



Exploring Variation in Glycemic Control Across and Within Eight High-Income Countries: A Cross-sectional Analysis of 64,666 Children and Adolescents With Type 1 Diabetes

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OBJECTIVE

International studies on childhood type 1 diabetes (T1D) have focused on whole-country mean HbA_{1c} levels, thereby concealing potential variations within countries. We aimed to explore the variations in HbA_{1c} across and within eight high-income countries to best inform international benchmarking and policy recommendations.

RESEARCH DESIGN AND METHODS

Data were collected between 2013 and 2014 from 64,666 children with T1D who were <18 years of age across 528 centers in Germany, Austria, England, Wales, U.S., Sweden, Denmark, and Norway. We used fixed- and random-effects models adjusted for age, sex, diabetes duration, and minority status to describe differences between center means and to calculate the proportion of total variation in HbA_{1c} levels that is attributable to between-center differences (intraclass correlation [ICC]). We also explored the association between within-center variation and children's glycemic control.

RESULTS

Sweden had the lowest mean HbA_{1c} (59 mmol/mol [7.6%]) and together with Norway and Denmark showed the lowest between-center variations (ICC ≤4%). Germany and Austria had the next lowest mean HbA_{1c} (61–62 mmol/mol [7.7–7.8%]) but showed the largest center variations (ICC ~15%). Centers in England, Wales, and the U.S. showed low-to-moderate variation around high mean values. In pooled analysis, differences between counties remained significant after adjustment for children characteristics and center effects (*P* value <0.001). Across all countries, children attending centers with more variable glycemic results had higher HbA_{1c} levels (5.6 mmol/mol [0.5%] per 5 mmol/mol [0.5%] increase in center SD of HbA_{1c} values of all children attending a specific center).

CONCLUSIONS

At similar average levels of HbA_{1c}, countries display different levels of center variation. The distribution of glycemic achievement within countries should be considered in developing informed policies that drive quality improvement.

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For children with type 1 diabetes (T1D), achievement of optimal metabolic control, as measured by levels of glycated hemoglobin (HbA_{1c}), is important in reducing the risk of vascular complications in later life (1). Guidelines from national and international organizations set specific standards of care and recommend a target HbA_{1c} of <48–58 mmol/mol (6.5–7.5%) for most children with T1D (2–5). Despite the evidential and clinical consensus, many children with T1D in developed Western nations fail to achieve their target for glycemic control. Management of T1D requires ongoing patient education, access to appropriate treatment, and coordinated guidance from multidisciplinary teams, thus providing important insights into various elements of national health systems and their communication (6). Within-country studies have reported substantial differences in glycemic control across pediatric diabetes centers (7–9). Although some of these variations could be related to differences in patient case mix or preferences, some others may reflect differences in quality of, or access to, diabetes care. These unwarranted variations raise concerns about the equity of health care systems.

To date, analyses of between-center variations in childhood T1D outcomes typically have been conducted within individual countries, with existing international studies focusing on crude center comparisons (10) or on comparisons between selected centers that are not representative of their respective countries (11–13). Although this approach has provided national opportunities for improvement, it has been less informative about the performance of systems relative to other countries. At the same time, international comparisons of T1D have predominantly focused on whole-country mean or median HbA_{1c} levels (14,15). Such comparisons are inherently limited, because they may conceal within-country variations. This represents a missed opportunity for cross-country learning. Each child with

T1D should receive equal quality of care, regardless of the child's country of residence or the center coordinating the child's diabetes care within a specific country. Therefore, exactly how between-center variation in glycemic control differs across countries remains an important unanswered question. Similarly, variation within each center and country is of interest, because consistently good results are desired.

In the current study, we aimed to describe the extent of variation in glycemic control across and within eight high income countries, seven in Western Europe plus the U.S. Our specific objectives were as follows: to describe the variation in HbA_{1c} values across countries and between centers within countries; to explore what proportion of the total variation in children's glycemic control is attributable to differences between centers in each country; to examine cross-country differences in the association between within-center variation and children's metabolic control; and finally to examine whether differences in country mean that HbA_{1c} levels persist after adjusting for patient characteristics and center effects.

RESEARCH DESIGN AND METHODS

Study Design and Participants

Anonymized data from six large registries/audits of children with T1D were used, representing eight countries: Germany and Austria from the Prospective Diabetes Follow-up Registry (DPV) (16), England and Wales from the National Pediatric Diabetes Audit (NPDA) (17), U.S. from the T1D Exchange (T1DX) (18), Sweden from the Swedish Pediatric Diabetes Quality Registry (SWEDIABKIDS) (8), Denmark from the Danish National Diabetes Registry (DanDiabKids) (19), and Norway from the Norwegian Childhood Diabetes Registry (NCDR) (20). All data sources were population-based registries or audits covering >80% of the national population of children with T1D, except for T1DX, which was a clinic-based registry (Table 1). Participants were included in the analysis

if they had received a diagnosis of T1D at least 3 months before inclusion (since levels of HbA_{1c} during the first 3 months after diagnosis are not reflective of ongoing diabetes care delivered by the center), were <18 years of age, and had at least one HbA_{1c} measurement in 2013 (except for England and Wales, where data were collected between April 2013 and March 2014). We excluded children with missing information on risk adjusters and children who changed clinics during the study period. Finally, we excluded clinics with available data for <10 children for confidentiality reasons. The final sample consisted of 64,666 children with T1D across 528 centers (Supplementary Fig. 1). The study was approved by the individual registry/audits in each country with ethical approval to collect patient data.

Outcome and Risk Adjustment

Glycemic control was assessed by levels of HbA_{1c}. All registries reported HbA_{1c} in mmol/mol in accordance with the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) (21). Corresponding National Glycohemoglobin Standardization Program units (%) are given in parenthesis. The median HbA_{1c} value over the study period was used for each child; however, two countries provided only a single HbA_{1c} measurement for each child (first registered value during 2013 in Norway and the value closest to the child's birthday in Denmark).

To ensure a fair comparison between centers, we adjusted our analyses for four clinically important glycemic determinants that are outside the control of the clinic, including children's sex, age (<6 years, 6 to <12 years, and 12–18 years), duration of diabetes (<2 years, 2 to <5 years, and ≥5 years), and minority status (yes/no). We also allowed for the association between diabetes duration and HbA_{1c} to vary across age categories by including age-duration interaction terms. Minority status was defined using the patient's/parent's country of birth or the patient's ethnicity status (Table 1).

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Given the differences in the definition of minority status between countries, we repeated our analyses after excluding minority status from risk-adjusted models and observed any differences in center variations across countries.

Statistical Analysis

We first used country-specific, risk-adjusted, fixed-effects models to obtain estimates of mean HbA_{1c} levels for each center following established methodology (22). Estimates derived from these models are akin to comparing centers in each country as if they had the same composition of children in terms of age, sex, diabetes duration, and minority status. We visualized variation between adjusted center means in each country by constructing boxplots with the distance between the top and the bottom of the box representing the middle 50% of centers. Given the traditional emphasis of international comparisons on mean HbA_{1c} values, we presented center variations together with crude national mean values. To convey the absolute difference in glycemic control between centers with relatively low versus high HbA_{1c} value within each country, we calculated the difference in adjusted glycemic levels between centers in the highest and lowest decile of the distribution in each country (i.e., the middle 80% range).

In addition to describing differences between center means, we further used risk-adjusted models with a random effect for center to calculate the proportion of total variation in glycemic control attributable to differences between centers in each country:

$$\text{Intraclass correlation [ICC]} = \frac{\text{between-center variance}}{\text{total variance}}$$

(23). The ICC provides important information about how glycemic control is distributed across centers within a country and helps to determine the national scope for improvement that might be possible by reducing variation between centers (23). For example, large values of ICC suggest that children's glycemic outcomes are heterogeneously distributed across centers and interventions targeting low-performing centers are likely to capture most of the poorly controlled children in the country. By contrast, a low

ICC indicates that glycemic control is homogeneously achieved across centers and geographically targeted interventions aiming to only reduce variation between centers may have a limited influence on nationwide improvements. Therefore, this analysis could help a national health system or registry to target resources to most efficiently improve outcomes.

Additionally, we measured the variability in glycemic results within each center by calculating the SD of HbA_{1c} values of all children attending a specific center (HbA_{1c}-SD). The HbA_{1c}-SD reflects the average deviation of a child from its center mean and provides an indicator of how consistent the glycemic performance of the center is. We extended the above country-specific, risk-adjusted models with a random effect for center by introducing HbA_{1c}-SD as a center-level variable. Since center variability may be influenced by the number of children attending the center, we also adjusted all models for center volume. We extracted country-specific HbA_{1c}-SD regression coefficients and pooled them by random-effects meta-analysis.

Finally, we conducted a pooled analysis of glycemic data including children from all countries to explore whether differences in mean HbA_{1c} values between countries persist after removing center effects and differences in the risk profile of children across countries. In the pooled data set, we ran a risk-adjusted model with a random effect for center and introduced country as a fixed effect. Estimates of country means from the above model yield results similar to those from the comparison of countries as if they had the same composition of children and the same center characteristics. Hence, any differences can be fairly attributed to countries.

Parameters in random effects models were estimated using the maximum likelihood method. Model fit was examined by using the likelihood ratio test. The distribution of individual and center-level residuals was checked in all models and showed approximate normality. *P* values <0.05 were considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and Stata version 13 (StataCorp, College Station, TX).

RESULTS

Characteristics of children in each country are presented in Table 1. Children had a

similar sex and age profile across all eight countries. The mean duration of diabetes was lowest in Germany and Austria (4.6 years) and highest in the U.S. (5.7 years). Minority status varied considerably from 5% in Wales to >26% in Austria and England. Achievement of the International Society for Pediatric and Adolescent Diabetes (ISPAD) HbA_{1c} target of <58 mmol/mol (7.5%) ranged from 17% in Wales to 49% in Sweden. Characteristics of diabetes centers are presented in Supplementary Table 1.

Figure 1A shows how adjusted center mean HbA_{1c} levels vary around crude national mean values in each of the eight countries. Table 2 also shows the difference in mean HbA_{1c} levels achieved between centers in the highest and lowest deciles of the distribution of their country. National mean levels of HbA_{1c} showed a 1.2-fold variation across countries from 59 mmol/mol (7.6%) in Sweden to 72 mmol/mol (8.8%) in Wales. Sweden and Norway showed the lowest variation between centers; in both countries, the difference in risk-adjusted mean HbA_{1c} between centers in the lowest and highest deciles was 6–7 mmol/mol (0.6%). Germany and Austria had the second and third lowest mean HbA_{1c} values. However, they both showed the largest between-center variations, with centers in the highest decile having higher mean HbA_{1c} levels by >14 mmol/mol (1.3%) compared with centers in the lowest decile. Figure 1B shows the distribution of adjusted center means by registry/audit against the ISPAD glycemic target.

Table 2 shows the share of the total variation in HbA_{1c} that is attributable to differences between centers in each country after controlling for characteristics of the children. Adjusted ICC values in most countries were low, indicating that centers accounted for only a small proportion of the total variation in children's glycemic control. However, adjusted ICC values varied considerably across countries, ranging from ≤4% in Nordic countries to ~15% in Germany and Austria. The exclusion of minority status from risk adjustment only marginally affected center differences and ICCs except for the U.S., where the exclusion of minority status resulted in a substantial reduction in ICC from 7.9% to 6.6%.

We also looked at how the association between center HbA_{1c}-SD and children's glycemic outcomes varies across the eight

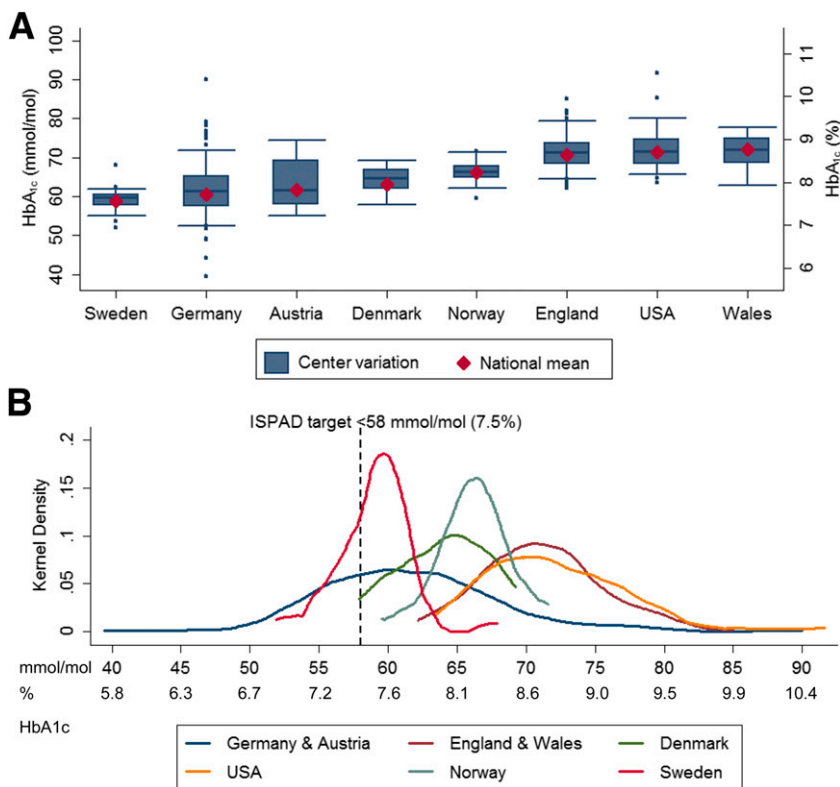


Figure 1—Between-center variation in HbA_{1c} across countries. Center means derived from linear fixed-effects regression models adjusted for patient characteristics (sex, age, duration of diabetes, and minority status). **A:** Boxplots showing center variation in adjusted mean HbA_{1c} across eight countries. The shaded box represents the interquartile range capturing the middle 50% of the centers. Whiskers extend to include centers within 1.5 times the interquartile range beyond the upper and lower quartiles; dots outside the whiskers represent outlying centers; crude national average HbA_{1c} values are represented by diamonds. **B:** Kernel-smoothed distribution of adjusted center HbA_{1c} means by registry/audit. The dashed vertical line represents the ISPAD glycemic target recommended for children with diabetes.

countries. Across all countries, children who attended centers with larger variation in their glycemic performance (i.e., higher center HbA_{1c}-SD values) had, on average,

higher HbA_{1c} values. Overall, there was a deterioration in glycemic control by 5.6 mmol/mol (0.5%) per 5 mmol/mol (0.5%) increase in center HbA_{1c}-SD values;

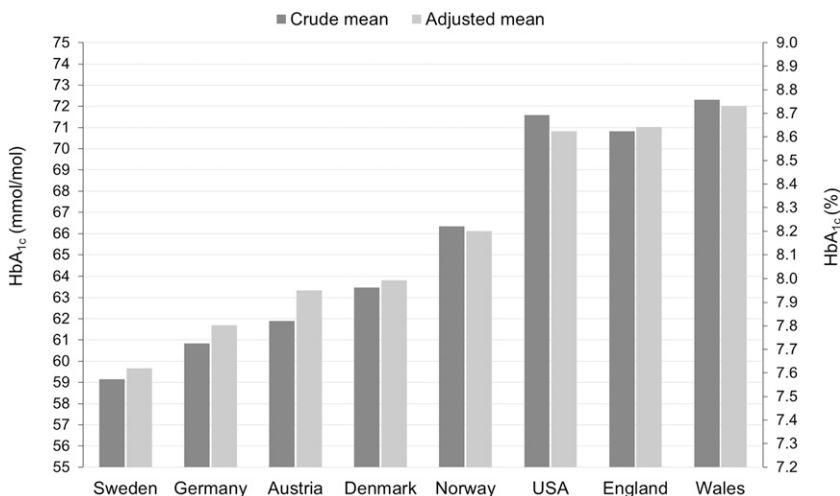


Figure 2—Country mean HbA_{1c} before and after adjustment for cross-country differences in the characteristics of children (age, sex, diabetes duration, and minority status) and center effects. Estimates of adjusted country means derived from a two-level model with a random effect for center including data from all eight countries.

however, this varied from 2.8 mmol/mol (0.3%) in Norway to 7.2 mmol/mol (0.7%) in Austria (Supplementary Fig. 2).

In the pooled analysis, differences between country mean HbA_{1c} values were slightly attenuated after controlling for cross-country differences in patient characteristics and center effects (Fig. 2). However, the addition of country to the risk-adjusted random-effects model showed that the country where a child received care was a significant determinant of glycemic control regardless of center and children characteristics (*P* value of likelihood ratio test <0.001).

CONCLUSIONS

We described variations in glycemic control between and within eight high-income countries using data from multicenter registries/audits for children with T1D. We found that the crude mean HbA_{1c} level varied by 1.2-fold across countries. However, in some countries the variations between centers was even larger than these cross-country differences. We also calculated the proportion of the total variation in HbA_{1c} which is attributable to differences between centers, and we found this to vary from ≤4% in Nordic countries to ~15% in Germany and Austria. Across all countries, children who attended centers with larger variability in their glycemic performance had poorer glycemic control. Finally, differences between country mean HbA_{1c} levels remained significant even after controlling for differences in patient and center characteristics.

We found that Sweden had the lowest mean HbA_{1c} value and together with the other Nordic countries demonstrated small center variations indicating that low levels of glycemic control are homogeneously achieved by most children regardless of the clinic they attend. In Nordic countries, the establishment of collaboration between quality registries has been a major effort in promoting performance improvement in pediatric diabetes (10). Sweden has been particularly successful in establishing a nationwide program of continuous quality improvement in pediatric diabetes care that includes transparent public reporting of center performance, systematic monitoring of variations, the use of performance data as a clinical tool for professional development, and active participation of centers in quality improvement “collaboratives.” This system-wide approach probably accounts,

Table 1—Participant characteristics and data sources by country

Country	Registry/audit	National coverage	HbA _{1c} completeness, %	N of children	Male, %	Age, years*	Diabetes duration, years*	Minority status		HbA _{1c} *		ISPAD target achievement, %
								Definition	%	mmol/mol	%	
Sweden	SWEDIABKIDS	~98%	~100	6,204	53	12.2 (4.0)	4.7 (3.7)	Patient born outside of Sweden	13	59 (13)	7.6 (1.2)	49
Germany	DPV	~95%	98	19,820	52	12.0 (3.9)	4.6 (3.6)	Patient or at least one parent born outside of Germany/Austria	20	61 (15)	7.7 (1.4)	46
Austria	DPV	~80%	99	1,571	55	11.9 (4.0)	4.6 (3.7)	Patient or at least one parent born outside of Germany/Austria	28	62 (16)	7.8 (1.4)	43
Denmark	DanDiabKIDS	~100%	91	1,877	51	12.7 (3.6)	5.1 (3.6)	Both parents born outside of Denmark	8	64 (16)	8.0 (1.5)	38
Norway	NCDR	>95%	96	2,315	52	12.7 (3.7)	5.2 (3.5)	Mother born outside of the Nordic countries	6	66 (14)	8.2 (1.3)	29
England	NPDA	>95%	95	20,751	52	12.4 (3.8)	4.7 (3.7)	Any nonwhite ethnicity	27	71 (18)	8.6 (1.6)	20
U.S.	T1DX	N/A	83	10,846	52	12.6 (3.5)	5.7 (3.5)	Other than non-Hispanic white ethnicity	22	72 (17)	8.7 (1.6)	18
Wales	NPDA	>95%	93	1,282	52	12.2 (3.7)	4.7 (3.6)	Any nonwhite ethnicity	5	72 (18)	8.8 (1.6)	17

ISPAD HbA_{1c} target of <58 mmol/mol (7.5%), HbA_{1c} completeness is defined as the proportion of eligible children in each country having a recorded HbA_{1c} measurement during the study period. *Data are shown as the mean (SD).

at least in part, for the improved glycemic outcomes in Sweden (24).

Another important finding was that a lower national average glycemic control does not necessarily reflect homogenous distribution within a country. For example, large center variations were observed in Germany and Austria, countries with average HbA_{1c} levels that are comparable to those of Sweden. In those countries, ~15% of the total variation in HbA_{1c} levels was located at the level of the center, which suggests that targeted interventions aiming to reduce center variability could have an appreciable impact on glycemic outcomes. Such large variations may be partly related to the structure of diabetes care. Unlike the U.K. and Nordic countries, where diabetes care is predominantly provided by hospital-based clinics normally treating children in their catchment areas, in Germany and Austria patients are free to choose their providers by a blend of hospital-based and private practices. This open competition might result in centers exhibiting variations in their discretionary policies. However, the magnitude of center variation is unlikely to be solely explained by uncaptured differences in patient mix or preferences.

In Germany and Austria, nationwide benchmarking has been provided to participating pediatric diabetes teams since 1995 in anonymized form. Analyses reporting quality indicators with each center openly identified have been available since 2000 for regional quality circles and since 2016 for all pediatric diabetes institutions in both countries. However, deanonimized reports are not openly available to the public (16). Benchmarking schemes were absent in the U.S. registry, where moderate center variations were observed. Public reporting of performance indicators in pediatric diabetes care has long been used as a core component of the accountability for quality improvement in Nordic countries and since 2012 in England and Wales. Evidence from other medical specialties shows that public disclosure of provider performance measures is linked to improved performance and has limited impact on patient movements (25). However, a climate of mutual trust needs to be created between clinicians and other stakeholders when implementing such policies to avoid defensive behaviors potentially leading to the discontinuing of information sharing.

Policies aiming to narrow center variation in pediatric diabetes care should

Table 2—Absolute and relative measures of center variation in HbA_{1c} by country after adjustment for patient characteristics

	Sweden	Germany	Austria	Denmark	Norway	England	U.S.	Wales
HbA _{1c} difference between centers in the highest and lowest decile, mmol/mol (%)*	6.0 (0.6)	14.5 (1.3)	15.7 (1.4)	9.8 (0.9)	6.6 (0.6)	11.0 (1.1)	12.8 (1.2)	12.3 (1.1)
Proportion of total variance in HbA _{1c} attributable to differences between centers (ICC)†	4.0%	16.8%	13.9%	4.0%	1.8%	5.5%	7.9%	4.7%

All analyses conducted separately in each country and were adjusted for patient characteristics with regard to individual sex, age, duration of diabetes, and minority status. *Fixed-effects models. †Models with a random effect for center.

be prioritized, yet such policies might not be sufficient to address cases where all centers in a nation are performing sub-optimally. This might be the case in countries with high average HbA_{1c} levels and low-to-moderate ICC values such as England, Wales, and the U.S. Some of the best clinics in those countries performed poorly when compared even with Swedish centers at the higher end of the distribution. This implies that quality improvement in those countries might best be achieved not only by targeting poor performers, but also by “shifting the curve” of overall pediatric diabetes practice toward higher quality levels. The recent changes toward tighter HbA_{1c} targets for all children of <48 mmol/mol (6.5%) in the U.K. (2) and <58 mmol/mol (7.5%) in the U.S. (3) could help to achieve this goal. International experience has also shown that patient-centered policies might be effective in stimulating whole-system improvements (26). For example, the introduction of patient-reported experience measures for pediatric diabetes care in England and Wales in 2013 is considered an important step in informing local decision-making (27).

In all countries, children who attended centers with more variable glycemic results had, on average, higher HbA_{1c} levels. This finding may reflect a range of factors related to goal setting, team cohesiveness, and organizational culture. Previous reports from the Hvidøre Study Group on Childhood Diabetes (28) demonstrated improved glycemic performance in centers where the team set consistent HbA_{1c} targets. Achievement of higher consistency within a center also requires focusing attention on the management of challenging populations of children who are more likely to exhibit greater variability in their metabolic control (e.g., adolescents). Taken together, our findings suggest that, in addition to helping a higher percentage of their patients achieve target glycemic control, centers should also aim for lower variability in their glycemic performance.

We also found significant differences between countries’ glycemic levels over and above the characteristics of children and center differences. Several aspects of pediatric diabetes care could contribute to these differences, including the use of insulin pumps, patient education, lifestyle factors, the training of health care professionals, the impact of low socioeconomic status, and reimbursement schemes. However, the link with glycemic outcomes is not straightforward. For example, a previous study (29) showed that although pump use in children with T1D was much lower in England and Wales (14%) compared with Germany, Austria (41%), and the US (47%), country differences in glycemic control could not be adequately explained by differences in insulin delivery method. The results may have also been influenced by national HbA_{1c} target levels. At the time of the study, these were ≤58 mmol/mol (7.5%) in Germany, Norway, England, and Wales; 52 mmol/mol (6.9%) in Sweden; 53 mmol/mol (7.0%) in Austria; 55 mmol/mol (7.2%) in Denmark; 69 mmol/mol (8.5%) for children <6 years of age; 64 mmol/mol (8.0%) for children 6–12 years of age; and 58 mmol/mol (7.5%) for children ≥13 years of age in the US. However, in our figures we presented the ISPAD HbA_{1c} target of <58 mmol/mol (7.5%), which has been adopted by most countries in order to put country data in context by providing an internationally agreed upon target.

Our study should be interpreted within the context of its limitations. First, risk adjustment was restricted to the availability of comparable data. It is possible that unaccounted factors such as comorbidities and socioeconomic status might systematically vary between centers and therefore explain some of the observed variations. Second, in line with previous studies (14,29), we used the median HbA_{1c} measurement for each child to avoid the effects that outliers can have on the mean. However, this approach may not accurately represent glycemic exposure over

the observation period. Third, although all registries reported IFCC-aligned HbA_{1c} values, it is likely that differences in laboratory methods across countries might have contributed to the observed variations. Fourth, we excluded centers with <10 children, which might have underestimated center variations in countries with many small practices (i.e., Germany). Fifth, differences in the definition of minority status across countries might have affected our comparisons. However, the exclusion of minority status from risk adjustment only minimally affected our results in most countries. In the U.S., larger center differences were masked by failing to adjust for minority status; such a result could occur, for example, when poorly performing centers have fewer minority children who tend to have poorer outcomes than non-Hispanic whites (30). Moreover, data from the U.S. were based on a selective group of diabetes clinics and might not be directly comparable with data from the European population-based registries. Finally, our analysis was a snapshot comparison of glycemic levels; a more dynamic comparison would be needed to address the link between quality improvement initiatives and glycemic performance.

In summary, our findings from this large international study showed considerable differences in mean HbA_{1c} levels between and within countries. At similar average levels of glycemic control, countries displayed very different levels of center variation. This suggests that whole-country mean HbA_{1c} levels are an inadequate summary of the glycemic performance of a country. The distribution of glycemic achievement across centers within countries should be considered, alongside national mean values, in developing informed policies that drive quality improvement.

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