestry.<sup>17</sup>

## Statistical analysis

Data were analysed using Stata version 18.0. Participants were included in the analysis if study recruitment criteria were met, and islet autoantibody results were available. Participants were excluded if their BMI was more than or

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equal to 30 kg/m<sup>2</sup>, to avoid inadvertent inclusion of those with young-onset type 2 diabetes.

We compared clinical and biological characteristics of participants who were islet autoantibody positive versus those with islet autoantibody-negative diabetes, using  $\chi^2$  and Mann–Whitney U tests for all comparisons between groups for categorical and continuous variables, respectively. Specific features of autoimmune type 1 diabetes that were assessed included the GRS for type 1 diabetes and severe insulin deficiency (as defined by C-peptide <200 pmol/L).<sup>18</sup> GRS for type 1 diabetes was also compared with control populations without diabetes.

To compare our participants from Cameroon, Uganda, and South Africa with a similar cohort in a high-income country, we restricted our data to participants with newly diagnosed youth-onset diabetes (ie, diagnosed at age <20 years and within the previous 1 year), to match the recruitment criteria for the SEARCH study. We compared the prevalence of positive islet autoantibodies in our sub-Saharan African cohorts with those with clinically defined type 1 diabetes who self-reported Black and White ethnicity in the SEARCH study and compared the GRS for type 1 diabetes, C-peptide, and clinical features by islet autoantibody status.

#### Role of the funding source

The funder of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

#### Results

A total of 1072 participants were enrolled into the primary studies: 260 from Cameroon, 388 from Uganda, and 424 from South Africa (appendix 2 p 3). Over the course of the study, 178 recruited participants were excluded due to absence of an available stored sample for autoantibody measurement (n=88) or BMI more than 30 kg/m<sup>2</sup> (n=90).

In total, 894 individuals were included in the analysis: 248 from Cameroon, 370 from Uganda, and 276 from South Africa. Appendix 2 p 4 shows the participants of Black (n=429) and White (n=2602) ancestry who were selected from the SEARCH study for inclusion in the analysis.

Participant characteristics are shown in table 1. The median duration of diabetes at the time of study was 5 years (IQR 2–10) and 440 (49.2%) of 894 participants were female. The median age at diagnosis was 15 years (IQR 11–19), with a BMI of 21.7 kg/m<sup>2</sup> (19.5–24.1). The majority of participants (573 [71.6%] of 800) had severe insulin deficiency (plasma C-peptide <200 pmol/L).

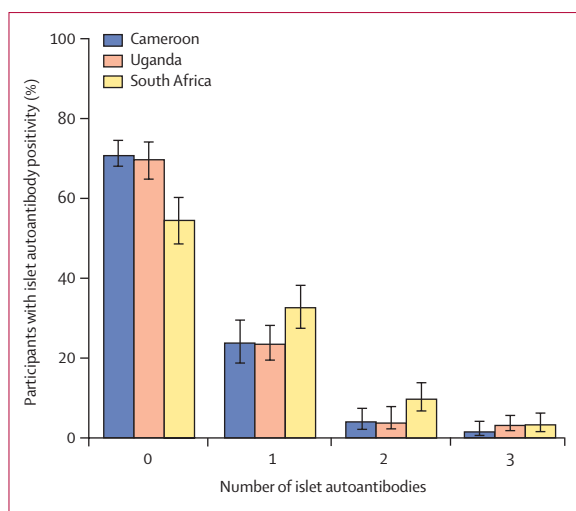
Figure 1 shows that the majority (582 [65.1%] of 894) of participants from the sub-Saharan Africa cohorts were negative for islet autoantibodies (Cameroon, 175 [70.6%] of 248; Uganda, 257 [69.5%] of 370; and South Africa, 150 [54.3%] of 276). Even when considering only participants within 1 year of diabetes diagnosis (n=143), 84 (58.0%) were still islet autoantibody negative (Cameroon, 34 [69.4%] of 49; Uganda 31 [57.4%] of 54; and South Africa, 18 [45.0%] of 40; appendix 2 p 5). GADA was by far the most prevalent islet autoantibody across the sub-Saharan African cohorts (258 [28.8%] of 894), followed by ZnT8A (86 [9.6%] of 894), and IA-2A (69 [7.7%] of 894). GADA rates were highest in South Africa (101 [36.6%] of 276), followed by Uganda (98 [26.5%] of 370), then Cameroon (59 [23.8%] of 248; appendix 2 p 6). Multiple islet autoantibodies (two or more) were uncommon, occurring in just 76 (8.5%) of 894 participants and 24 (16.7%) of 143 assessed within 1 year of diagnosis.

Islet autoantibody-positive participants had low endogenous insulin secretion, with 225 (82.7%) of 272 having plasma C-peptide concentrations of less than 200 pmol/L (table 2), and a high genetic susceptibility to type 1 diabetes compared with individuals from

	Total (n=894)	Cameroon (n=248)	Uganda (n=370)	South Africa (n=276)
Sex				
Male, n (%)	454 (50.8%)	139 (56.1%)	175 (47.3%)	140 (50.7%)
Female, n (%)	440 (49.2%)	109 (43.9%)	195 (52.7%)	136 (49.3%)
Rural residence, n/N (%)	225/618 (36.4%)	97/248 (39.1%)	128/370 (34.6%)	NA
Parental history of diabetes, n/N (%)	149/874 (17.0%)	44/248 (17.7%)	45/351 (12.8%)	60/275 (21.8%)
Age at diabetes diagnosis, years	15 (11–19)	15 (12–17)	14 (10–18)	17 (12–23)
Diabetes duration, years	5 (2–10)	4 (2–8)	6 (3–10)	6 (3–11)
Height, cm	162 (154–169)	165 (157–171)	159 (151–166)	162 (156–170)
BMI, kg/m <sup>2</sup>	21.7 (19.5–24.1)	21.5 (18.7–23.8)	21.3 (19.3–23.6)	22.5 (20.3–25.3)
HbA <sub>1c</sub> , mmol/mol	90 (68–114)	85 (61–114)	90 (70–122)	91 (70–118)
HbA <sub>1c</sub> , %	10.4% (8.4–12.6)	9.9% (7.8–12.6)	10.4% (8.6–12.4)	10.5% (8.6–13.0)
Plasma C-peptide*, pmol/L	72 (5–235)	84 (17–226)	79 (3–285)	33 (5–141)
Severe insulin deficiency†, n/N (%)	573/800 (71.6%)	178/248 (71.7%)	250/370 (67.6%)	145/182 (79.7%)

Unless indicated otherwise, data are median (IQR). NA=not available. \*Plasma C-peptide was random non-fasting. †Severe insulin deficiency defined as plasma C-peptide <200 pmol/L.

**Table 1: General characteristics of the sub-Saharan African participants clinically diagnosed with type 1 diabetes as children or young adults**



**Figure 1: Proportion of individuals in the sub-Saharan African cohorts, by number of islet autoantibodies**

The first set of bars (0) show the proportions of participants who have no islet autoantibodies (islet autoantibody negative), which is the majority of sub-Saharan African participants with clinically defined type 1 diabetes. Error bars represent 95% confidence intervals.

African population control cohorts (median GRS 11.76 [IQR 10.49–12.91] in islet autoantibody-positive participants vs 8.50 [7.05–9.76] in controls;  $p < 0.0001$ ; figure 2). In islet autoantibody-positive participants, genetic susceptibility to type 1 diabetes was similar across the individual sub-Saharan Africa country cohorts (appendix 2 p 7).

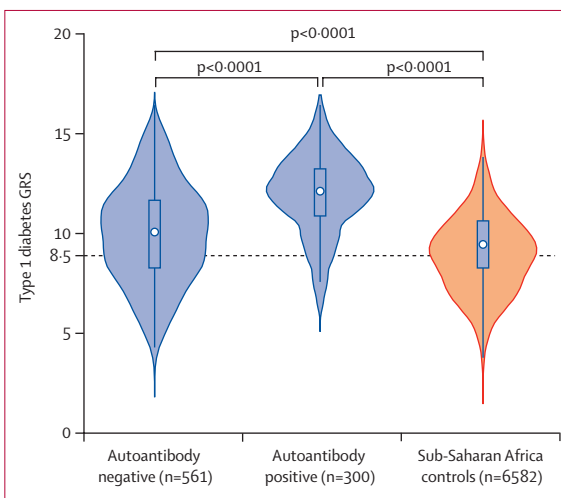
Participants who were islet autoantibody negative had a markedly lower GRS for type 1 diabetes than those with diabetes with an autoimmune cause confirmed by positive islet autoantibodies (median GRS 9.66 [IQR 7.77–11.33] in autoantibody-negative participants vs 11.76 [10.49–12.91] in autoantibody-positive participants;  $p < 0.0001$ ; figure 2). Although substantially reduced in comparison with autoantibody-positive participants, the GRS for type 1 diabetes in this autoantibody-negative group was higher than in a control population without diabetes ( $p < 0.0001$ ). These findings were similar when analysed by country (appendix 2 p 8), and appendix 2 p 9 shows the frequencies of some specific HLA class II haplotypes by islet autoantibody status in the sub-Saharan Africa cohorts.

Table 2 shows participant characteristics by islet autoantibody status. Although participants without islet autoantibodies had higher plasma C-peptide concentrations than those with autoantibodies, most autoantibody-negative participants were severely insulin deficient, and almost all had C-peptide below the range seen in type 2 diabetes (expected plasma C-peptide in type 2 diabetes  $> 600$  pmol/L).<sup>18</sup> The clinical characteristics of autoantibody-negative participants were broadly similar to those with autoantibody-positive diabetes, and thus not reflective of type 2 diabetes.

	Islet autoantibody negative (n=582)	Islet autoantibody positive (n=312)	p value
Sex			
Male, n (%)	293 (50.3%)	161 (51.6%)	0.73
Female, n (%)	289 (49.7%)	151 (48.4%)	0.73
Rural residence*, n/N (%)	164/432 (37.9%)	61/186 (32.8%)	0.24
Parental history of diabetes, n/N (%)	112/567 (19.7%)	37/307 (12.1%)	0.0040
Age at diabetes diagnosis, years	15 (12–20)	14 (10–18)	0.0058
Diabetes duration, years	6 (3–10)	5 (2–9)	0.0235
Height, cm	162 (154–168)	162 (154–170)	0.76
BMI, kg/m <sup>2</sup>	21.7 (19.7–24.2)	21.7 (19.2–23.8)	0.22
HbA <sub>1c</sub> , mmol/mol	90 (67–114)	90 (70–114)	0.36
HbA <sub>1c</sub> , %	10.4% (8.3–12.6)	10.4% (8.6–12.6)	0.36
Plasma C-peptide, pmol/L	103 (8–308)	25 (3–145)	$< 0.0001$
Severe insulin deficiency†, n/N (%)	348/528 (65.9%)	225/272 (82.7%)	$< 0.0001$

Unless indicated otherwise, data are median (IQR) and are for Cameroon, Uganda, and South Africa study populations combined. Islet autoantibody positive represents participants positive for one or more islet autoantibody. \*Data for Cameroon and Uganda only. †Severe insulin deficiency is defined as plasma C-peptide  $< 200$  pmol/L.

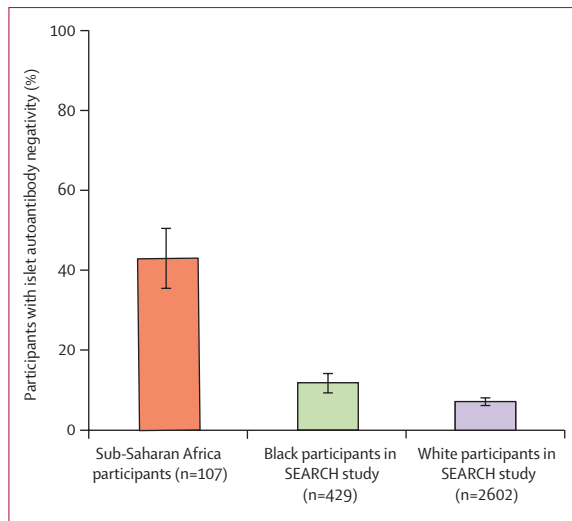
**Table 2: Comparison of characteristics of sub-Saharan African participants diagnosed with type 1 diabetes by islet autoantibody status**



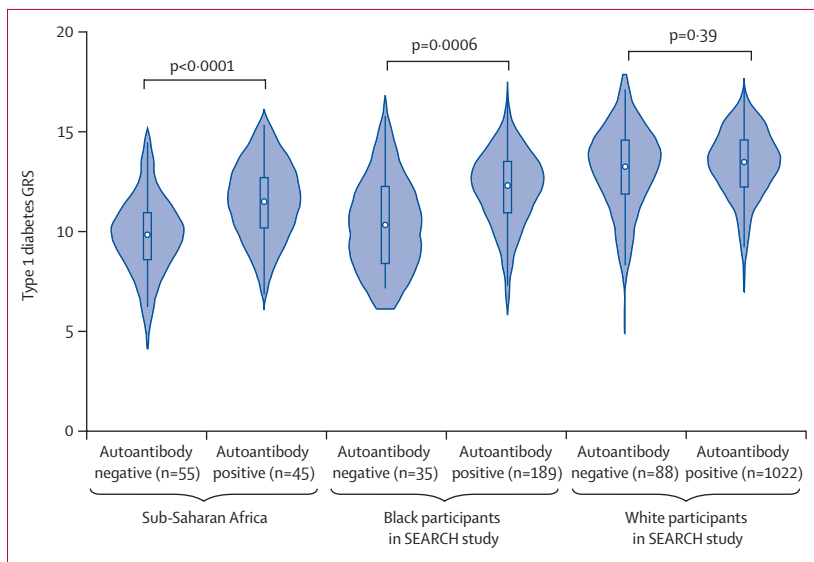
**Figure 2: Distribution of the type 1 diabetes GRS in participants from sub-Saharan Africa with type 1 diabetes (stratified by islet autoantibody status) compared with control populations from sub-Saharan Africa without diabetes**

The dashed horizontal line represents the median GRS for type 1 diabetes in the combined sub-Saharan African population (Cameroon, Uganda, and South Africa). The shaded areas indicate the density or frequency of the GRS data within each category. The central point represents the median GRS values and the boxes show the interquartile ranges. The vertical bar represents the full range of the GRS data within each category. GRS=genetic risk score.

However, parental history of diabetes was significantly more common in the islet autoantibody-negative group. Genetic risk of type 2 diabetes was not enriched in those with negative islet autoantibodies (median GRS 17.15 [IQR 16.95–17.38]) compared with control participants (GRS 17.22 [16.99–17.44]) or those with positive islet autoantibodies (GRS 17.22 [17.06–17.38]; appendix 2 p 10). Reported characteristics



**Figure 3: Proportion of individuals with islet autoantibody-negative diabetes, by study cohort and ethnicity**  
 Data are shown for participants from sub-Saharan Africa with recent-onset (duration  $\leq 1$  year), clinically diagnosed type 1 diabetes diagnosed before age 20 years compared with Black and White individuals in the SEARCH study in the USA. Error bars represent 95% confidence intervals.



**Figure 4: Distribution of the type 1 diabetes GRS, stratified by islet autoantibody status, in participants from sub-Saharan Africa, and Black and White participants in the SEARCH study**  
 Data shown for participants from sub-Saharan Africa was limited to those diagnosed with diabetes at younger than age 20 years who were recruited within 1 year of diagnosis, to match the recruitment criteria for the SEARCH cohort. The shaded areas indicate the density or frequency of the GRS data within each category. The central point represents the median GRS values and the boxes, the interquartile ranges. The vertical bar represents the full range of the GRS data within each category. GRS=genetic risk score.

of malnutrition-associated diabetes, such as reduced height, rural residence, and male sex, did not differ by autoantibody status in the overall study population (table 2) and the individual sub-Saharan Africa cohorts (appendix 2 p 11). Overall, results were broadly similar by subgroup analysis by age at diabetes diagnosis (appendix 2 p 12).

We compared the 107 sub-Saharan African participants diagnosed with diabetes at younger than 20 years and recruited within 1 year of diagnosis with similar participants with type 1 diabetes from the USA-based SEARCH study. The clinical features of the sub-Saharan African and SEARCH study participants diagnosed with type 1 diabetes are shown in appendix 2 p 13. The proportion of individuals with islet autoantibody-negative diabetes was significantly higher in participants from the sub-Saharan Africa cohorts (59 [55.1%] of 107) than in Black participants (65 [15.1%] of 429) and White participants (241 [9.3%] of 2602) from the SEARCH study (figure 3). In Black SEARCH participants who were autoantibody negative, the GRS for type 1 diabetes was markedly lower than in those who were autoantibody positive (median 10.41 [IQR 8.65–12.22] vs 12.31 [10.78–13.31];  $p=0.0006$ ), consistent with findings in the sub-Saharan Africa cohorts (median 9.63 [8.28–10.77] vs 11.37 [9.94–12.60];  $p=0.0001$ ). In contrast, in White SEARCH participants, median GRS for type 1 diabetes did not differ by autoantibody status (13.42 [11.80–14.61] in autoantibody-negative participants vs 13.49 [12.29–14.58] in autoantibody-positive participants;  $p=0.39$ ; figure 4).

**Discussion**

The principal finding of this study is that a non-autoimmune, insulin-deficient subtype of diabetes is common in individuals diagnosed with type 1 diabetes as children or young adults across three sub-Saharan African countries. Those with type 1 diabetes confirmed by islet autoantibody testing have high genetic susceptibility to type 1 diabetes and severe endogenous insulin deficiency, which are characteristic of type 1 diabetes described in high-income countries. In comparison, however, the majority of individuals without islet autoantibodies have substantially lower genetic susceptibility to type 1 diabetes, and higher endogenous insulin secretion. This finding suggests the presence of diabetes with a non-autoimmune cause within this subgroup. Evidence of this atypical phenotype was also present in Black individuals diagnosed with type 1 diabetes in the USA, although it was far less common than confirmed autoimmune type 1 diabetes in that setting. Conversely, in White individuals in the USA, genetic susceptibility to type 1 diabetes did not differ by autoantibody status, suggesting that even those who have a clinical diagnosis of type 1 diabetes and are autoantibody negative have autoimmune diabetes.

These findings support the common existence of a non-autoimmune, insulin-deficient subtype of diabetes among children and young adults with diabetes in sub-Saharan Africa, which is different from classic autoimmune type 1 diabetes, and does not have features consistent with type 2 diabetes or malnutrition-associated diabetes.<sup>10</sup> Therefore, alternative causes must be considered in this group of individuals.

To our knowledge, this is the first multicountry study to use standardised immunological assays and genetic investigation to examine the cause of type 1 diabetes in sub-Saharan African countries. Our finding of low rates of islet autoantibody positivity in participants diagnosed with type 1 diabetes in our sub-Saharan Africa cohorts is consistent with previous research, showing rates varying between 20% and 60%.<sup>7</sup> In our study, multiple islet autoantibody positivity was rare, occurring in only 76 (8.5%) of 894 participants. We found an overwhelming predominance of GADA when autoantibodies were present and extremely low rates of IA-2A and ZnT8A, consistent with other studies in which all three autoantibodies were measured.<sup>19–21</sup> These findings are in stark contrast to those from studies of type 1 diabetes in other settings. For example, studies from European and Asian populations have shown that at least one islet autoantibody is present in approximately 90% of individuals with young-onset type 1 diabetes when GADA, IA-2A, and ZnT8A are measured close to diagnosis.<sup>21–24</sup> Although islet autoantibody prevalence reduces with longer diabetes duration, this does not explain the low prevalence in our sub-Saharan African cohorts. In European children and young adults diagnosed with type 1 diabetes, genetic susceptibility to type 1 diabetes is similar in islet autoantibody-negative and autoantibody-positive individuals, as they have the same autoimmune cause.<sup>23</sup> We found a similar result in White Americans younger than 20 years recruited to SEARCH. The markedly lower GRS for type 1 diabetes that we observed in our sub-Saharan African participants who were islet autoantibody negative, therefore, suggests a non-autoimmune cause. However, it is important to note that some sub-Saharan African individuals who are islet autoantibody negative will still have islet autoantibody-negative autoimmune diabetes, as evidenced by the higher GRS for type 1 diabetes in this group than in controls.

Although genetic studies of type 1 diabetes in sub-Saharan Africa are scarce, our finding of reduced genetic susceptibility to type 1 diabetes in those diagnosed with type 1 diabetes without islet autoantibodies is consistent with lower overall rates of HLA susceptibility to type 1 diabetes reported in previous studies of clinically diagnosed type 1 diabetes in sub-Saharan Africa.<sup>7</sup> They are also largely consistent with findings from northwest Ethiopia, which show islet autoantibody status and genetic susceptibility to type 1 diabetes in a population that is genetically distinct from other African populations.<sup>20</sup>

In our study, the sub-Saharan African participants with islet autoantibodies had both clinical and genetic features of classic type 1 diabetes as described in other populations. These findings suggest that classic type 1 diabetes is present, and that the phenotype and genotype of true autoimmune type 1 diabetes in sub-Saharan Africa is similar to type 1 diabetes in other populations.

The apparent non-autoimmune diabetes present in our cohort does not fit with other known subtypes of diabetes. Type 2 diabetes is unlikely to be the major cause of islet autoantibody-negative diabetes in this study, as evidenced by a median age of onset of 15 years, absence of increased adiposity, extremely low endogenous insulin concentrations, and lack of enrichment for genetic susceptibility to type 2 diabetes.<sup>18</sup> Malnutrition-associated diabetes has also been described in African and other populations, and has been suggested to contribute to the development of apparent type 1 diabetes in Africa.<sup>10,25</sup> However, current or childhood protein or calorie malnutrition appears unlikely to be the cause of non-autoimmune diabetes in our cohort as this phenotype is not associated with reduced height, low bodyweight, or male predominance, which are all factors that have been described to be common in malnutrition-associated diabetes.<sup>6,10,25</sup>

Our study has strengths that support the robustness and generalisability of our findings across sub-Saharan Africa. We measured islet autoantibodies using one of the highest performing methods in the international Islet Antibody Standardization Program,<sup>26</sup> and, importantly, have used positivity thresholds derived from a Ugandan population of children and young adults. These methods are particularly important as our analysis of individuals without diabetes from Uganda, and the study conducted in northwest Ethiopia,<sup>20</sup> revealed that population-specific thresholds are essential, as thresholds derived from European populations have low specificity. We did not measure insulin autoantibodies as the assay is unreliable in individuals already treated with insulin and, in northern European populations, increases overall sensitivity only by 1–2%.<sup>27</sup> We assessed genetic susceptibility to type 1 diabetes using a GRS that has shown accurate discrimination between type 1 diabetes and other types of diabetes, including in people of Black and south Asian ethnicity, and were able to compare these findings both with African control cohorts and findings in a high-income country.<sup>28,29</sup> The inclusion of countries from western-central, eastern, and southern Africa, with similar results despite the high genetic and environmental heterogeneity in these regions, means our findings are likely to apply more broadly to other sub-Saharan African populations.

A limitation of our study is its cross-sectional nature, and the inclusion of individuals with varying durations of diabetes without autoantibody testing at diabetes diagnosis. Therefore, islet autoantibody titres might have declined in those with a longer duration of diabetes, reducing test sensitivity. However, compelling evidence suggests that islet autoantibody titres—particularly GADA and IA-2A—can persist for many years after the onset of diabetes.<sup>30</sup> Restricting study inclusion to individuals within 1 year of diagnosis did not meaningfully alter our findings. It is also possible that differential survival might have altered the relative proportions of autoimmune and non-autoimmune diabetes in our study,

as mortality of type 1 diabetes in sub-Saharan Africa is likely to be high and might be associated with C-peptide concentrations. While our analysis in people recently diagnosed offers some reassurance, we cannot rule out the potential impact of deaths occurring before diagnosis. In addition, we did not capture detailed data on some potential causes of non-autoimmune diabetes, such as a history of past severe infections, early childhood malnutrition, and diet. Finally, we did not test for tetraspanin-7, a recently identified autoantigen associated with type 1 diabetes. However, current research suggests it offers only little additional value beyond testing for GADA, IA-2A, and ZnT8A.<sup>31,32</sup>

This study has important clinical implications. Our findings suggest that there is heterogeneity in the causes of youth-onset diabetes among individuals across sub-Saharan Africa, with clear evidence of a non-autoimmune cause of diabetes being the most predominant subtype in those diagnosed with apparent type 1 diabetes at younger than 30 years of age. In addition, there was evidence of non-autoimmune diabetes in Black Americans diagnosed with type 1 diabetes (albeit much less commonly), but this finding was absent in White Americans, indicating that the principal cause or causes might be strongly linked to an environmental exposure common to sub-Saharan Africa or a combination of the interaction between environmental exposition and genetic susceptibility. Identifying causes of this diabetes subtype will be crucial to setting in place strategies for prevention and treatment in the future.

Our findings might also be relevant to individuals currently diagnosed with type 2 diabetes in sub-Saharan Africa who are lean (BMI <25 kg/m<sup>2</sup>) and often diagnosed young, and who appear to have insulin deficiency, without evidence of central adiposity or insulin resistance.<sup>33</sup> It is possible that the individuals included in our study represent one end of a spectrum of atypical youth-onset diabetes with a shared underlying cause. Those with the same underlying cause but who are older or have less pronounced  $\beta$ -cell dysfunction might instead be diagnosed with type 2 diabetes. The cause is not clear at this stage but might relate to infection, nutritional factors, or other possible environmental insults. Further work is needed to address these different areas to identify the triggers and pathogenesis of this young-onset subtype of non-autoimmune, insulin-deficient diabetes.

In conclusion, clinically diagnosed type 1 diabetes in sub-Saharan Africa is heterogenous, comprising individuals with classic autoimmune type 1 diabetes and others who lack the immune or genetic characteristics typically associated with autoimmune type 1 diabetes. These findings support the existence of a novel, non-autoimmune, insulin-deficient subtype of diabetes. Preliminary evidence also supports the existence of this subtype in young Black individuals in the USA but, in that setting, it is less common than autoimmune type 1 diabetes.

#### Contributors

JCK, MJN, TJM, ES, and AGJ conceived and designed the study. JCK, MYD, SSa, PAB, SB, TP, CN-T, ESM, KCM, KR, MJN, and ES researched the data in Uganda and Cameroon; CJP, NJC, AAM, PR, FJP, and JCVD for the South Africa cohort; and ASS, CP, JD, and DD for the SEARCH cohort. SSq, KAP, DS, and RAO generated the genetic risk scores. SF, JCM, MJN, and ES provided the non-diabetic control genotype data. JCK analysed the data supported by BMS, TJM, ATH, ES, and AGJ. JCK, AGJ, and BMS accessed and verified the data. JCK and AGJ wrote the first draft of the manuscript. All authors reviewed the draft, had access to the raw data, and had final responsibility for the decision to submit for publication.

#### Declaration of interests

We declare no competing interests.

#### Data sharing

The individual participant data along with supporting documentation are available in response to any reasonable request addressed to the corresponding author.

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