Exploring variation in glycaemic control across and within eight high-income countries: A cross-sectional analysis of 64,666 children and adolescents with type 1 diabetes.

Short title: Exploring variation in glycaemic control across and within eight high-income countries

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Abstract

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 variation 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 2013/14 from 64,666 children with T1D <18 years across 528 centres in Germany, Austria, England, Wales, USA, Sweden, Denmark, and Norway. We used fixed and random effect models adjusted for age, gender, diabetes duration, and minority status to describe differences between centre means and calculate the proportion of total variation in HbA_{1c} that is attributable to between-centre differences (Intra-Class Correlation-ICC). We also explored the association between within-centre variation and children's glycaemic control.

Results: Sweden had the lowest mean HbA_{1c} (59mmol/mol; 7.6%) and together with Norway and Denmark showed the lowest between-centre variations (ICC≤4%). Germany and Austria had the next lowest mean HbA_{1c} (61-62mmol/mol;7.7-7.8%) but showed the largest centre variations (ICC~15%). Centres in England, Wales, and the USA showed low-to-moderate variation around high mean values. In pooled analysis, differences between counties remained significant after adjustment for children characteristics and centre effects (p-value<0.001). Across all countries, children attending centres with more variable glycaemic results had higher HbA_{1c} (5.6 mmol/mol [0.5%] per 5 mmol/mol [0.5 %] increase in centre HbA_{1c}-standard deviation).

Conclusion: At similar average levels of HbA_{1c}, countries display different levels of centre variation. Distribution of glycaemic achievement within countries should be considered in developing informed policies that drive quality improvement.

Introduction

For children with type 1 Diabetes (T1D), achievement of optimal metabolic control, as measured by levels of glycated haemoglobin (HbA_{1c}), is important in reducing the risk of vascular complications in later life (1). Guidelines from national and international organisations set specific standards of care and recommend a target HbA_{1c} of less than 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 target glycaemic 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 glycaemic control across paediatric diabetes centres (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-centre variation in childhood T1D outcomes have been typically conducted within individual countries, with existing international studies focusing on crude centre comparisons (10) or on comparisons between selected centres 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 systems' performance relative to other countries. At the same time, international comparisons on T1D have predominantly focused on whole country mean or median HbA_{1c} levels (14; 15). Such comparisons are inherently limited, as 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 centre coordinating the child's diabetes care within a specific country. Therefore, exactly how between-centre variation in glycaemic control differs across countries remains an important unanswered question. Similarly, variation within each centre and country is of interest, as consistently good results are desired.

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

Methods

Study design and participants

Anonymised data from six large registries/audits on 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 Paediatric Diabetes Audit (NPDA) (17), USA 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 (see Table 1). Participants were included in the analysis if they were diagnosed with T1D for at least 3 months (since levels of HbA_{1c} during the first 3 months post diagnosis are not reflective of ongoing diabetes care delivered by the centre), were aged <18 years, and they 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 adjustors and children who changed clinic during the study period. Finally, we excluded clinics with available data for less than 10 children for confidentiality reasons. The final sample consisted of 64,666 children with T1D across 528 centres (see supplemental Figure S1). The study was approved by the individual registry/audits in each country with ethical approval to collect patient data.

Outcome and risk adjustment

Glycaemic 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 (IFCC) (21). Corresponding NGSP units (%) are given in parenthesis. The median HbA_{1c} value over the study period was used for each child; however, two countries only provided a single HbA_{1c} measurement for each child (first registered value during 2013 in Norway and value closest to child's birthday in Denmark).

To ensure a fair comparison between centres we adjusted our analyses for four clinically important glycaemic determinants that are outside the control of the clinic; these included children's gender, age (<6 years, 6 to <12 years, and 12 to 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 patient/parent's country of birth or patient's ethnicity status (Table 1). 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 centre variations across countries.

Statistical analysis

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

In addition to describing differences between centre means, we further used risk-adjusted models with a random effect for centre to calculate the proportion of total variation in glycaemic control attributable to differences between centres in each country (Intra-Class Correlation -ICC= $\frac{between\ centre\ variance}{total\ variance}$)(23). ICC provides important information about how glycaemic control is distributed across centres within a country and helps determine the national scope for improvement that might be possible by reducing variation between centres

(23). For example, large values of ICC suggest that children's glycaemic outcomes are heterogeneously distributed across centres and interventions targeting low performing centres are likely to capture most of the poorly controlled children in the country. By contrast, a low ICC indicates that glycaemic control is homogeneously achieved across centres and geographically targeted interventions aiming to only reduce variation between centres 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 variability in glycaemic results within each centre by calculating the standard deviation of HbA_{1c} values of all children attending a specific centre (HbA_{1c}-SD). The HbA_{1c}-SD reflects the average deviation of a child from its centre mean and provides an indicator of how consistent the glycaemic performance of the centre is. We extended the above country-specific, risk-adjusted models with a random effect for centre by introducing HbA_{1c}-SD as a centre-level variable. Since centre variability may be influenced by the number of children attending the centre, we also adjusted all models for centre 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 glycaemic data including children from all countries to explore whether differences in mean HbA_{1c} between countries persist after removing centre effects and differences in the risk profile of children across countries. In the pooled dataset, we ran a risk-adjusted model with a random effect for centre and introduced country as a fixed effect. Estimates of country means from the above model are similar to comparing countries as if they had the same composition of children and the same centre 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 (LRT). Distribution of individual and centre-level residuals were checked in all models and showed approximate normality. P-values <.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 gender and age profile across all eight countries. Mean duration of diabetes was lowest in Germany and Austria (4.6 years) and highest in the USA (5.7 years). Minority status varied considerably from 5% in Wales to >26% in Austria and England. Achievement of the International Society of 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 centres are presented in Supplemental Table S1.

Figure 1A shows how adjusted centre 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 centres in the highest and lowest decile of their country's distribution. 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 centres; in both countries, the difference in risk-adjusted mean HbA_{1c} between centres in the lowest and highest decile 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-centre variations with centres in the highest decile having higher mean HbA_{1c} levels by more than 14 mmol/mol (1.3%) as compared to centres in the lowest decile. Figure

1B shows the distribution of adjusted centre means by registry/audit against the ISPAD glycaemic target.

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

We also looked at the association between centre HbA_{1c}-SD and children's glycaemic outcomes varies across the eight countries. Across all countries, children who attended centres with larger variation in their glycaemic performance (i.e. higher centre HbA_{1c}-SD) had, on average, higher HbA_{1c}. Overall, there was a deterioration in glycaemic control by 5.6 mmol/mol; (0.5%) per 5 mmol/mol (0.5%) increase in centre HbA_{1c}-SD, however this varied from 2.8 mmol/mol (0.3%) in Norway to 7.2 mmol/mol (0.7%) in Austria (see supplemental figure S2).

In the pooled analysis, differences between country mean HbA_{1c} values were slightly attenuated after controlling for cross-country differences in patient characteristics and centre effects (see Figure 2). However, addition of country in the risk-adjusted random effects model showed that the country where a child received care was a significant determinant of glycaemic control regardless of centre and children characteristics (p value of LRT<0.001).

Discussion

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

We found that Sweden had the lowest mean HbA_{1c} and together with the other Nordic countries demonstrated small centre variations indicating that low levels of glycaemic 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 paediatric diabetes (10). Sweden has been particularly successful in establishing a nationwide program of continuous quality improvement in paediatric diabetes care which includes transparent public reporting of centre performance, systematic monitoring of variations, use of performance data as a clinical tool for professional development, and active participation of centres in Quality Improvement "Collaboratives". This system-wide approach probably accounts, at least in part, for the improved glycaemic outcomes in Sweden (24) .

Another important finding was that a lower national average glycaemic control does not necessarily reflect homogenous distribution within a country. For example, large centre variations were observed in Germany and Austria, countries with average HbA_{1c} levels comparable to those of Sweden. In those countries, around 15% of the total variation in HbA_{1c} was located at the level of the centre which suggests that targeted interventions aiming to reduce centre variability could have an appreciable impact on glycaemic outcomes. Such large variations may be partly related to the structure of diabetes care. Unlike the UK 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 centres exhibiting variations in their discretionary policies. However, the magnitude of centre 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 are available since 2000 for regional quality circles and since 2016 for all pediatric diabetes institutions in both countries. However, de-anonymized reports are not openly available to the public (16). Benchmarking schemes were absent in the USA registry, where moderate centre variations were observed. Public reporting of performance indicators in paediatric 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 discontinuing of information sharing.

Policies aiming to narrow centre variation in paediatric diabetes care should be prioritised, yet such policies might not be sufficient to address cases where all centres in a nation are performing sub-optimally. This might be the case in countries with high average HbA_{1c} levels and low-to-moderate ICCs such as England, Wales, and the USA. Some of the best clinics in those countries performed poorly when compared even with Swedish centres 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 paediatric diabetes practice towards higher quality levels. The recent changes towards tighter HbA_{1c} targets for all children of <48 mmol/mol (6.5%) in the UK (2) and <58 mmol/mol (7.5%) in the USA (3) could help towards achieving 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 (PREM) for paediatric 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 centres with more variable glycaemic results had, on average, higher HbA_{1c}. This finding may reflect a range of factors related to goal setting, team cohesiveness and organizational culture. Previous reports from the Hvidore study group demonstrated improved glycaemic performance in centres where the team set consistent HbA_{1c} targets (28). Achievement of higher consistency within a centre also requires focusing attention on 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, centres should also aim for lower variability in their glycaemic performance.

We also found significant differences between countries' glycaemic levels over and above children characteristics and centre differences. Several aspects of paediatric diabetes care could contribute to these differences, including use of insulin pumps, patient education, lifestyle factors, training of healthcare professionals, impact of low socioeconomic status, and reimbursement schemes. However, the link with glycaemic outcomes is not straightforward. For example, a previous study showed that although pump use in children with T1D was much lower in England and Wales (14%) as compared to Germany, Austria (41%), and the USA (47%), country differences in glycaemic control could not be adequately explained by differences in insulin delivery method (29). The results may have also been influenced by national HbA_{1c} target levels. At the time of the study these were equal to or below 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 under 6 years of age, 64 mmol/mol (8.0%) for children 6-12 years old, and 58 mmol/mol (7.5%) for children ≥13 years of age in the USA. 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 target.

Our study should be interpreted within the context of its limitations. First, risk adjustment was restricted to availability of comparable data. It is possible that unaccounted factors such as co-morbidities and socioeconomic status might systematically vary between centres 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 glycaemic 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 centres with less than 10 children which might have underestimated centre 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, exclusion of minority status from risk adjustment only minimally affected our results in most countries. In the USA, larger centre differences were masked by failing to adjust for minority status; such a result could occur, for example, when poorly performing centres have fewer minority children who tend to have poorer outcomes than non-Hispanic whites (30). Moreover, data from the USA were based on a selective group of diabetes clinics and might not be directly comparable with that of the European population-based registries. Finally, our analysis was a snapshot comparison of glycaemic levels; a more dynamic comparison would be needed to address the link between quality improvement initiatives and glycaemic performance.

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

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JMH 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.

Authors contribution

RH, RWH, TS had the general supervision of the study. RH, DC, RWH, JMH, KA, LH, AMS, TS, AKD, JTW, DMM contributed to study conception. RH, DC, RWH, JMH, KA, LH, AMS, JS, AJ, NHB, SF, TS, AKD, JTW, TS, DMM were involved in the design of the study. DC conducted the literature search, contributed to statistical analyses, and wrote the first draft of the manuscript. JMH performed the statistical analyses. JMH, AMS, AJ, TS, AKD, SJK were responsible for data cleaning and management. RH, RWH, SHE, BRM, KA, LH, AMS, JS, AJ, NHB, SF, TS, KDJ, AKD, SJK, JTW, DMM, KMM, MC, NF contributed to data acquisition. All authors provided substantial contributions to data interpretation, critically reviewed and commented on several drafts of the paper.

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Declaration of interests

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Ethics

The study was approved by all individual registry/audits in each country who have ethical approval to collect patient data.

Figure legends

Figure 1. Between-centre variation in HbA_{1c} across countries. Centre means derived from linear fixed effect regression models adjusted for patient characteristics (gender, age, duration of diabetes, and minority status).

(A) Boxplots showing centre variation in adjusted mean HbA_{1c} across eight countries. The shaded box represents the interquartile range (IQR) capturing the middle 50% of the centres. Whiskers extend to include centres within 1.5 times the IQR beyond the upper and lower quartile; dots outside the whiskers represent outlying centres; crude national average HbA_{1c} values are represented by diamonds.
(B) Kernel-smoothed distribution of adjusted centre HbA_{1c} means by registry/audit. The dashed vertical line represents the International Society of Pediatric and Adolescent Diabetes (ISPAD) glycaemic target recommended for children with diabetes.

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

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Country	Registry/Audit	National coverage	HbA_{1c} completeness, %	No 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 non-white ethnicity	27	71 (18)	8.6 (1.6)	20
USA	T1D Exchange	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 non-white ethnicity	5	72 (18)	8.8 (1.6)	17

* Data shown as mean (standard deviation). International Society of Pediatric and Adolescent Diabetes (ISPAD) HbA_{1c} target of <58 mmol/mol (7.5%).
DPV: Prospective Diabetes Follow-up Registry, DanDiabKids: Danish National Diabetes Registry, NPDA: National Paediatric Diabetes Audit, NCDR: Norwegian Childhood Diabetes Registry, SWEDIABKIDS: Swedish Pediatric Diabetes Quality Registry. HbA_{1c} completeness defined as proportion of eligible children in each country having a recorded HbA_{1c} measurement during the study period.

Table 1. Participant characteristics and data sources by country

	Sweden	Germany	Austria	Denmark	Norway	England	USA	Wales
HbA_{1c} difference between centres 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 centres (Intra-Class Correlation) †	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 gender, age, duration of diabetes and minority status.
* fixed effect models
† models with a random effect for centre

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