Worldwide differences in childhood type 1 diabetes: The SWEET experience

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Abstract
Objective: To study worldwide differences in childhood diabetes, comparing relevant indicators among five regions within the SWEET initiative.

Subjects: We investigated 26,726 individuals with type 1 diabetes (T1D) from 54 centers in the European region; 7,768 individuals from 30 centers in the Asia/Middle East/Africa region; 2,642 people from five centers in Australia/New Zealand; 10,839 individuals from seven centers in North America, and 1,114 patients from five centers in South America.

Methods: The SWEET database was analyzed based on the following inclusion criteria: T1D, time period 2015-2019, and age < 21 years, with analysis of the most recent documented year of therapy. For the statistical analysis, we used multivariable linear and logistic regression models to adjust for age (<6 years, 6- < 12 years, 12- < 18 years, 18- < 21 years), gender, and duration of diabetes (<2 years, 2- < 5 years, 5- < 10 years, ≥10 years).

Results: Adjusted HbA1c means ranged from 7.8% (95%-confidence interval: 7.6-8.1) in Europe to 9.5% (9.2-9.8) in Asia/Middle East/Africa. Mean daily insulin dose ranged from 0.8 units/kg in Europe (0.7-0.8) and Australia/New Zealand (0.6-0.9) to 1.0 unit/kg (0.9-1.1) in Asia/Middle East/Africa. Percentage of pump use was highest in North America (80.7% [79.8-81.6]) and lowest in South America (4.2% [3.2-5.6]). Significant differences between the five regions were also observed with regards to body mass index SD scores, frequency of blood glucose monitoring and presence of severe hypoglycaemia.

Conclusions: We found significant heterogeneity in diabetes care and outcomes across the five regions. The aim of optimal care for each child remains a challenge.

KEYWORDS
type 1 diabetes, children and adolescents, diabetes care, SWEET registry, worldwide differences
1 | INTRODUCTION

Type 1 diabetes mellitus (T1D) is the most prevalent type of diabetes among children and adolescents, particularly those of European origin. Across the globe, an estimated 98,000 children below the age of 15 years develop T1D annually. International guidelines for the diagnosis and management of T1D provide guidance on care strategies for children and adolescents. Delivering optimal care across the spectrum of available resources, cultural barriers, and national health systems is challenging. A previous international comparison of 19 countries showed substantial variations in HbA1c and a high proportion of individuals with T1D in poor glycaemic control. Disparities in the access to innovative treatment and diabetes technology, diabetes education and multidisciplinary care are one of the explanations for the observed variations.

There are large differences in how national health services in high- and low-income countries provide analogue insulin, blood glucose test strips, insulin pumps and continuous glucose monitoring (CGM). Low diabetes education and diabetes awareness are additional challenges in low-income countries.

However, differences in diabetes care and outcomes also exist within and between high-income countries. For example, among children with T1D <6 years of age in the diabetes patients follow-up registry (DPV) in Germany/Austria and the T1D Exchange (T1DX) in the United States there was a higher rate of insulin pump use in DPV (74%) compared to T1DX (50%). Moreover, 0-6 year old patients with T1D in DPV were more likely to achieve HbA1c targets of <7.5% than those in T1DX (56% vs 22%). Another comparison of outcomes in eight high-income countries (Germany, Austria, England, Wales, United States, Sweden, Denmark and Norway), reported the lowest mean HbA1c values in Sweden and the other Nordic countries. Different structures of diabetes care (hospital-based vs private practice) are suggested to be one of the potential reasons for the observed high variation in HbA1c.

One of the objectives of the “better control in paediatric and adolescent diabetes: Working to create centers of reference” (SWEET) initiative is to bring low- and high-income countries together to exchange expertise as a step towards standardization of diabetes care for children and adolescents with diabetes. Previously, SWEET centers from developing countries in India, Mali, Argentina and Costa Rica reported to benefit from participating in the initiative by exchanging knowledge with centers from developed countries and by learning from their expertise. The purpose of this study was to conduct a baseline comparison among the SWEET regions to describe worldwide differences in pediatric T1D care and to address issues and possibilities for optimizing diabetes care based on the respective available resources.

2 | METHODS

The SWEET network facilitates continuous evaluation of diabetes treatment and outcome variables and benchmarking data to exchange best practices and reduce inequalities. The mission of SWEET is to harmonize care to optimize outcomes of children and adolescents with diabetes worldwide.

This retrospective study used SWEET database records from 2015 to 2019. Within the SWEET initiative five regions were defined based on the location and number of available centers and patients: Europe, Asia/Middle East/Africa, Australia/New Zealand, North America, and South America (Figure 1). The European region included data from 54 diabetes centers in Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, England, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovenia, Spain and Sweden. The 30 centers in the Asia/Middle East/Africa region were in Bangladesh, Democratic Republic of the Congo, Egypt, India, Iran, Israel, Japan, Korea, Kuwait, Mali, Mauritius, Morocco, Pakistan, Tanzania and Turkey. Five diabetes centers in Argentina, Brazil, Chile, Costa Rica and Ecuador represent the South American region, and the North America region included seven diabetes centers in Canada and the United States. The Australia/New Zealand region had five centers.

The SWEET initiative was approved by the ethical committee of the Hannover Medical School, Germany. Each participating center is responsible for obtaining individual ethical approval and informed consent from each patient. Anonymised data are provided by the DPV (Diabetes-Patienten-Verlaufsdokumentation) software (https://sweet.zibmt.uni-ulm.de/software.php), DIAMAX software, Excel files, national registries or local archives. Every 6 months centers transfer pseudonymized data to the SWEET database at the Institute of Epidemiology and Medical Biometry, University of Ulm, Ulm, Germany. The pseudonymized data from individual centers are then integrated into a completely anonymized database which is solely used for statistical analysis and benchmarking. Inconsistent and implausible data are reported back for verification or correction after each data upload.

The SWEET database entails a list of quality indicators accumulated via routine pediatric care, and comprises information on process and structural aspects in addition to diabetes outcome. All patients <21 years of age were included. For the underlying analysis we aggregated data (median) of the most recent treatment year per patient. We analyzed patients’ current age, age at diabetes onset, treatment modality, most recent glycated hemoglobin (HbA1c), body mass index SD score (BMI-SDS), the frequency of severe hypoglycaemia, daily insulin dose (units/kg), frequency of blood glucose monitoring (SMBG), and frequency of pump usage. The presence of severe hypoglycaemia was defined as at least one episode during the year of observation. BMI-SDS, weight-SDS and height-SDS were calculated using the WHO growth curves.

Age groups included <6 years, 6-< 12 years, 12-< 18 years, 18-< 21 years. Patients were also grouped by diabetes duration of <2 years, 2-< 5 years, 5-< 10 years, ≥10 years. According to treatment received, patients were classified as receiving conventional therapy (CT) (1-3 injection time points/day), intensified conventional therapy (ICT) (4-8 injection time points/day), and continuous subcutaneous insulin infusion (CSII/Pump).
2.1 | Statistical analysis

Descriptive analysis were conducted with continuous variables represented as median (lower (Q1) and upper quartile (Q3)) and binary variables as percentages. Unadjusted comparisons were conducted using Kruskal-Wallis test for continuous outcomes and Chi square test for binary outcomes. The P-values were corrected for multiple testing using the False Discovery Rate (FDR). In order to adjust comparisons for differences in demographics, multivariable regression models were used: linear regression models for continuous outcomes and logistic regression models for binary outcomes. All models were adjusted for sex, age and diabetes duration groups. Results from regression models are presented as least-square means (LS-means) together with 95%-confidence intervals estimated using observed marginal distributions of covariates. Outcomes were compared between the five SWEET regions Europe, Asia/Middle East/Africa, Australia/New Zealand, North America, and South America. In order to test the robustness of the results, we conducted a sensitivity analysis with Africa as a separate group. All analyses were performed with Statistical Analysis Software 9.4 (SAS, SAS Institute Inc., Cary, NC).

3 | RESULTS

Data from 101 centers from the SWEET database were analyzed, which included 66 059 individuals with all diabetes types. Of these 61 707 were < 21 years of age and 53 820 (49 089 T1D) individuals were documented between 2015 and 2019. The patient selection process is summarized in Figure 2. There were 29 469 (26 726 T1D) children and adolescents from 54 centers in the European region; 8331 (7768 T1D) individuals from 30 centers in the Asia/Middle East/African region; 2895 (2642 T1D) individuals from five centers in Australia/New Zealand; 11 785 (10 839 T1D) individuals from seven centers in North America, and 1340 (1114 T1D) children and adolescents from five centers in South America. In 2019 a median number of 251 (Q1-Q3: 133-486) individuals per center were treated in Europe, 64 (26-180) patients per center in Asia/Middle East Africa, 124 (102-469) patients per center in Australia/New Zealand, 580 (355-1694) individuals per center in North America and 65 (57-271) patients per center in South America. The proportion of people with T1D ranged from 83% in South America to 93.2% in Asia/Middle East Africa.

Of the 49 089 individuals with T1D, 52% were males (Table 1). Median age at diabetes onset as well as age during most recent
treatment year in children and adolescents with T1D differed significantly between the SWEET regions \((P < 0.001)\). Age at diabetes onset was lowest in the Australia/New Zealand region \((7.6 \text{ years} [4.4-10.9])\) and highest in the Asia/Middle East/Africa region \((8.5 \text{ years} [4.8-12.1])\). Median age at most recent treatment year was lowest in the South American region \((\text{median} 12.6 \text{ years} [9.7-15.1])\) and highest in the North America region \((\text{median} 15.4 \text{ years} [11.7-18.1])\).

With respect to treatment, 14.8% of the total study population were on CT, 40.5% were on ICT, while 44.7% used insulin pump. The percentage of T1D people with at least 1 severe hypoglycaemic episode during the preceding year for different regions were 0.9% in Europe, 1.1% in Asia/Middle East/Africa, 2.5% in Australia/New Zealand, 2.0% in North America, and 1.2% in South America respectively, \((P < .001)\).

Results from linear and logistic regression models adjusted for sex, age and diabetes duration are presented in Figure 3. Adjusted HbA1c means ranged from 7.8% \((95\%-\text{confidence interval}: 7.6-8.1)\) in Europe to 9.5% \((9.2-9.8)\) in Asia/Middle East/Africa \((P < .001)\). Lowest mean BMI-SDS was observed in Asia/Middle East/Africa \((-0.1 [-0.3-0.0])\), whereas highest BMI-SDS was found in Australia/New Zealand \((0.8 [0.5-1.2])\) \((P < .001)\). Moreover, number of SMBG differed significantly between the regions and ranged from 3.1 \((2.5-3.7)\) in Asia/Middle East/Africa to 5.5 \((5.0-5.9)\) in the European region \((P < .001)\). We observed the lowest mean daily insulin dose in Europe \((0.8 \text{ units/kg} [0.7-0.8])\) and Australia/New Zealand \((0.8 \text{ units/kg} [0.6-0.9])\) and highest dose in Asia/Middle East/Africa \((1.0 \text{ units/kg} [0.9-1.1])\) \((P < .001)\). Use of insulin pumps was lowest in South America \((4.2\% [3.2-5.6])\) and highest in North America \((80.7\% [79.8-81.6])\) \((P < .001)\). Around 1% of individuals with T1D in Europe \((0.9\% [0.8-1.0])\), Asia/Middle East/Africa \((1.1\% [0.9-1.3])\) and South America \((1.1\% [0.7-2.0])\) reported at least one severe hypoglycaemic event during the most recent treatment year. The proportion of patients

### TABLE 1
Demographic, treatment and outcome variables of type 1 diabetes patients, stratified by region

| Region                        | Total \(\text{n} = 49,089\) | Europe \(\text{n} = 26,726\) | Asia/Middle East/Africa \(\text{n} = 7,768\) | Australia/New Zealand \(\text{n} = 26,42\) | North America \(\text{n} = 10,839\) | South America \(\text{n} = 11,14\) |
|-------------------------------|-------------------------------|-------------------------------|-------------------------------------------|-------------------------------------------|-------------------------------------|-------------------------------------|
| Age (years)                   | 14.6 (10.8-17.6)              | 14.6 (10.8-17.6)              | 14.0 (10.2-17.1)                          | 14.3 (10.7-16.6)                          | 15.4 (11.7-18.1)                   | 12.6 (9.7-15.1)                     |
| Age at diabetes onset (years) | 7.9 (4.5-11.3)                | 7.7 (4.3-11.0)                | 8.5 (4.8-12.1)                            | 7.6 (4.4-10.9)                            | 8.3 (4.8-11.5)                     | 8.2 (4.9-10.6)                     |
| Diabetes duration (years)     | 5.1 (2.4-8.6)                 | 5.3 (2.5-8.8)                 | 4.0 (1.7-7.2)                             | 4.9 (2.4-8.4)                             | 5.5 (2.6-9.3)                      | 3.5 (1.8-6.2)                      |
| HbA1c (%)                     | 8.0 (7.1-9.2)                 | 7.6 (6.9-8.5)                 | 8.9 (7.8-10.6)                            | 8.0 (7.2-9.0)                             | 8.7 (7.7-10.1)                     | 7.9 (7.2-9.0)                      |
| BMI-SDS                       | 0.5 (-0.2-1.2)                | 0.5 (-0.2-1.2)                | 0.0 (-0.9-0.9)                            | 0.8 (0.1-1.4)                             | 0.7 (0.0-1.5)                      | 0.7 (0.0-1.4)                      |
| Weight-SDS                    | 2.7 (1.2-3.5)                 | 2.7 (1.3-3.6)                 | 1.8 (0.3-2.9)                             | 2.8 (1.5-3.7)                             | 3.1 (1.6-3.8)                      | 2.1 (0.7-3.1)                      |
| Height-SDS                    | 0.2 (-0.5-1.0)                | 0.4 (-0.3-1.1)                | -0.6 (-1.6-0.2)                           | 0.5 (-0.2-1.2)                            | 0.3 (-0.4-0.9)                     | -0.1 (-0.8-0.6)                    |
| Daily insulin dose (units/kg) | 0.8 (0.6-1.0)                 | 0.8 (0.6-1.0)                 | 0.9 (0.7-1.1)                             | 0.8 (0.6-1.0)                             | 0.8 (0.7-1.0)                      | 0.9 (0.7-1.0)                      |
| SMBG per day                  | 4.1 (3.0-6.0)                 | 5.0 (4.0-7.0)                 | 2.0 (1.0-3.0)                             | 4.0 (3.0-6.0)                             | 4.0 (3.0-6.0)                      | 4.0 (4.0-5.0)                      |
| Males (%)                     | 51.8                          | 52.1                          | 49.6                                      | 52.0                                      | 53.1                               | 47.3                               |
| HbA1c <7.5% (%)               | 34.9                          | 46.3                          | 18.1                                      | 34.5                                      | 18.8                               | 33.3                               |
| conventional therapy (%)      | 14.8                          | 7.1                           | 50.0                                      | 16.6                                      | 7.7                                | 4.3                                |
| intensified conventional therapy (%) | 40.5                          | 48                            | 38.7                                      | 32.2                                      | 11.5                               | 91.1                               |
| Insulin pump (%)              | 44.7                          | 44.9                          | 11.3                                      | 51.2                                      | 80.8                               | 4.6                                |
| ≥1 severe hypoglycaemia/year  | 1.3                           | 0.9                           | 1.1                                       | 2.5                                       | 2.0                                | 1.2                                |
with at least one severe hypoglycaemic event was higher in Australia/New Zealand (2.3% [1.8-3.0]) and North America (2.0% [1.8-2.3]) than in Europe, Asia/Middle East/Africa and South America, (Figure 3F, $P < .001$). Sensitivity analysis with Africa as a separate region showed similar results (Supplemental Figure 1).

**DISCUSSION**

The motive of SWEET being a standardized documentation of pediatric diabetes care, such a diverse and rich data pool offers a unique opportunity to analyze the differences in practice and outcomes across the planet. Comparing the five SWEET regions, we found significant differences in HbA1c, BMI-SDS, SMBG, mean daily insulin dose, insulin pump use, and the proportion of people reporting at least one severe hypoglycaemic event during the most recent treatment year.

Results from the SWEET initiative showed adjusted HbA1c means from 7.8% (7.6-8.1 Europe) to 9.5% (9.2-9.8 Asia/Middle East/Africa). Differences in HbA1c between countries were also reported in previous studies. However, most studies so far included high-income countries only. Charalampopoulos et al$^{11}$ compared HbA1c values between children and adolescents with T1D < 18 years of age...
from Austria, Denmark, England, Germany, Norway, Sweden, U.S. and Wales. The authors observed HbA1c means from 7.6% in Sweden to 8.8% in Wales and high HbA1c variation within countries was found. HbA1c levels strongly depend on the level of diabetes care in children and adolescents with T1D, which has been clearly demonstrated in a “levels of care” framework by Ogle and colleagues.4 Level of diabetes care depends on access to insulin, SMBG test strips, HbA1c testing, complications screening, diabetes education and multidisciplinary care. Low income countries often show a low level of diabetes education and limited expertise of the care team. In a study conducted on children and youth ≥25 years of age in East Africa, HbA1c decreased significantly after the establishment of systematic HbA1c testing and an enhanced diabetes education program.19 Moreover, benchmarking, particularly the public report of quality indicators, has been shown to improve outcomes and was discussed as a reason for the lowest HbA1c values in Nordic countries in comparison to other high-income countries.10 International benchmarking within SWEET strengthens the exchanges of knowledge between centers in order to identify transferable processes for improving diabetes care.15

BMI-SDS was highest in Australia/New Zealand (0.8 [0.5-1.2]) whereas lowest in Asia/Middle East/Africa (−0.1 [−0.3-0.0]). These results are in line with a previous comparison among individuals with T1D < 18 years of age from the DPV registry, T1DX and the Australasian Diabetes Data Network (ADDN).20 People with T1D were followed from the age of 8 to 17 years and children registered in ADDN showed higher BMI-SDS baseline values (median 1.0 [Q1-Q3: 0.3-1.6]) compared to the DPV 0.7 (0.2-1.3) as well as T1DX registry 0.8 (0.2-1.5). Diabetes management, nutrition and management of exercise were discussed as potential reasons for the variation in BMI-SDS.20 Moreover, availability of food and lifestyle factors might play an important role. Exchanging expertise between the regions in comparing diabetes education programmes on diabetes management and nutrition might identify factors associated with lower BMI-SDS.

Lowest number of SMBG per day was observed in Asia/Middle East/Africa (3.1 [2.5-3.7]) which also showed highest HbA1c values. Whereas highest SMBG was found in the European region (5.5 [5.0-5.9]). This is in line with previous studies showing an association between frequency of SMBG and an improvement in HbA1c.21,22 SMBG is essential for optimal diabetes care in children and adolescents and is also a key component of the intermediate level of diabetes care which is recommended for less-resourced countries. In a literature review Klatman and colleagues recommended the inclusion of SMBG supplies in national health insurance systems.7 Moreover, SMBG should be regarded as essential medicine and diabetes education of both health care professionals and patients should be strengthened.7

Use of insulin pumps was lowest in South America (4.2% [3.2-5.6]) and highest in North America (80.7% [79.8-81.6]) in the current analysis. Sherr et al12 compared insulin pump usage among high income countries German/Austrian DPV registry, the US T1DX and the English/Welsh National Pediatric Diabetes Audit (NPDA). Insulin pump use was more frequent in DPV and T1DX compared to NPDA. Moreover, insulin pumps were less frequently used in children and adolescent of ethnic minority.12 Although insulin pumps are covered by health insurances for a wide age range in high-income countries, technological literacy and readiness of patients and physicians might differ between and within countries. The included SWEET centers from North America are large clinics with a median of 580 patients per centers and might be more specialized in insulin pump usage compared to smaller facilities. As reported by Ogle and colleagues, access to innovative diabetes technology such as insulin pump therapy is available only at the highest, comprehensive level of care.4 This might explain the low proportion of insulin pump use that we have found for South America.

Moreover, in the present study the proportion of patients with at least one severe hypoglycaemic event was higher in Australia/New Zealand (2.3% [1.8-3.0]) and North America (2.0% [1.8-2.3]) compared to Europe, Asia/Middle East/Africa and South America. Diabetes education is an essential part in order to prevent events of severe hypoglycaemia.17 Therefore, the observed differences might reflect the intensity of diabetes education or usage of different types of insulin. Due to financial reasons, human insulin is preferred in the intermediate care level, while insulin analogues might be more frequent in well-resourced countries.4 However, as our results show self-reported episodes of severe hypoglycaemia, recall bias might also be an explanation. Underreporting is possible, especially in regions with limited access to SMBG supplies where blood glucose monitoring might not be available when symptoms of severe hypoglycaemia arise.4

Main reasons for the observed differences might be different health care systems and differences in the access and quality of diabetes care which were discussed as reasons also in high-income countries.10 Resource availability has been previously reported to differ by geographical regions,6,16 and this is clearly reflected in the present study by the wide differences in insulin pump use across the globe. Resources to achieve comprehensive diabetes care are usually covered by the national health system in high-income countries. However, diabetes care should be effectively delivered to all individuals in urban as well as rural areas and from different socioeconomic backgrounds.4 Ogle and colleagues4 emphasized that intermediate care with human insulin in a basal bolus regimen, SMBG, point-of-care HbA1c testing, diabetes education, basic complications screening, and access to experienced doctors and nurses are the key components and should be available also in less-resourced countries. The introduction of intermediate care was shown to be effective in the improvement of metabolic control and outcome. Moreover, benchmarking reports are an important method to improve quality of diabetes care on intermediate as well as comprehensive level.15 Regions with limited resources within the SWEET initiative might benefit from international comparisons and exchange of knowledge, which helps to identify processes and structures that can be transferred between the centers in order to find the best practice based on the locally available resources. A standardized documentation with high quality data is essential for comparing centers on an international level. The concept of benchmarking has been shown to increase the motivation to report data of high quality.15

One limitation of this analysis was that some regions are only represented by a small number of centers and therefore, the results are not representative for individuals with T1D of the respective country. Reporting is likely more thorough and nationally representative in
Europe, but less so in North America. This same applies to highly populated areas such as Asia and Africa. The five SWEET regions were defined based on the location and number of available centers, but it has to be considered that the regions are heterogeneous also with regard to cultural and socio-economic factors. Nevertheless, analyzing data of the SWEET data is a unique opportunity to compare diabetes care in children and adolescents on an international level.

The method of data collection and accuracy might differ between regions and events of severe hypoglycaemia might be underreported. However, this is one of the first analysis on worldwide differences in childhood diabetes using a large sample size of around 50,000 children and adolescents. These data should be used to identify tools and practices in order to help lower-resourced regions to reduce disparities in outcomes. Effective practices should be identified and disseminated among centers with similar resource availability regardless of geographical separation. Clinical documentation of structured data needs to be improved in order gain reliable insights. An international comparison between diabetes centers strengthens the exchange of knowledge and may identify transferable processes and structures for improving diabetes care in order to find the best practice based on locally available resources.

5 | CONCLUSION

Based on our analysis of the SWEET data including centers from five different regions, we found dramatic differences in diabetes care and outcome. The aim for high-quality care for every child remains a global challenge.

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CONFLICT OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

Mahira Saiyed contributed to data analysis, manuscript writing and editing; Dhruvi Hasnani contributed to interpretation of data, manuscript writing and editing; G. Todd Alonso, Erick Richmond, Stéphane Besançon, Cotterill Andrew, Ursula Ngwu, Carmen Mazza, and Diane Rottembourg contributed to interpretation of data, reviewed the manuscript and contributed to manuscript editing; Stefanie Lanzinger is the principal investigator of the study and contributed to data analysis, manuscript writing and editing. All co-authors approved the final version to be published. Stefanie Lanzinger is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

PEER REVIEW

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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