# Identification of a sub-group of black South Africans with type 1 diabetes with an older age at diagnosis but lower levels of GAD65 and IA-2 autoantibodies

**Running title:** Autoantibody positivity in black South Africans with type 1 diabetes

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**Conflicts of interest statement**

The authors declare that there is no conflict of interest associated with their contribution to the manuscript.

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**Contribution statement**

NJC conceived the study. NJC, PR and CJP were involved in study design. All authors were involved in recruitment of study participants. CJP generated the laboratory data. NJC, PR and CJP were responsible for analysis of data. CJP drafted the manuscript. All authors read and revised the manuscript and approved the final version.

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## Novelty statement

- Autoantibodies to islet cell specific antigens are markers of type 1 diabetes development.
- There are limited data on the prevalence of type 1 diabetes-related autoantibodies in sub-Saharan African people with type 1 diabetes.
- A lower prevalence of IA-2 autoantibodies was found in black compared to white South Africans with type 1 diabetes.
- In black but not white participants the prevalence of GAD65 and IA-2 autoantibody positivity was significantly lower in participants diagnosed at ≥21 years-of-age.
- These data suggest ethnic differences in type 1 diabetes immune-related aetiology which may give greater insight into the pathophysiology of the disease and allow the development of targeted interventions.

**Abstract**

*Aims:*

There is sparse information regarding the immunological aetiology of type 1 diabetes in sub-Saharan African populations. The aims of this cross sectional observational study were to compare the age at diagnosis and prevalence of islet autoantibody (GAD65 and IA-2) positivity in black and white participants with type 1 diabetes in South Africa. The relationship between age at diagnosis and the presence of autoantibodies was also analysed.

*Methods:*

Participants were recruited from diabetes out-patient departments and autoantibodies to GAD65 and IA-2 were measured by ELISA.

*Results:*

We recruited 472 [353 black, 119 white] participants with type 1 diabetes. Age at diagnosis of diabetes was later in black (19.7 ± 10.5) than white (12.7 ± 10.8 years) ($p<0.001$) participants with a median [interquartile range] disease duration of 5.0 [2.0; 10.0] and 8.5 [4.0; 20.0] years ($p<0.001$), respectively. An older age at diagnosis (≥21 years) was more frequent in blacks (152 of 340, 45%) than in whites (24 of 116, 21%) ($p<0.001$). The prevalence of IA-2 autoantibodies was 19% (66 of 352) in black and 41% (48 of 118) ($p<0.001$) in white participants. There was no significant difference in GAD65 autoantibody positivity in black (212 of 353, 60%) and white (77 of 117, 66%) participants ($p=0.269$). In black, but not white, participants the prevalence of both GAD65 and IA-2 autoantibody positivity was significantly lower in participants diagnosed at ≥21 years of age ($p<0.001$ for both comparisons).

*Conclusions:*

The older age at diagnosis, lower prevalence of IA-2 autoantibodies and a distinct sub-group of participants with type 1 diabetes with age at diagnosis above 20 years of age in the black compared to white population suggest a difference in the immunological aetiology of type 1 diabetes in these two population groups.

**Keywords:** autoantibodies, black population, GAD65, IA-2, older age at diagnosis, South Africa, type 1 diabetes

## Introduction

Autoantibodies to the 65kDa isoform of glutamic acid decarboxylase (GAD65), tyrosine phosphatase-like insulinoma antigen 2 (IA-2), insulin (IAA) and zinc transporter 8 (ZnT8) [1] are the most useful markers of the autoimmune process in type 1 diabetes. Over 90% of newly diagnosed individuals are positive for at least one of these autoantibodies. The 10 year risk of progression to type 1 diabetes increases with a higher number and titre of autoantibodies, a younger age at seroconversion and with the presence of high risk HLA genotypes [2].

The prevalence of autoantibodies in participants with type 1 diabetes has been investigated in a variety of population groups. A study conducted on 194 white Europeans newly diagnosed with type 1 diabetes (<40 years of age) found a frequency of 76% and 58% for GAD65 and IA-2 autoantibodies, respectively. GAD65 and IA-2 autoantibody positivity declined to 60% and 45%, respectively, after four years [3]. The prevalence of GAD65 and IA-2 autoantibodies in 57 Japanese children (<15 years old) with new onset type 1 diabetes was 75% and 72%, respectively whilst in 97 adults (≥18 years old) the frequencies were 78% and 41%, respectively [4]. A study in Bangalore, India, found frequencies of 65% and 19% for GAD65 and IA-2 autoantibodies, respectively, in 88 children diagnosed before 18 years of age with a disease duration less than 48 months [5]. Libman et al. reported frequencies of 58% and 77% GAD65 autoantibody positivity, and 42% and 63% IA-2 autoantibody positivity, in 437 newly diagnosed (before 19 years of age) black and white Americans, respectively [6]. The percentage autoantibody positivity can thus vary depending on the patient's age at onset, duration of disease and ethnicity [7].

Only two papers have studied the prevalence of GAD65 autoantibodies in South African participants with type 1 diabetes. A study from Johannesburg, South Africa reported that 44% of 100 black participants with type 1 diabetes of varying disease duration were GAD65 autoantibody positive [8]. Rheeder et al., [9] showed that the prevalence of GAD65 autoantibodies was significantly lower in 43 black compared to 17 white South Africans presenting with diabetic ketoacidosis (33% vs. 67%). However, there are no studies which have examined the prevalence of both GAD65 and IA-2 autoantibodies in black individuals with type 1 diabetes. In addition, a South African study has shown that the age at diagnosis in black participants with type 1

diabetes is older than that in white participants [10]. We therefore hypothesize that GAD65 and IA-2 autoantibodies occur at lower frequencies in black compared to white individuals with type 1 diabetes and that this may be related to differences in age at diagnosis in the two ethnic groups. Thus, this study aimed to determine the prevalence of GAD65 and IA-2 autoantibodies, the relationship between autoantibody positivity and age at diagnosis, and to examine any ethnic differences between black and white South Africans with type 1 diabetes.

## Methods

### Study population

Black and white South African participants with type 1 diabetes were recruited by convenience sampling from private and government diabetes clinics in Pretoria, Johannesburg and Durban over a five year period (November 2007 - December 2012). Anthropometric measurements were taken and demographic data collected using a questionnaire including date of birth, age at diagnosis and gender. Participants with known type 2 diabetes, secondary diabetes or gestational diabetes were excluded from the study.

### Classification of diabetes

Participants with type 1 diabetes were classified using clinical criteria: age at diagnosis <30 years and insulin therapy within the first year of diagnosis (therapy initiated immediately in children). Participants older than 30 years of age at diagnosis but requiring insulin treatment within the first year of diagnosis and who were not obese were classified as type 1 diabetes.

### Ethics clearance

Ethics clearance was obtained from the University of the Witwatersrand Human Research Ethics Committee (M10978, M150885) as well as the University of Pretoria (85/2009) and the University of KwaZulu Natal (BE224/010). Informed consent was obtained from participants or parents/legal guardians where necessary.

### Autoantibody measurement

The concentration of GAD65 and IA-2 autoantibodies were measured by ELISA kits (Kronus, Star, ID, USA) according to the manufacturer's instructions. All assays were

run in the same laboratory and the inter-assay coefficient of variation was <5% for both ELISAs. Each individual ELISA was run using samples from both ethnic groups and from participants with a range of ages at diagnosis. Participants were considered GAD65 and IA-2 autoantibody positive when the concentration was ≥5 IU/mL and ≥15 IU/ml, respectively, based on the manufacturer's recommendations.

**Statistical analysis**

Data were analysed using R version 3.5.0 (2018-04-23) [11]. The Shapiro-Wilk W test was used to test for normality of continuous variables and those that were not normally distributed (age, age at diagnosis, duration of disease and BMI) were presented as median [interquartile range] and compared between groups using the Mann-Whitney U test. Categorical data were compared between groups using the $\chi^2$ test and were presented as proportions and percentages. Odds ratios were calculated with 95% confidence intervals (CI) and p-values using the mid-p method (using compareGroups in R). For all analyses, $p<0.05$ was considered statistically significant. Multivariable logistic regression analyses were performed using autoantibody status as the dependent variable. The independent variables were ethnicity, duration of disease, age at diagnosis and gender. The age cut off <21 or ≥21 years was selected based on data from Kalk and colleagues [10] who showed a peak age of onset at 22-23 years of age in the black population and this was also the midpoint between the two peaks for age at diagnosis (see Figure 1) observed in the black participants in the current study.

A sample size calculation was performed based on the only data from South Africa comparing GAD65 autoantibody prevalence between black (33%) and white (67%) people with type 1 diabetes [9]. We assumed an underestimation of GAD65 autoantibody prevalence in the African population in this study and set the prevalence to 50%. Thus, the minimum n per group was calculated to be 65 participants. To account for any inaccuracies in our estimations we chose to recruit a minimum of 100 participants within the white type 1 diabetes group (fewer white than black people with type 1 diabetes attend the public hospitals from which the majority of participants were recruited).

## Results

### Clinical and laboratory characteristics

472 participants with type 1 diabetes [353 (75%) black and 119 (25%) white] were recruited for this study, with 74 (16%) participants recruited within a year of their diagnosis. The clinical and anthropometric characteristics of the study population are shown in Table 1. Black participants were significantly older at diagnosis ($p<0.001$) and had a shorter duration of disease ($p<0.001$). Amongst the black participants, there were more women (n=194, 55%), whereas amongst the white participants, men predominated (n=66, 56%). White participants had a significantly lower BMI ($p=0.023$).

### Age at diagnosis

Figure 1 shows the distribution of age at diagnosis by ethnicity. In the white population, most participants (64 of 116, 55%) were diagnosed by 10 years of age. Only 22% (74 of 340) of black participants were diagnosed by 10 years of age ($p<0.001$). Two distinct peaks for age at diagnosis were observed in the black population, 11-15 years and 26-30 years. A higher percentage of black compared to white participants (45%, 152 of 340 vs. 21%, 24 of 116; $p<0.001$) were diagnosed at ≥ 21 years of age.

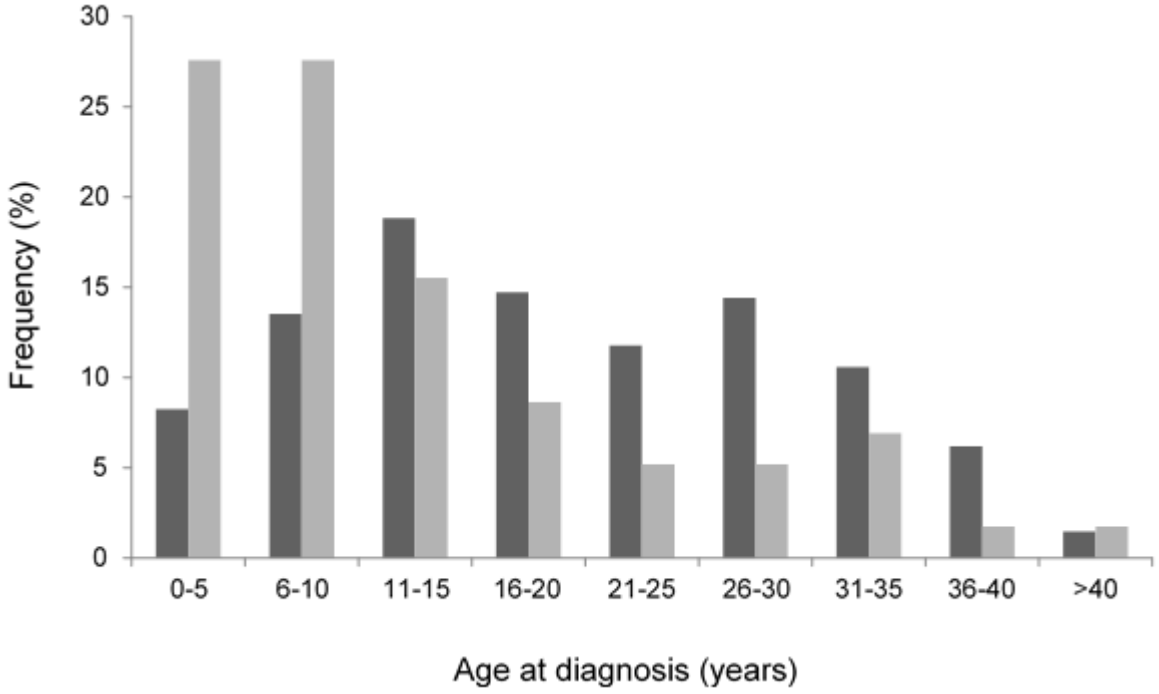


Figure 1: Frequency of affected participants by age at diagnosis in black and white South Africans with type 1 diabetes

Dark grey bars represent black participants with type 1 diabetes and light grey bars represent white participants with type 1 diabetes

**Autoantibody positivity, age at diagnosis and disease duration**

The overall prevalence of autoantibody positivity was 65% (304 of 470), with 62% (289 of 470) GAD65 autoantibody positive, 24% (114 of 470) IA-2 autoantibody positive and 21% (99 of 469) of all participants positive for both autoantibodies (Table 2). The prevalence of GAD65 autoantibodies was similar in black (60%, 212 of 353) and white participants (66%, 77 of 117) ($p=0.269$). By contrast, significantly more white participants were IA-2 autoantibody positive than black participants (41%, 48 of 118 vs. 19%, 66 of 352; $p<0.001$). Furthermore, more white than black participants were GAD65 and/or IA-2 autoantibody positive (74%, 86 of 117 vs. 62%, 218 of 353; $p=0.028$) or GAD65 and IA-2 autoantibody positive (33%, 39 of 117 vs. 17%, 60 of 352; $p<0.001$).

In both population groups the GAD65 and IA-2 autoantibodies were more frequent in participants with an age at diagnosis less than 21 years (Table 3). However, these differences were only significantly different in the black population.

A significantly younger median age at diagnosis was found only in GAD65 and IA-2 autoantibody positive black participants when compared to antibody negative participants ($p<0.001$ for both comparisons) (Table 4). No significant difference in disease duration was observed in either ethnic group when comparing those with or without GAD65 or IA-2 autoantibodies (Table 4).

**Autoantibody positivity and interaction of ethnicity with age at diagnosis and disease duration**

The data in Tables 3 and 4 suggest that IA-2 and GAD65 autoantibody positivity were associated with a lower age at diagnosis, but only in the black population. Therefore, to determine whether the differential relationship between age at diagnosis and autoantibody levels was robust and not due to confounding, multivariable logistic regression models were developed using autoantibody status as the dependent variable and age at diagnosis, ethnicity, duration of disease and gender as

independent variables (Table 5). Interaction between ethnicity and age at diagnosis and disease duration was also analysed. The models for GAD65 and IA-2 autoantibody positivity for the combined ethnic groups (models 1 and 2, respectively) both demonstrate that the presence of these autoantibodies was associated with a lower age at diagnosis (odds ratio [95% CI]: 0.95 [0.93, 0.97]; p<0.001, in both models). In the IA-2 autoantibody model only (model 2), autoantibody positivity was associated with shorter disease duration (0.97 [0.94, 0.99]; p=0.015) and white ethnicity (2.86 [1.72, 4.77]; p<0.001). When an interaction term for ethnicity x age at diagnosis was introduced into models 1 and 2, significant associations were observed with both GAD65 autoantibody positivity (1.08 [1.03, 1.12]; p<0.001) and IA-2 autoantibody positivity (1.07 [1.02, 1.12]; p=0.003). An interaction term for ethnicity x disease duration was also added to both models and was found to be significant in model 1 (1.06 [1.00, 1.11]; p=0.029) but not model 2 (0.99 [0.94, 1.05]; p=0.84). To further investigate the interaction of ethnicity and age at diagnosis and disease duration, multivariable logistic regression models were set up for each antibody for each ethnic group (models 3-6; see Table 5). There was a reduced risk of being autoantibody positive, with increasing age at diagnosis, only in black participants (models 3 and 5), whilst increasing disease duration was associated with a lower risk of being positive for GAD65 autoantibodies only in black participants (model 3).

If participants diagnosed at >30 years-of-age (possible LADA [latent autoimmune diabetes in adults] participants) were excluded from models 1 and 2, minimal effects on the outcomes were observed.

**Discussion**

There are limited immunological and genetic data for type 1 diabetes in sub-Saharan African populations. The current study has demonstrated a difference in the distribution of age at diagnosis between black and white participants with type 1 diabetes, with two peaks (11-15 and 26-30 years of age) observed in the black individuals whereas a single peak (0-10 years of age) was seen for the white individuals. The prevalence of GAD65 autoantibody positivity was similar in black and white participants (60% vs. 66%, respectively), however, IA-2 autoantibody positivity was significantly lower in the former group (19% vs. 41%). In the black participants, autoantibody positivity was associated with a significantly younger age at diagnosis.

In addition, the prevalence of autoantibody positivity was significantly lower in black, but not white, participants with type 1 diabetes diagnosed at ≥ 21 years of age.

A previous study from Johannesburg [10], showed the peak age of onset in black people with type 1 diabetes at 22-23 years of age; a decade later than that observed in white people with type 1 diabetes. Another South African study similarly showed a peak age of onset of type 1 diabetes between 21-30 years of age in 86 black participants [12]. These findings were confirmed in the present study and were extended by comparing the distribution of age at diagnosis between white and black people with type 1 diabetes. This demonstrated very different distribution patterns, with the peak frequency for diagnosis occurring between birth and 10 years of age in the white participants and two peaks occurring in the black population at ages 11-15 and 26-30 years. The high frequency of diagnoses in participants younger than 10 years observed in the white participants was unexpected but may be due to the shift to a younger age at diagnosis that is being seen in European populations [13]. The reason for the low frequency of diagnoses in participants <10 years-of-age in the black population is not known. It has been suggested that in African countries there may be high rates of mortality in individuals with type 1 diabetes diagnosed in infancy as a result of diabetic ketoacidosis and poor access to appropriate health care facilities, especially in rural areas [14]. This is less likely in South Africa where health care coverage and access to health care facilities is greater than in other regions of Africa [15], and in the present study all the clinics from which participants were recruited were based in urban areas. It is also possible that the autoimmune response is less aggressive in black compared to white participants, as illustrated by the lower frequency of IA-2 autoantibodies in the former group. This may give rise to a longer prodromal period and hence a shift in the age of diagnosis of type 1 diabetes in the black population to an older age than that observed in white participants.

The reason for the lower prevalence of IA-2 autoantibodies in black compared to white participants with type 1 diabetes in not known. However, IA-2 autoantibody positivity has been shown to be associated with HLA-DR4 [16]. In addition, the 11th International Histocompatibility Workshop Study, which compared HLA class II allele frequencies between white and black participants with type 1 diabetes, showed that HLA-DR4 is more common in white than black individuals [17].

To our knowledge, this is the first report of the frequency of IA-2 autoantibodies in South Africans with type 1 diabetes. The prevalence reported here (19%) is within the range of other studies in sub-Saharan Africa which reported frequencies of 6.4% (n=47) [18], 10% (n=302) [19] and 21% (n=94) [20] in black people with diabetes from Cameroon [18, 19] and Tanzania [20]. Also, a study conducted in East African migrants resident in the USA showed a prevalence of 25% for participants with type 1 diabetes [21]. The frequency of this autoantibody is higher in studies conducted in Caucasian (54-65%) individuals with type 1 diabetes [6, 22-24], which mirrors the higher prevalence observed in white than black participants in the current study.

With regards to the prevalence of GAD65 autoantibodies in sub-Saharan African populations, a study conducted in Cameroon [18], showed a prevalence of 34% in 47 participants with type 1 diabetes. In a cohort of 94 individuals with type 1 diabetes from Tanzania, 30% of participants were GAD65 autoantibody positive [20]. In the present study, the frequency of GAD65 autoantibodies in the black (60%) and white (66%) South Africans with type 1 diabetes was not significantly different and was similar to that reported in white Europeans and African Americans [6, 25]. It is possible that the higher prevalence of GAD65 autoantibodies detected in our cohort, compared to other studies from sub-Saharan Africa is due to differences in assays used (ELISA versus radioimmunoassay) with different specificity levels, the age at diagnosis of the participants, the diabetes classification of the participants and the disease duration.

The prevalence of GAD65 and IA-2 autoantibody positivity was lower in both ethnic groups in individuals with an age at diagnosis ≥ 21 years of age, however these differences were only significant in the black population. Furthermore, both GAD65 and IA-2 autoantibody positivity were associated with a significantly younger age at diagnosis of type 1 diabetes in the black but not the white participants. Multivariable logistic regression models confirmed these results with a significant interaction observed between ethnicity and age at diagnosis in both the GAD65 and IA-2 autoantibody regression models. Regression models for each ethnic group further showed that only in black participants was a significant negative relationship observed between increasing age at diagnosis and autoantibody positivity. These data suggest that the black participants with type 1 diabetes who are diagnosed at a later age are

immunologically distinct from those diagnosed at an earlier age but this immunological differentiation is not as pronounced in the white participants. These two sub-groups of type 1 diabetes in the black population have not been observed previously and require further investigation. The regression models also showed that GAD65 autoantibody positivity fell with increasing disease duration only in the black participants with type 1 diabetes. This further emphasises possible immunological differences in disease pathology in these two ethnic groups.

Participants with LADA can include individuals requiring insulin within the first year following diagnosis [26], and may therefore have been included within the group of participants diagnosed after 21 years-of-age. Although there are no definitive diagnostic criteria for LADA, many studies use an age cut-point of >30 years-of-age [27]. Therefore, all participants who were older than 30 years at diagnosis were excluded from all the multivariable logistic regression models, and this had minimal effects on the outcomes. Thus, none of the associations demonstrated in this study, particularly the negative association between age at diagnosis and antibody positivity observed in the black population, can be ascribed to the inclusion of participants with LADA.

Possible limitations of this study are the lower number of white participants with type 1 diabetes, the lack of data for other type 1 diabetes autoantibodies such as IAA and ZnT8, the lack of data on socioeconomic status and the low number of newly diagnosed individuals with type 1 diabetes. The IAAs were not measured as most of the participants were already on insulin treatment and current IAA assays are unable to distinguish these antibodies from those induced by exogenous insulin therapy [28]. The GAD65 and IA-2 autoantibodies were measured in preference to ZnT8 autoantibodies because the former two antibodies are more commonly measured, particularly in those few studies performed in Africa, allowing us to make comparisons between this and previous studies. However, ZnT8 autoantibodies will be measured in a future study. A further limitation of this study is that we did not perform HLA genotyping but this will be undertaken in a future study. It has been reported that HLA-DR3 is associated with GAD65 autoantibodies and HLA-DR4 with IA-2 autoantibodies [16]. It is also known that HLA haplotypes differ based on ethnicity. Thus, the HLA DR3/DR4 heterozygous haplotype confers the greatest genetic risk in Europeans

whereas HLA DR7, DR9 and DR13 haplotypes are common in African Americans [29, 30].

One of the strengths of this study is the large sample size for the black participants with type 1 diabetes, which we believe to be the biggest study conducted to date in sub-Saharan Africa. In addition, this is the first study to compare the prevalence of both GAD65 and IA-2 autoantibodies in black and white individuals with type 1 diabetes in South Africa.

## Conclusions

This study has demonstrated an older age at diagnosis of type 1 diabetes in black than white participants. In addition, we have shown a distinct sub-group of black individuals with type 1 diabetes with an age at diagnosis above 21 years of age who display lower levels of autoantibody positivity than participants diagnosed at an earlier age. This is a novel finding and requires further investigation. The lower level of autoantibody positivity in this group may reflect a less aggressive autoimmune response against the islet beta cells, resulting in a longer prodromal period and a delay in clinical symptomology. However, this must be confirmed in future studies. Data on the immunological aetiology of type 1 diabetes in sub-Saharan African populations are sparse and the current study has provided valuable new information on this topic.

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## Tables

Table 1: Anthropometric and clinical characteristics among black and white participants with type 1 diabetes

| Characteristic | Total (n=472) | Black (n=353) | White (n=119) | p-value[d] |
|---|---|---|---|---|
| **Age (years)** | 26.2 [16.2; 35.4] | 26.9 [17.7; 35.2] | 23.3 [12.5; 37.7] | 0.129 |
| **Gender** | | | | |
| **Male, n (%)** | 224 (48) | 158 (45) | 66 (56) | 0.059 |
| **Female, n (%)** | 247 (52) | 194 (55) | 53 (44) | |
| **Age at diagnosis (years)**[a] | 16.0 [9.0; 27.0] | 19.0 [11.0; 29.0] | 8.5 [5.0; 17.0] | <0.001 |
| **Disease duration (years)**[b] | 6.0 [3.0; 11.0] | 5.0 [2.0; 10.0] | 8.5 [4.0; 20.0] | <0.001 |
| **BMI (kg/m$^2$)**[c] | 23.4 [20.1; 28.0] | 24.0 [20.3; 28.7] | 22.4 [18.9; 26.1] | 0.023 |

Results are presented as median (interquartile range); missing information for [a]age at diagnosis (n=17), [b]disease duration (n=16), [c]BMI (n=30); [d]p-value for comparison between black and white participants

Table 2: Frequency of GAD65 and IA-2 autoantibody positivity in black and white participants with type 1 diabetes

| | All | Black | White | Odds ratio [95% CI][a] | p-value[b] |
|---|---|---|---|---|---|
| **GAD65 autoantibody positive (%)** | 289/470 (62) | 212/353 (60) | 77/117 (66) | 1.28 [0.83, 1.99] | 0.269 |
| **IA-2 autoantibody positive (%)** | 114/470 (24) | 66/352 (19) | 48/118 (41) | 2.96 [1.88, 4.68] | <0.001 |
| **GAD65 and/or IA-2 autoantibody positive (%)** | 304/470 (65) | 218/353 (62) | 86/117 (74) | 1.71 [1.09, 2.76] | 0.028 |
| **GAD65 and IA-2 autoantibody positive (%)** | 99/469 (21) | 60/352 (17) | 39/117 (33) | 2.43 [1.50, 3.90] | <0.001 |

Results are presented as number of participants who are antibody positive/total number of participants (%); [a]Reference group are black participants; [b]p-value for comparison of autoantibody positivity of white with black participants

Table 3: GAD65 and IA-2 autoantibody positivity based on age at diagnosis and duration of disease in black and white participants with type 1 diabetes

| | **Age at diagnosis (years)** | | | | | |
|---|---|---|---|---|---|---|
| | **Black (n=340)** | | | **White (n=116)** | | |
| | **<21 (n=188)** | **≥21 (n=152)** | **p-value** | **<21 (n=92)** | **≥21 (n=24)** | **p-value** |
| **Disease duration (years)** | 6.0 [2.0; 11.0] | 4.5 [2.0; 9.0] | 0.227 | 9.0 [4.8; 21.0] | 8.0 [4.0; 16.2] | 0.621 |
| **GAD65 autoantibody positivity (%)** | 137/188 (73) | 64/152 (42) | <0.001 | 61/90 (68) | 15/24 (63) | 0.807 |
| **IA-2 autoantibody positivity (%)** | 51/188 (27) | 11/151 (7.3) | <0.001 | 40/91 (44) | 8/24 (33) | 0.480 |
| **GAD65 and/or IA-2 autoantibody positivity (%)** | 143/188 (76) | 64/152 (42) | <0.001 | 67/90 (74) | 18/24 (75) | 1.000 |

Results are presented as number of participants who are antibody positive/total number of participants (%) and median [interquartile range]

Table 4: Age at diagnosis and disease duration according to autoantibody status

| | GAD65 autoantibodies | | | | | |
|---|---|---|---|---|---|---|
| | Black (n=340) | | | White (n=114) | | |
| | GAD65 autoantibody positive (n=201) | GAD65 autoantibody negative (n=139) | p-value | GAD65 autoantibody positive (n=76) | GAD65 autoantibody negative (n=38) | p-value |
| **Age at diagnosis (years)** | 15.0 [10.0; 23.0] | 25.0 [16.0; 32.5] | <0.001 | 10.0 [6.0; 17.0] | 7.0 [4.0; 15.0] | 0.108 |
| **Duration of disease (years)** | 5.0 [2.0; 9.0] | 5.0 [3.0; 11.0] | 0.276 | 9.0 [4.0; 20.0] | 8.0 [5.0; 14.0] | 0.923 |
| | **IA-2 autoantibodies** | | | | | |
| | **Black (n=339)** | | | **White (n=115)** | | |
| | IA-2 autoantibody positive (n=62) | IA-2 autoantibody negative (n=277) | p-value | IA-2 autoantibody positive (n=48) | IA-2 autoantibody negative (n=67) | p-value |
| **Age at diagnosis (years)** | 12.5 [8.2; 17.8] | 21.0 [12.0; 30.0] | <0.001 | 10.0 [6.0; 16.2] | 8.0 [4.0; 18.5] | 0.523 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Duration of disease (years)** | 5.0 [2.0; 9.0] | 5.0 [2.0; 11.0] | 0.463 | 7.0 [4.0; 14.0] | 9.0 [5.0; 21.0] | 0.074 |

Results are presented as median [interquartile range]

Table 5: Multivariable logistic regression models for risk factors associated with antibody positivity in the combined ethnic groups and in the individual ethnic groups

| Model number | Ethnicity | Dependent variable | Independent variables | OR [95% CI]; p-value |
|---|---|---|---|---|
| **1** | Black and white combined | GAD65 autoantibody positivity | Age at diagnosis | 0.95 [0.93, 0.97]; <0.001 |
| | | | Disease duration | 0.99 [0.96, 1.01]; 0.295 |
| | | | Ethnicity[a] | 1.00 [0.60, 1.67]; 0.984 |
| | | | Gender[b] | 0.68 [0.46, 1.00]; 0.050 |
| **2** | Black and white combined | IA-2 autoantibody positivity | Age at diagnosis | 0.95 [0.93, 0.97]; <0.001 |
| | | | Disease duration | 0.97 [0.94, 0.99]; 0.015 |
| | | | Ethnicity[a] | 2.86 [1.72, 4.77]; <0.001 |
| | | | Gender[b] | 0.87 [0.55, 1.38]; 0.558 |
| **3** | Black | GAD65 autoantibody positivity | Age at diagnosis | 0.93 [0.90, 0.95]; <0.001 |
| | | | Disease duration | 0.95 [0.92, 0.99]; 0.010 |
| | | | Gender[b] | 0.62 [0.39, 1.00]; 0.049 |
| **4** | White | GAD65 autoantibody positivity | Age at diagnosis | 1.00 [0.97, 1.04]; 0.816 |
| | | | Disease duration | 1.01 [0.98, 1.05]; 0.360 |
| | | | Gender[b] | 0.90 [0.42, 1.94]; 0.784 |
| **5** | Black | IA-2 autoantibody positivity | Age at diagnosis | 0.92 [0.89, 0.96]; <0.001 |
| | | | Disease duration | 0.96 [0.92, 1.01]; 0.146 |
| | | | Gender[b] | 0.93 [0.52, 1.67]; 0.804 |
| **6** | White | IA-2 autoantibody positivity | Age at diagnosis | 0.99 [0.96, 1.02]; 0.556 |
| | | | Disease duration | 0.97 [0.93, 1.00]; 0.053 |
| | | | Gender[b] | 0.80 [0.37, 1.71]; 0.560 |

[a]Ethnicity was coded as black 1, white 2; [b]gender was coded as male 1, female 2