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**Title:**

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**Date:**

2021-07-01

**Citation:**

Mebrahtu, G., Maniam, J., James, S. & Ogle, G. D. (2021). High incidence of type 1 diabetes in adolescents and young adults in Eritrea. *Diabetic Medicine*, 38 (7), <https://doi.org/10.1111/dme.14544>.

**Persistent Link:**

<https://hdl.handle.net/11343/298310>

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Article type : Research Article

## High incidence of type 1 diabetes in adolescents and young adults in Eritrea

### RUNNING TITLE

Incidence of type 1 diabetes in young people in Eritrea

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### AUTHORS' CONTRIBUTIONS

GM co-designed the study, collected data, assisted with confirming patient information, and contributed to the manuscript. JM analysed the data and contributed to the manuscript. SJ co-wrote the manuscript. GO co-designed the study and co-wrote the manuscript.

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/DME.14544](https://doi.org/10.1111/DME.14544)

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## **WORD COUNT**

Abstract=237; and Manuscript=2,435.

## **CONFLICTS OF INTEREST**

None declared.

## **DATA STORAGE AND DOCUMENTATION**

Data collected are not being made accessible to others.

## **NOVELTY STATEMENT**

- **What is already known?**

Eritrea has no data on type 1 diabetes incidence in children and youth. However, reports suggest high incidence rates in immigrant populations from the Horn of Africa.

- **What this study has found?**

Type 1 diabetes incidence in Eritrea is moderate <15 years, and high 15-24 years. The 15-19 and 20-24 year rates appear to be the highest published to date from anywhere in the world.

- **What are the clinical implications of the study?**

Further study of type 1 diabetes phenotypes that are occurring in Eritrea, and ongoing surveillance to document future incidence trends, are indicated.

## **ACKNOWLEDGEMENTS**

This work was supported by a grant from The Leona M and Harry B Helmsley Charitable Trust.

## **ABSTRACT**

### **BACKGROUND**

Eritrea has no data on type 1 diabetes incidence in children and youth, therefore a study was undertaken to determine this in persons aged <25 years (y).

### **METHODS**

Data were collected on new type 1 diabetes diagnoses during 2019, from district, provincial and national hospitals. Type 1 diabetes was diagnosed according to standard WHO criteria. No secondary ascertainment source was available. 95% confidence intervals were computed based on approximation to the Poisson distribution, and age and gender effects were analysed with Poisson regression.

### **RESULTS**

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There were 532 new cases of type 1 diabetes. Mean±SD (minimum-maximum) age of diagnosis was 16.2±5.7 (1.5-24.9) y, and peak age group was 15-19 y (n=200, 37.6%), with mode at 18 y. Incidence <15 y was 11.5/100,000 individuals [9.9-13.2], with the highest incidence in the 10-14 y group (19.0/100,000 [15.5-23.1]). Incidence then peaked in the 15-19 y age group (50.2/100,000 [43.5-57.7]) and remained high in the 20-24 y group (46.2/100,000 [39.0-54.3]).

There was a male:female ratio of 1.37 (p=0.001). Two hundred and thirty-eight (44.7%) presented in diabetic ketoacidosis.

## **CONCLUSION**

Type 1 diabetes incidence in Eritrea is moderate <15 y, and high 15-24 y. The 15-19 and 20-24 y rates appear to be the highest published to date. Given the study was only for one year, further confirmatory prospective information will clarify the situation and document trends. Assessment of the type 1 diabetes phenotypes that are occurring in Eritrea is also indicated.

## **KEYWORDS**

Adolescents; Children; Eritrea; Incidence; Type 1 diabetes; Young adults

## **1. INTRODUCTION**

The State of Eritrea is a country in the Horn of Africa with its capital at Asmara. It is bordered by Sudan in the west, Ethiopia in the south, and Djibouti in the southeast. Since gaining independence from Ethiopia in 1993, Eritrea has faced substantial political, socio-economic, health and reconstruction challenges. It is classified by the United Nations as a Least Developed Country (1).

There are very limited data on type 1 diabetes in Eritrea (2). In estimating type 1 diabetes incidence and prevalence rates in Eritrea in children and youth aged <15 and 15-19 years (y) of age, the International Diabetes Federation Diabetes Atlas uses data from Sudan (3). Given the importance of epidemiological data to help guide adequate allocation of health resources, health professional education, and advocacy, a study was undertaken to determine the incidence of type 1 diabetes in children and youth aged <25 y in Eritrea. The Life for a Child Program (4) has, since 2011, provided insulin and other diabetes supplies, educational materials, and other support to the Government health system via the Eritrean National Diabetes Association. This study also aimed to inform that work.

## **2. METHODS**

## **2.1. Data collection**

Eritrea is divided into six administrative regions (zobas/provinces): the Maekel/Central, Anseba, Gash-Barka, Debub/Southern, Northern Red Sea and the Southern Red Sea. All children in Eritrea aged <5 y that are thought to have type 1 diabetes are routinely referred to the provincial hospital where they commence treatment, and then subsequently receive follow-up at nearest district hospital. Children aged 5-15 y, however, commence treatment for type 1 diabetes at the local district hospital, but are then referred to the provincial hospital for diagnosis confirmation. Finally, youth aged 16-24 y are treated and have their type 1 diabetes diagnosis confirmed at a district hospital, where they continue for follow up, unless they have co-morbidities in which case they are seen at the provincial hospital. In this study, data were collected on new type 1 diabetes diagnoses during 2019, from district, provincial and national hospitals. No secondary ascertainment source could be identified.

## **2.2. Diagnosis of type 1 diabetes and diabetic ketoacidosis (DKA)**

Type 1 diabetes was diagnosed according to standard World Health Organization criteria (5). Such criteria included the abrupt onset of symptomatic hyperglycaemia, need for insulin replacement therapy from diagnosis, and no acanthosis nigricans. Diabetes autoantibody and C-peptide assays are not available in Eritrea.

DKA was clinically diagnosed when there was a high blood glucose level ( $\geq 200$  mg/dL (11.1 mmol/L)), accompanied by ketonuria or sweet-smelling breath, as well as weakness or fatigue, and, when available, venous pH <7.3 or bicarbonate <15 mmol/L. Urine ketone strips are rarely available in Eritrean hospitals.

## **2.3. Source population**

The last census conducted in Eritrea was in 1984, well before independence (6). Population estimates vary widely. The United Nations Department of Economic and Social Affairs estimated that the national population was 3,497,117 in July 2019 (7). However, the National Health Information Statistics (NHIS) office of the Eritrean Ministry of Health, estimated a population of 4,019,769 at the end of 2019 (internal data released to G.M. in July 2020). This office uses a 3% annual growth rate. Therefore, the population in mid-2019 in the middle of the study period would have been approximately 1.5% less at 3,902,688. This is the figure that was used in the study; documented Eritrean age structure percentages were applied (8). The median Eritrean population age in 2020 was estimated at 19.2 y (7).

## **2.4. Data analyses**

Descriptive statistics (frequencies, central tendency and dispersion) were calculated to describe the sample, with age at type 1 diabetes diagnosis expressed as mean $\pm$ standard

deviation (range). The significances of sex and presentation in DKA were assessed using the Chi-square ( $\chi^2$ ) test. Annual incidence of type 1 diabetes was calculated as number of newly diagnosed cases/100,000 children and youth in 5-y age brackets (0-4, 5-9, 10-14, 15-19 and 20-24), and also <15 and <25 y age brackets. Crude and standardised rates were computed, with standardised rates based on the 2019 world population <25 y (7). 95% confidence intervals (95% CI) were computed based on approximation to the Poisson distribution. Age and gender effects on incidence were analysed with Poisson regression. Descriptive analysis was conducted with IBM SPSS Statistics Version 25, 2017 (Armonk, USA), and Poisson regression using the statistical program Stata (Version 16.1, StataCorp, College Station, Texas). Statistical significance was set at  $p < 0.05$ .

## **2.5. Ethical considerations**

The study was approved by the Eritrean Ministry of Health Ethical Committee, which included the decision that informed consent was not required.

## **3. RESULTS**

### **3.1 Diagnoses and demographic data**

There were 532 new cases of type 1 diabetes diagnosed in children and youth aged <25 y (Table 1), with a mean  $\pm$  standard deviation (minimum-maximum) age of type 1 diabetes diagnosis of  $16.2 \pm 5.7$  (1.5-24.9) y. The mode was 18 y. Cases per 5-y age group progressively increased until peaking in the 15-19 y group ( $n=200$ , 37.6%), and then falling slightly in the 20-24 group ( $n=146$ , 27.4%), with the least ( $n=29$ , 5.5%) occurring amongst those aged 0-4 y (Table 1 and Figure 1). There was a significant male preponderance, with a male:female ratio of 1.37 ( $n=308$  vs.  $n=224$ ,  $p=0.001$ ), with ages at type 1 diabetes diagnosis being similar (males  $16.2 \pm 5.8$  (1.5-24.9) y vs. females  $16.1 \pm 5.7$  (1.8-24.9) y). When examined per 5-y age group, a male excess was also significant in the 20-24 y group ( $p=0.01$ ). When assessed by quarter, there was no difference in numbers of new cases across the 12 months: there were 145 cases (27.3%) in January-March, 153 (28.8%) April-June, 150 (28.2%) July-September, and 84 (15.8%) October-December ( $p=0.25$ ).

### **3.2 Type 1 diabetes incidence**

Crude incidence per 5-y age group progressively increased up until 14 y, rose sharply to peak in the 15-19 y age group (50.2/100,000 [95% CI 3.5-57.7]), and then fell slightly in the 20-24 group (46.2/100,000 population [39.0-54.3]) (Table 1). The lowest incidence was in those aged 0-4 y (5.3/100,000 [3.5-7.6],  $p < 0.001$ ) (Table 1 and Figure 2). Standardised rates for <15 and <25 y were 11.4/100,000 [10.0-13.0] and 25.4/100,000 [23.6-27.2], respectively.

### 3.3 Presentation in DKA

There were 238 (44.7%) cases of DKA at diagnosis of type 1 diabetes (Table 2). There were no significant differences in DKA rates between any 5-y age group.

## 4. DISCUSSION

This is the first study to provide epidemiological data on type 1 diabetes in children and youth in Eritrea. The 2019 type 1 diabetes incidence of 11.5/100,000 individuals <15 y is a moderate incidence in comparison to other countries (3, 9), and the incidences of 50.2 and 46.2/100,000 in persons aged 15-19 y and 20-24 y respectively, are high.

Reported type 1 diabetes incidence is highest in northern-European-origin populations (particularly in Scandinavia) and also some Arab populations in the Middle East and North Africa (3, 9). With respect to countries neighbouring Eritrea, Djibouti has no data, Khartoum in Sudan had an incidence of 10.1/100,000 in 0.5-19 y (10), and a study from Gondar and Jimma in Ethiopia found a rate of 2.1/100,000 across all age groups (11). Life for a Child program observations suggest higher rates of type 1 diabetes in the Tigray Region of northern Ethiopia (12), where the ethnic make-up of the population is similar to Eritrea. Further south, rates are low in the limited data reported from sub-Saharan African populations (3, 9, 12, 13): for instance, the rates in Rwanda from 2007-2011 were 1.2 <15 y and 2.7 <26 y (13).

The <15 y incidence in Eritrea (11.5) is substantially lower than that seen northern European populations. In Finland, type 1 diabetes incidence peaks in the 5-9 y age group (14), and in most other non-European origin populations in the 10-14 y group (9, 15). Type 1 diabetes onset has become earlier over the last few decades in these populations (9).

In the current study, the most remarkable finding is the high incidences in the 15-19 y and 20-24 y age groups. The incidences of 50.2 (15-19 y), and 46.2 (20-24 y) are higher than any other reports we could find in the literature, from examining the review by Diaz-Valencia et al. (15), and other more recent studies.

This later age of peak onset is also seen in data from Rwanda (13) (where the mode also was at 18 y), and other sub-Saharan African populations (12). In the Ethiopian study by Alemu et al. (11), peak age of onset was 25-29 y. It is possible that the temporal shift in earlier onset seen in European populations (9, 14) has not yet occurred in Eritrea. It is also possible that some cases die at onset misdiagnosed with another condition, as had been imputed from clinical experience and changing incidence data from some other less-resourced countries (12, 13, 16). This tragic outcome may be relatively more common in young children as in this age-group classic symptoms and signs of type 1 diabetes can be less obvious, and infectious diseases are common (12).

This observed high incidence in Eritrea is consistent with findings in populations, of varying ages from the Horn of Africa, that emigrated to Scandinavia (17, 18), the United States (19, 20), and Israel (21). For instance, in comparison to children born of native Swedish families, type 1 diabetes prevalence is higher in children born in Sweden to Eritrean families and similar in children born in Eritrea but now living in Sweden (18). Furthermore, a comparison of the prevalence and characteristics of diabetes between Somali and Finnish children (<16 y) in Helsinki, diabetes prevalence was 40 vs. 37/10,000, respectively (17); and in King County, Washington, USA, O'Connor et al. found type 1 diabetes prevalence was nearly four times higher among youth aged  $\leq 17$  y from East African compared to non-immigrant Blacks (6.20 vs. 1.56/1,000) (20).

Eritrea is a mainly coastal nation just across the Red Sea from Saudi Arabia and Yemen. Saudi Arabia, as well as Kuwait and Qatar, have type 1 diabetes incidences for the 0-14 y age-group that are in the top 10 of global rates (3). With this proximity, there are extensive historical interactions between Eritrea and the Arab populations of the Middle East. Arabic is one of the three working languages in Eritrea (along with Tigrinya and English), and 36.6% of the population are estimated to be Muslim (22). Furthermore, there is strong evidence of a 'back to Africa' migration in the pre-agriculture period. These migrations may have increased the frequency of HLA haplotypes that confer higher type 1 diabetes risk, such as *DRB03* and *04*. The HLA profile of Somali children with diabetes in the USA has been reported to have a high prevalence of the *DRB1\*04:01* allele and relative paucity of *DR4* alleles compared with African Americans with type 1 diabetes (19). Studies of HLA associations with type 1 diabetes in Arabic (23) and Ethiopian (24) populations show many similarities but some differences with European-origin populations. Further studies would be needed to determine the particular associations in Eritrea.

There was also a male predominance in the Eritrean data. Type 1 diabetes is generally slightly more common in males in high-incidence countries (9), but in the current study the male excess was pronounced. This was also seen in a recent Ethiopian study: males represented 72.6% and 77.6% of cases in the 16-25 y and 26-35 y age groups respectively (24). One possible contributor to this could be that male children are preferentially presented for medical care, however we are not aware of any data or observations to support this from this region of Africa.

It is increasingly recognised that there is substantial heterogeneity in type 1 diabetes phenotype, with variations in age of onset, pattern of diabetes autoantibodies, rate of progression, insulin secretion, and other factors (25, 26). In the recent Ethiopian study (24), type 1 diabetes cases in children <15 y were more typical of 'classic' type 1 diabetes cases than those in adolescents and young adults. Only glutamic acid decarboxylase (GAD-65) autoantibodies were common, with zinc transporter 8 (ZnT8) autoantibodies uncommon and

islet antigen 2 (IA2) autoantibodies rare, and GAD-65 autoantibody positivity declined with age. Median C-peptide levels were also higher in youth and young adults than in children.

The incompletely characterised entity of 'malnutrition-related' diabetes has been described in various less-resourced countries, including Ethiopia, where adolescents and young adults with type 1 diabetes were often malnourished at type 1 diabetes onset, and smaller-framed (11, 27). It is not clear if this is a distinct entity, or if it is associated with and possibly modifying the impact of a more indolent autoimmune process (24). Like Ethiopia, Eritrea is a low-income country with a history of famines, and malnutrition is common (28).

A relatively high percentage (45.7%) of patients in this study presented in DKA at the time of type 1 diabetes diagnosis (29). This rate was stable across 5-y age groups, and indicates the need for public and healthcare professional education of the signs and symptoms at onset of type 1 diabetes.

The study has a number of limitations. No secondary ascertainment source was available, and therefore it is not possible to determine, through a capture-recapture method, if there was full case ascertainment. Because incidence data are from only one year, it is possible that rates reported may include some earlier cases not previously recognised or documented, as the impact of Life for a Child support and associated organisation of care is steadily increasing in Eritrea. Furthermore, as discussed above, it may be that some cases may have been missed due to misdiagnosis. Type 1 diabetes diagnosis was based on clinical assessment only: assays for diabetes autoantibodies and C-peptide are not available in Eritrea. Finally, the population estimate used has substantially more uncertainty than for most other countries, as no census has been done since 1984 and estimates are further confounded by an unknown but substantial rate of emigration, particularly of young adults (30).

## **5. CONCLUSION**

Eritrea has a moderate incidence of type 1 diabetes in children, rising to a very high incidence in those aged 15-24 y. Ongoing surveillance will be required to document future trends. Further study is warranted on the phenotypes and endotypes occurring. This could include examination of genetics, autoimmunity, beta-cell reserve, and relationship to malnutrition and other environmental factors. Such studies may yield information that would contribute to the global understanding of type 1 diabetes pathogenesis.

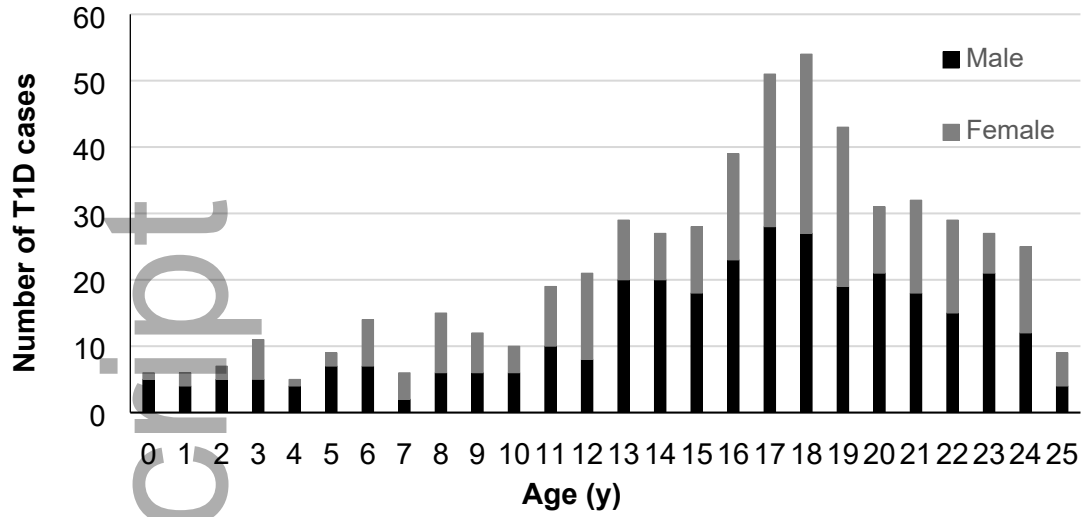
Finally, these data demonstrate that type 1 diabetes is very common in Eritrea. Efforts are needed to further improve access to and organisation of care, so that a very substantial burden of serious long-term complications and early mortality can be prevented. This is applicable not just for Eritrea but also for the Eritrean diaspora.

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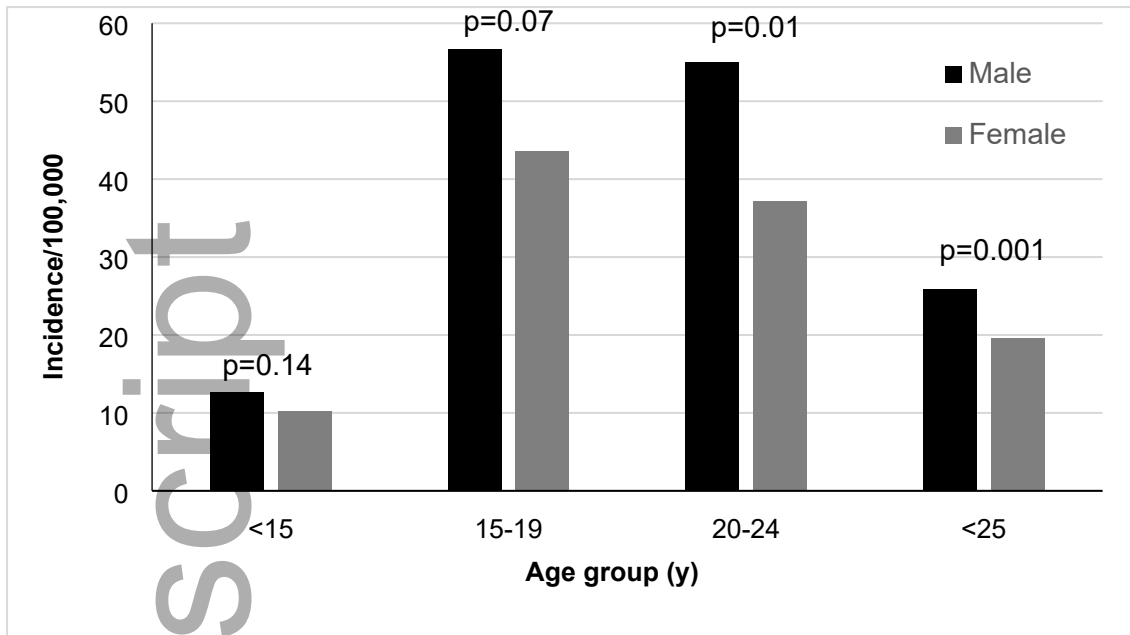
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*y=Years; and T1D=Type 1 diabetes.*

**Figure 1: Age onset of type 1 diabetes in Eritrean children and youth aged <25 y**



T1D=Type 1 diabetes; and y=Years.

**Figure 2: Incidence of type 1 diabetes by gender in Eritrean children and youth aged <25 y**

**Table 1: Type 1 diabetes cases and crude incidence in Eritrean children and youth aged <25 y**

Age	Males				Females				Overall			
	Pop.	Cases	Inc.	95% CI	Pop.	Cases	Inc.	95% CI	Pop.	Cases	Inc.	95%CI
<b>0-4 y</b>	280,994	18	6.4	3.8-10.1	269,286	11	4.1	2-7.3	550,279	29	5.3	3.5-7.6
<b>5-9 y</b>	277,091	28	10.1	6.7-14.6	265,383	28	10.6	7-15.2	542,474	56	10.3	7.8-13.4
<b>10-14 y</b>	269,286	59	21.9	16.7-28.3	261,481	42	16.1	11.6-21.7	530,766	101	19.0	15.5-23.1
<b>15-19 y</b>	202,940	115	56.7	46.8-68	195,135	85	43.6	34.8-53.9	398,074	200	50.2	43.5-57.7
<b>20-24 y</b>	160,011	88	55.0	44.1-68	156,108	58	37.2	28.2-48	316,118	146	46.2	39.0-54.3
<b>&lt;15 y</b>	827,371	105	12.7	10.4-15.4	796,149	81	10.2	8.1-12.7	1,623,519	186	11.5	9.9-13.2
<b>&lt;25 y</b>	1,190,321	308	25.9	23.1-28.9	1,147,391	224	19.5	17.1-22.2	2,337,711	532	22.8	20.9-24.8

*y=Years; Pop.=Population; Inc.=Incidence; and CI=Confidence Interval. Incidence per 10<sup>5</sup>. Figures rounded.*

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**Table 2: Presentation of DKA in Eritrean children and youth aged <25 y**

Age	New T1D cases			DKA cases			DKA %		
	Male	Female	Overall	Male	Female	Overall	Male	Female	Overall
0-4 y	18	11	29	8	4	12	44.4%	36.4%	41.4%
5-9 y	28	28	56	16	13	29	57.1%	46.4%	51.8%
10-14 y	59	42	101	31	18	49	52.5%	42.9%	48.5%
15-19 y	115	85	200	47	42	89	40.9%	49.4%	44.5%
20-24 y	88	58	146	33	26	59	37.5%	44.8%	40.4%
<15 y	105	81	186	55	35	90	52.4%	43.2%	48.4%
<25 y	308	224	532	135	103	238	43.8%	46.0%	44.7%

*DKA=Diabetic ketoacidosis; y=Years; and T1D=Type 1 diabetes.*

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**Table 1: Type 1 diabetes cases and crude incidence in Eritrean children and youth aged <25 y**

Age	Males				Females				Overall			
	Pop.	Cases	Inc.	95% CI	Pop.	Cases	Inc.	95% CI	Pop.	Cases	Inc.	95%CI
<b>0-4 y</b>	280,994	18	6.4	3.8-10.1	269,286	11	4.1	2-7.3	550,279	29	5.3	3.5-7.6
<b>5-9 y</b>	277,091	28	10.1	6.7-14.6	265,383	28	10.6	7-15.2	542,474	56	10.3	7.8-13.4
<b>10-14 y</b>	269,286	59	21.9	16.7-28.3	261,481	42	16.1	11.6-21.7	530,766	101	19.0	15.5-23.1
<b>15-19 y</b>	202,940	115	56.7	46.8-68	195,135	85	43.6	34.8-53.9	398,074	200	50.2	43.5-57.7
<b>20-24 y</b>	160,011	88	55.0	44.1-68	156,108	58	37.2	28.2-48	316,118	146	46.2	39.0-54.3
<b>&lt;15 y</b>	827,371	105	12.7	10.4-15.4	796,149	81	10.2	8.1-12.7	1,623,519	186	11.5	9.9-13.2
<b>&lt;25 y</b>	1,190,321	308	25.9	23.1-28.9	1,147,391	224	19.5	17.1-22.2	2,337,711	532	22.8	20.9-24.8

*y=Years; Pop.=Population; Inc.=Incidence; and CI=Confidence Interval. Incidence per 10<sup>5</sup>. Figures rounded.*

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**Table 2: Presentation of DKA in Eritrean children and youth aged <25 y**

Age	New T1D cases			DKA cases			DKA %		
	Male	Female	Overall	Male	Female	Overall	Male	Female	Overall
0-4 y	18	11	29	8	4	12	44.4%	36.4%	41.4%
5-9 y	28	28	56	16	13	29	57.1%	46.4%	51.8%
10-14 y	59	42	101	31	18	49	52.5%	42.9%	48.5%
15-19 y	115	85	200	47	42	89	40.9%	49.4%	44.5%
20-24 y	88	58	146	33	26	59	37.5%	44.8%	40.4%
<15 y	105	81	186	55	35	90	52.4%	43.2%	48.4%
<25 y	308	224	532	135	103	238	43.8%	46.0%	44.7%

*DKA=Diabetic ketoacidosis; y=Years; and T1D=Type 1 diabetes.*

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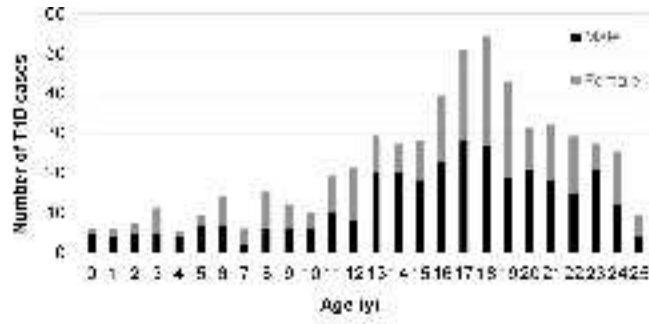
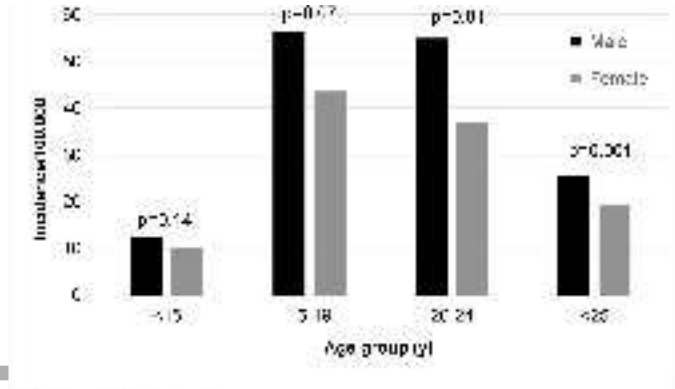


Figure 1. Number of T1D cases by age group and sex.

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T1D Type 1 diabetes, µU/kg/min

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