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Regional variations in definitions and rates of hypoglycaemia: findings from the global HAT observational study of 27 585 people with Type 1 and insulin-treated Type 2 diabetes mellitus

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Abstract

Aim To determine participant knowledge and reporting of hypoglycaemia in the non-interventional Hypoglycaemia Assessment Tool (HAT) study.

Methods HAT was conducted in 24 countries over a 6-month retrospective/4-week prospective period in 27 585 adults with Type 1 or insulin-treated Type 2 diabetes mellitus. Participants recorded whether hypoglycaemia was based on blood glucose levels, symptoms or both.

Results Hypoglycaemia rates were consistently higher in the prospective compared with the retrospective period. Most respondents (96.8% Type 1 diabetes; 85.6% Type 2 diabetes) knew the American Diabetes Association/European Association for the Study of Diabetes hypoglycaemia definition, but there were regional differences in the use of blood glucose measurements and/or symptoms to define events. Confirmed symptomatic hypoglycaemia rates were highest in Northern Europe/Canada for Type 1 diabetes (63.9 events/year) and in Eastern Europe for Type 2 diabetes (19.4 events/year), and lowest in South East Asia (Type 1 diabetes: 6.0 events/year; Type 2 diabetes: 3.2 events/year). Unconfirmed symptomatic hypoglycaemia rates were highest in Eastern Europe for Type 1 diabetes (5.6 events/year) and South East Asia for Type 2 diabetes (4.7 events/year), and lowest for both in Russia (Type 1 diabetes: 2.1 events/year; Type 2 diabetes: 0.4 events/year). Participants in Latin America reported the highest rates of severe hypoglycaemia (Type 1 diabetes: 10.8 events/year; Type 2 diabetes 3.7 events/year) and severe hypoglycaemia requiring hospitalization (Type 1 diabetes: 0.56 events/year; Type 2 diabetes: 0.44 events/year). The lowest rates of severe hypoglycaemia were reported in South East Asia (Type 1 diabetes: 2.0 events/year) and Northern Europe/Canada (Type 2 diabetes: 1.3 events/year), and the lowest rates of severe hypoglycaemia requiring hospitalization were in Russia (Type 1 diabetes: 0.15 events/year; Type 2 diabetes: 0.09 events/year). The blood glucose cut-off used to define hypoglycaemia varied between regions (Type 1 diabetes: 3.1–3.6 mmol/l; Type 2 diabetes: 3.5–3.8 mmol/l).

Conclusions Under-reporting of hypoglycaemia rates in retrospective recall and regional variations in participant definitions of hypoglycaemia may contribute to the global differences in reported rates. Discrepancies between participant definitions and guidelines may highlight a need to redefine hypoglycaemia criteria. (Clinical Trials Registry No: NCT01696266).

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Introduction

Insulin therapy, the most effective treatment for lowering blood glucose [1], comes with the attendant risk of hypoglycaemia, which may prevent people with diabetes from achieving glycaemic control [2,3]. Position statements from the American Diabetes Association (ADA) and European

What's new?

- This analysis of data from the Hypoglycaemia Assessment Tool (HAT), a prospective study on hypoglycaemia in 27 585 adults with Type 1 and Type 2 diabetes mellitus across 24 countries, investigated hypoglycaemia frequency and definitions in a large population that included countries/regions with little or no other hypoglycaemia data.
- Hypoglycaemia rates were consistently higher in the prospective vs. retrospective period across regions and definitions of hypoglycaemia varied between regions.
- Under-reporting and variations in the definitions of hypoglycaemia may result in global differences in reported rates.

Association for the Study of Diabetes (EASD) recommend a patient-centred approach with individualized glycaemic targets to minimize hypoglycaemia [4,5].

Despite the potentially serious consequences, it remains unclear how people with diabetes understand and define hypoglycaemia [6]. Hypoglycaemia definitions, including symptomatic vs. blood glucose measured and the use of different blood glucose cut-off points, vary in different studies, regions and guidelines [7–9]. For example, the ADA and American Academy of Clinical Endocrinologists consider blood glucose values $\leq$ 3.9 mmol/l as hypoglycaemia [5,8]; the International Hypoglycaemia Study Group and ADA/EASD recommend reporting all events with blood glucose < 3.0 mmol/l [10]; the Canadian Diabetes Association use a cut-off of 4 mmol/l [7]; whereas a cut-off of 3.5 mmol/l has been used to define clinically meaningful hypoglycaemia [6]. The use of different hypoglycaemia definitions has a major effect on reported hypoglycaemia incidence [10–12].

The Hypoglycaemia Assessment Tool (HAT) study examined the incidence and impact of hypoglycaemia in a large, insulin-treated global population with Type 1 or Type 2 diabetes mellitus in developed and developing countries. The epidemiological observational study covered a 6-month retrospective and 4-week prospective period. Baseline characteristics and overall hypoglycaemia rates from the prospective period, published previously, showed that rates were high compared with previous studies and that there were large differences between regions [13].

Our aim, in this post-hoc analysis, was to determine participants' knowledge, definitions and reporting of hypoglycaemia in the HAT study population, and to compare data from retrospective and prospective study periods, and from different geographic regions of the global study population.

Materials and methods

Study design and participants

Participant selection and study design have been reported in the primary article [13]. Briefly, consecutive participants were enrolled during routine clinical consultation if they had Type 1 or Type 2 diabetes and were treated with insulin for > 12 months, were $\geq$ 18 years of age at baseline and provided informed consent.

HAT was a non-interventional, multicentre, 6-month retrospective/4-week prospective investigation of hypoglycaemic events [13] (Appendix S1; Fig. S1), conducted during 2012–2013 at 2004 sites in 24 countries across six regions (Eastern Europe: Bulgaria, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovakia and Slovenia; Latin America: Argentina and Mexico; Middle East: Israel, Lebanon and Saudi Arabia; Northern Europe/Canada: Austria, Canada, Denmark, Finland, Germany, The Netherlands and Sweden; Russia: Russian Federation; South East Asia: India and Malaysia). The study was registered at clinicaltrials.gov (NCT01696266), conducted in accordance with the Declaration of Helsinki 2004 [14] and ICH Good Clinical Practice [15], and approved by country-specific regulatory agencies. All study materials were translated into local languages using independent forward and back-translation to secure comparability, and data obtained were translated back into English for analysis. Participants were excluded from the study because of non-ambulatory status and illiteracy, or other issues resulting in an inability to complete a written questionnaire. No incentives were provided to study participants.

Assessments

HAT was conducted using a two-part self-assessment questionnaire (part 1: baseline data and history of any hypoglycaemia over the previous 4 weeks, or 6 months for severe hypoglycaemia; part 2: hypoglycaemia during the 4-week prospective period) and participant diaries over the 4-week prospective study period (Appendix S1). For all but severe hypoglycaemia, retrospective rates were based on the 4 weeks pre-baseline and prospective rates on the 4 weeks post baseline. For severe hypoglycaemia, retrospective rates were based on the 6 months pre-baseline and prospective rates on the 4 weeks post baseline.

In the part 1 questionnaire, participants were asked at what blood glucose level they considered a hypoglycaemic event to have occurred. For the prospective period (part 2), a participant diary was used to record whether hypoglycaemia was based on blood glucose levels, symptoms of hypoglycaemia or both. Blood glucose was self-measured and self-reported by participants.

Confirmed hypoglycaemia definition

Hypoglycaemia categories recorded in the questionnaire included non-severe hypoglycaemia (a hypoglycaemic event

as judged by the participant and managed by the participant alone), severe hypoglycaemia [defined as (a) requiring third-party assistance, based on the ADA definition [16], or (b) leading to hospital admission] and nocturnal hypoglycaemia (any event occurring between midnight and 06:00 h). A combined measure of any hypoglycaemia, based on the sum of all individual hypoglycaemic events of any category, was calculated based on diary and questionnaire entries. Confirmed hypoglycaemia was defined as a blood glucose recording < 3.9 mmol/l in the participant diary.

Hypoglycaemia awareness

The degree of hypoglycaemia awareness was indicated by responses to the question 'Do you have symptoms when you have a low sugar level?', where 'Always' denotes normal, 'Usually' denotes impaired, and 'Occasionally' and 'Never' denote severely impaired awareness [17].

Statistical analysis

Hypoglycaemia rates are reported in episodes per year, with 95% confidence intervals (CIs). Differences in the estimated rates between the prospective and retrospective periods were calculated using a negative binomial regression model, adjusted for country and including a single binary covariate for period (4 weeks pre-baseline, 4 weeks post baseline), specifying a log-transformed exposure time offset term and using robust standard errors to adjust for repeated measurements on individuals and the potential dependence between participants sharing the same site (site-level clustering).

Blood glucose measurements, for the blood sugar levels that participants consider to be a hypoglycaemic event overall, and by which participants provided values consistent with standard definitions (≤ 3.9 mmol/l), were summarized descriptively.

Results

Study population

Overall, 85% of those invited to participate in the HAT study accepted the invitation, with 27 585 people participating and completing the part 1 questionnaire (Type 1 diabetes: 8022; Type 2 diabetes: 19 563). The part 2 questionnaire and participant diary were completed by 92.5% and 85.7% of participants, respectively. The baseline characteristics of the study population have been reported previously [13] and are summarized in the online Supporting Information (Appendix S1; Tables S1 and S2).

Hypoglycaemia rates: retrospective vs prospective periods

Higher estimated overall (any) hypoglycaemia rates were reported prospectively vs. retrospectively for the overall study population and in all regions for both Type 1 and Type 2 diabetes, except for Type 1 diabetes in South East Asia and Type 2 diabetes in the Middle East. The greatest increase in any hypoglycaemia incidence reported for the retrospective vs. prospective periods was in Latin America for both Type 1 and Type 2 diabetes.

Retrospectively, 83.4% of people with Type 1 diabetes and 50.8% with Type 2 diabetes reported a hypoglycaemic event. The estimated global annual rate of any hypoglycaemia was 51.5 (95% CI 50.9–52.1) episodes for people with Type 1 diabetes and 16.5 (95% CI 16.3–16.7) episodes for Type 2 diabetes (Table 1). Prospectively, the percentages of participants experiencing hypoglycaemic events were similar to those reported retrospectively: 83.0% with Type 1 diabetes and 46.5% with Type 2 diabetes. However, the estimated global annual rates of any hypoglycaemia in the prospective period were significantly higher than in the retrospective period for Type 1 diabetes [rate ratio (RR) prospective/retrospective: 1.47, 95% CI 1.41–1.53; $P < 0.001$) and Type 2 diabetes (RR prospective/retrospective: 1.20, 95% CI 1.15–1.24; $P < 0.001$).

Reported rates of severe hypoglycaemia were consistently higher for the prospective vs. the retrospective period (Table 1). Overall, in Type 1 diabetes, there was no significant difference in the prospective/retrospective rates (RR: 1.13, 95% CI 0.99–1.22), but in Type 2 diabetes the rate was significantly lower retrospectively (RR: 1.19, 95% CI 1.07–1.32; $P < 0.001$). The greatest increase in severe hypoglycaemia incidence reported for the prospective vs. retrospective period was in Latin America for both Type 1 and Type 2 diabetes.

During the 6-month retrospective period, 381 (4.8%) people with Type 1 diabetes and 673 (3.5%) with Type 2 diabetes experienced severe hypoglycaemia requiring hospital admission. In comparison, during the 4-week prospective period, 116 (1.7%) people with Type 1 diabetes and 265 (1.5%) people with Type 2 diabetes experienced severe hypoglycaemia requiring hospital admission. The rates of severe hypoglycaemia requiring hospitalization were higher in the prospective vs. retrospective period for Type 1 and Type 2 diabetes for the overall population and across regions (Table 1).

Hypoglycaemia rates: regional differences in the prospective period

For the prospective period, the highest rates of any hypoglycaemia for Type 1 diabetes were reported in Northern Europe/Canada and Latin America, and the lowest were in South East Asia; the rates for Type 2 diabetes were highest in Russia and lowest in South East Asia (Table 1) [13].

In the prospective period, the regions with the highest confirmed symptomatic hypoglycaemia rates were Northern Europe/Canada and Eastern Europe for Type 1 and Type 2 diabetes, respectively (Table 1). The lowest rate of confirmed

Table 1 Rates of hypoglycaemia (any, confirmed symptomatic, unconfirmed symptomatic and severe) by region

Region	Global		Northern Europe/Canada		Eastern Europe		Latin America		Middle East		Russia		South East Asia	
Time period	Retro-spective	Pro-spective	Retro-spective	Pro-spective	Retro-spective	Pro-spective	Retro-spective	Pro-spective	Retro-spective	Pro-spective	Retro-spective	Pro-spective	Retro-spective	Pro-spective
Type 1 diabetes, *n*	8022		2388		3135		531		1124		618		226	
Type 2 diabetes, *n*	19 563		3877		6369		1660		3073		737		3847	
Rate of hypoglycaemia (any)* PPY (95% CI)														
Type 1 diabetes	51.5 (50.9; 52.1)	73.3 (72.6; 74.0)	63.6 (62.4; 64.7)	91.6 (90.0; 93.2)	43.7 (42.9; 44.6)	66.9 (65.8; 67.9)	41.6 (39.7; 43.6)	93.9 (90.6; 97.3)	57.8 (56.2; 59.4)	66.2 (64.4; 68.1)	52.3 (50.2; 54.4)	69.2 (66.8; 71.6)	20.8 (18.7; 23.1)	17.5 (15.5; 19.6)
Type 2 diabetes	16.5 (16.3; 16.7)	19.3 (19.1; 19.6)	16.4 (16.0; 16.9)	18.1 (17.6; 18.7)	19.8 (19.4; 20.2)	23.7 (23.2; 24.1)	11.2 (10.7; 11.8)	19.7 (18.9; 20.6)	17.4 (16.9; 18.0)	15.4 (14.9; 15.9)	21.5 (19.9; 22.3)	28.1 (26.8; 29.6)	11.5 (11.1; 11.9)	14.6 (14.2; 15.1)
Rate of confirmed symptomatic hypoglycaemia* PPY (95% CI)														
Type 1 diabetes	N/R	51.1 (50.5; 51.7)	N/R	63.9 (62.6; 65.3)	N/R	50.2 (49.3; 51.2)	N/R	62.8 (60.1; 65.6)	N/R	36.9 (35.6; 38.4)	N/R	48.4 (46.4; 50.5)	N/R	6.0 (4.9; 7.3)
Type 2 diabetes		11.3 (11.1; 11.5)		11.1 (10.7; 11.5)		19.4 (19.0; 19.9)		11.0 (10.4; 11.6)		7.1 (6.8; 7.5)		16.4 (15.4; 17.5)		3.2 (3.0; 3.4)
Rate of unconfirmed† symptomatic hypoglycaemia* PPY (95% CI)														
Type 1 diabetes	N/R	4.3 (4.1; 4.5)	N/R	4.0 (3.6; 4.3)	N/R	5.6 (5.3; 5.9)	N/R	5.4 (4.6; 6.2)	N/R	2.3 (1.9; 2.6)	N/R	2.1 (1.7; 2.6)	N/R	3.1 (2.4; 4.1)
Type 2 diabetes		1.9 (1.9; 2.0)		0.9 (0.7; 1.0)		1.5 (1.4; 1.7)		1.3 (1.1; 1.5)		0.8 (0.7; 0.9)		0.4 (0.3; 0.6)		4.7 (4.5; 5.0)
Rate of severe hypoglycaemia* PPY (95% CI)														
Type 1 diabetes	2.1 (2.1; 2.2)	4.9 (4.7; 5.1)	1.9 (1.9; 2.0)	3.4 (3.1; 3.7)	1.6 (1.5; 1.7)	4.5 (4.3; 4.8)	3.0 (2.8; 3.2)	10.8 (9.7; 12.0)	3.3 (3.2; 3.5)	6.7 (6.1; 7.3)	3.1 (2.9; 3.3)	5.3 (4.7; 6.0)	1.4 (1.2; 1.7)	2.0 (1.4; 2.8)
Type 2 diabetes	0.9 (0.9; 0.9)	2.5 (2.4; 2.5)	0.6 (0.5; 0.6)	1.3 (1.2; 1.5)	0.7 (0.7; 0.7)	2.2 (2.1; 2.4)	1.0 (0.9; 1.0)	3.7 (3.3; 4.1)	1.6 (1.6; 1.7)	2.4 (2.2; 2.6)	0.6 (0.5; 0.7)	2.3 (2.0; 2.8)	0.9 (0.9; 1.0)	3.4 (3.2; 3.7)
Rate of severe hypoglycaemia leading to hospitalization* PPY (95% CI)														
Type 1 diabetes	0.17 (0.16; 0.18)	0.24 (0.20; 0.28)	0.10 (0.08; 0.12)	0.25 (0.17; 0.35)	0.09 (0.07; 0.10)	0.16 (0.11; 0.22)	0.20 (0.15; 0.26)	0.56 (0.33; 0.88)	0.42 (0.36; 0.48)	0.36 (0.24; 0.52)	0.35 (0.28; 0.42)	0.15 (0.06; 0.31)	0.29 (0.20; 0.42)	0.24 (0.07; 0.61)
Type 2 diabetes	0.12 (0.11; 0.13)	0.22 (0.20; 0.25)	0.12 (0.10; 0.14)	0.18 (0.13; 0.25)	0.06 (0.05; 0.07)	0.17 (0.13; 0.21)	0.11 (0.09; 0.13)	0.44 (0.33; 0.58)	0.16 (0.14; 0.19)	0.19 (0.14; 0.26)	0.06 (0.04; 0.09)	0.09 (0.03; 0.22)	0.20 (0.18; 0.22)	0.31 (0.24; 0.38)

*Data are rate of hypoglycaemia in the 28-day retrospective or prospective period of the study. For severe hypoglycaemia in the retrospective periods, data are based on 6 months pre-baseline.
†Participant experienced symptoms of hypoglycaemia but did not provide a blood glucose measurement.
CI, confidence interval; N/R, not reported; PPY, estimated number of events per participant-year.

symptomatic hypoglycaemia was in South East Asia for both Type 1 and Type 2 diabetes (Table 1).

For the prospective period, the highest rates of severe hypoglycaemia for Type 1 and Type 2 diabetes were reported in Latin America, with the lowest rates in South East Asia for Type 1 diabetes and Northern Europe/Canada for Type 2 diabetes (Table 1) [13]. The rate of severe hypoglycaemia leading to hospital admission was highest in Latin America for both Type 1 and Type 2 diabetes, and lowest in Eastern Europe and Russia for Type 1 diabetes and Russia for Type 2 diabetes (Table 1).

Hypoglycaemia incidence and frequency of blood glucose monitoring

In most regions (with the exception of South East Asia), there was a trend towards greater frequency of blood glucose monitoring with greater prevalence and incidence of hypoglycaemia in participants with Type 1 diabetes. The percentage of participants with Type 1 diabetes experiencing hypoglycaemia was lowest among those in the first quartile for frequency of blood glucose monitoring in Latin America (14.3%), and highest among those in the fourth quartile for in Latin America (90.0%). Similarly (with the exception of South East Asia), participants with Type 1 diabetes in the first quartile for blood glucose monitoring in Latin America reported the lowest incidence of hypoglycaemia [estimated annual incidence rate (IR) 7.45, 95% CI 2.03–19.09] and those in the fourth quartile reported the highest incidence (IR 91.31, 95% CI 85.48–97.44). There was no clear trend between incidence of hypoglycaemia and frequency of blood glucose monitoring in participants with Type 1 diabetes in South East Asia.

In Type 2 diabetes, the percentage of participants reporting hypoglycaemia was lowest in those in the first quartile for blood glucose monitoring in the Middle East (11.2%) and highest for those in the fourth quartile in Eastern Europe (67.0%). The incidence of hypoglycaemia was also lowest for those with Type 2 diabetes in the first quartile for blood glucose monitoring frequency in the Middle East (IR 2.67, 95% CI 2.05–3.41) and highest for participants in Latin America in the fourth quartile (IR 29.20, 95% CI 24.58–34.31). There was no clear trend between the prevalence or incidence of hypoglycaemia and frequency of blood glucose monitoring in participants with Type 2 diabetes in South East Asia or Northern Europe/Canada.

Hypoglycaemia definitions

Most participants were familiar with the ADA/EASD definition of hypoglycaemia [16], but there were regional variations (Table 2). The highest percentage of participants familiar with the ADA/EASD definition of hypoglycaemia was in Eastern Europe for Type 1 diabetes and Russia for Type 2 diabetes, whereas the lowest percentage was South East Asia for both Type 1 and Type 2 diabetes (Table 2).

Overall, 49.1% of people with Type 1 diabetes and 42.3% with Type 2 diabetes reported defining hypoglycaemia based on both blood glucose measurements and symptoms, whereas 26.8% and 35.6% of people with Type 1 and Type 2 diabetes, respectively, defined hypoglycaemia in the participant diary by symptoms alone (Fig. 1). The region with the highest proportion of participants defining hypoglycaemia by symptoms alone was South East Asia for Type 1 diabetes and Russia for Type 2 diabetes, compared with the lowest proportions in Northern Europe/Canada for both Type 1 and Type 2 diabetes (Fig. 1).

Globally, the mean (SD) blood glucose concentration cut-off below which participants considered (or defined) hypoglycaemia to have occurred was 3.4 (0.75) and 3.6 (0.82) mmol/l for Type 1 and Type 2 diabetes, respectively. However, there were wide regional differences, and differences between populations with Type 1 and Type 2 diabetes from the same region (Table 3). In general, people with Type 1 diabetes defined hypoglycaemia to have occurred at a lower blood glucose level than people with Type 2 diabetes from the same region. Among those with Type 1 diabetes, the lowest mean blood glucose cut-off at which participants defined a hypoglycaemic event to have occurred was 3.1 mmol/l (South East Asia) and the highest was 3.6 mmol/l (Russia). In Type 2 diabetes, the lowest defined blood glucose cut-off was 3.5 mmol/l (Northern Europe/Canada) and the highest was 3.8 mmol/l (Russia). Overall, hypoglycaemia rates were lowest in South East Asia for all hypoglycaemia definitions and the mean blood glucose definition for Type 1 diabetes (but not Type 2 diabetes) was the lowest for this region. The region with the highest mean blood glucose definition for Type 2 diabetes (Russia)

Table 2 Percentage of participants familiar with the American Diabetes Association/European Association for the Study of Diabetes definition of hypoglycaemia by region

	Global	Northern Europe/Canada	Eastern Europe	Latin America	Middle East	Russia	South East Asia
Type 1 diabetes	96.8	95.8	98.1	95.8	96.5	98.0	91.6
Type 2 diabetes	85.6	83.4	92.2	80.1	86.8	93.4	76.7

Percentages are based on the number of participants with evaluable data.

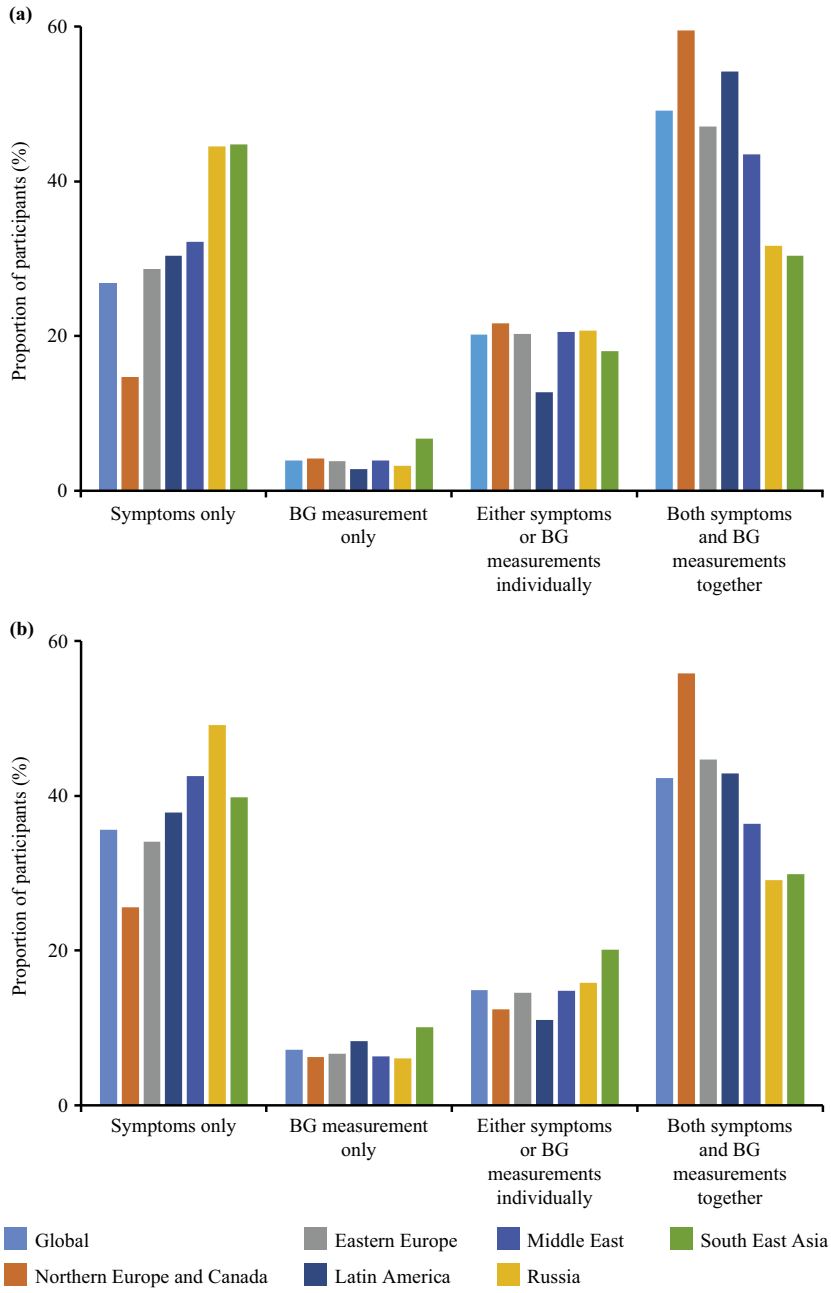

FIGURE 1 Definitions of hypoglycaemia used in the participant diary by participants with (a) Type 1 diabetes and (b) Type 2 diabetes. BG, blood glucose.

was also the region with the highest rate of any hypoglycaemia, whereas the region with the lowest mean blood glucose definition for Type 1 diabetes (South East Asia) had the lowest rates of any and confirmed symptomatic hypoglycaemia. Across the other regions, the blood glucose cut-off used to define hypoglycaemia did not appear to correlate with the rate of 'any' or confirmed symptomatic hypoglycaemia.

Stratifying the blood glucose definition according to gender or whether a participant was aware of the ADA/EASD hypoglycaemia definition did not have a substantial effect on the results (Table 3), suggesting that these two factors did not influence how participants define hypoglycaemia. When blood glucose definitions were stratified according to duration of diabetes, there was a trend towards a lower blood glucose threshold being used by participants with Type 1 diabetes with a longer duration of diabetes (> 10 vs. < 5 or 5–10 years) in each region, with the exception of Russia where the lowest blood glucose definition was used by those with a diabetes duration of 5–10 years (Table 3). Stratifying the blood glucose definitions according to the participants' levels of hypoglycaemia awareness revealed a

Table 3 Blood glucose measurement below which participants defined hypoglycaemic events in the 4 weeks pre-baseline

	Global	Northern Europe/Canada	Eastern Europe	Latin America	Middle East	Russia	South East Asia
Overall population, mmol/l							
Type 1 diabetes	3.4 (0.75)	3.3 (0.71)	3.4 (0.72)	3.5 (0.71)	3.5 (0.83)	3.6 (0.77)	3.1 (1.04)
Type 2 diabetes	3.6 (0.82)	3.5 (0.80)	3.6 (0.81)	3.6 (0.77)	3.7 (0.84)	3.8 (0.89)	3.7 (0.85)
Grouped by sex, mmol/l							
Type 1 diabetes							
Male	3.4 (0.72)	3.3 (0.73)	3.4 (0.69)	3.5 (0.63)	3.5 (0.76)	3.5 (0.71)	3.3 (0.86)
Female	3.4 (0.77)	3.3 (0.70)	3.4 (0.74)	3.4 (0.75)	3.5 (0.89)	3.6 (0.81)	3.1 (1.14)
Type 2 diabetes							
Male	3.6 (0.80)	3.5 (0.80)	3.6 (0.78)	3.6 (0.75)	3.7 (0.82)	3.7 (0.85)	3.7 (0.82)
Female	3.6 (0.84)	3.5 (0.79)	3.6 (0.83)	3.5 (0.78)	3.7 (0.87)	3.9 (0.90)	3.6 (0.89)
Grouped according to knowledge of ADA/EASD definition of hypoglycaemia, mmol/l							
Type 1 diabetes							
Knew definition	3.4 (0.74)	3.3 (0.70)	3.4 (0.71)	3.5 (0.70)	3.5 (0.83)	3.6 (0.77)	3.1 (1.04)
Did not know definition	3.4 (0.98)	3.5 (1.13)	3.3 (0.81)	3.5 (1.07)	3.5 (1.03)	3.5 (0.69)	N/C
Type 2 diabetes							
Knew definition	3.6 (0.81)	3.5 (0.78)	3.6 (0.80)	3.6 (0.76)	3.7 (0.82)	3.8 (0.88)	3.6 (0.85)
Did not know definition	3.7 (0.96)	3.5 (0.93)	3.6 (0.95)	3.6 (0.90)	4.0 (1.21)	3.5 (1.04)	4.0 (0.77)
Grouped by duration of diabetes, mmol/l							
Type 1 diabetes							
<5 years	3.5 (0.62)	3.4 (0.69)	3.4 (0.58)	3.6 (0.59)	3.6 (0.63)	3.5 (0.63)	3.2 (0.58)
5–10 years	3.4 (0.70)	3.4 (0.63)	3.4 (0.68)	3.5 (0.64)	3.5 (0.84)	3.4 (0.67)	3.2 (0.89)
>10 years	3.3 (0.78)	3.2 (0.73)	3.3 (0.75)	3.4 (0.75)	3.5 (0.86)	3.6 (0.82)	3.1 (1.20)
Type 2 diabetes							
<5 years	3.6 (0.79)	3.7 (0.77)	3.5 (0.69)	3.5 (0.73)	3.6 (1.06)	3.6 (0.80)	3.9 (0.88)
5–10 years	3.6 (0.83)	3.5 (0.82)	3.6 (0.81)	3.6 (0.79)	3.6 (0.81)	3.7 (0.84)	3.7 (0.87)
>10 years	3.6 (0.82)	3.5 (0.79)	3.6 (0.81)	3.6 (0.77)	3.7 (0.83)	3.9 (0.92)	3.6 (0.81)
Grouped by hypoglycaemia awareness*, mmol/l							
Type 1 diabetes							
Normal	3.4 (0.76)	3.3 (0.69)	3.4 (0.73)	3.5 (0.70)	3.6 (0.90)	3.5 (0.74)	3.1 (1.45)
Impaired	3.4 (0.69)	3.3 (0.69)	3.4 (0.63)	3.5 (0.74)	3.5 (0.73)	3.6 (0.77)	3.4 (0.82)
Severely impaired	3.2 (0.83)	3.1 (0.83)	3.2 (0.83)	3.3 (0.67)	3.4 (0.83)	3.7 (0.86)	3.0 (0.83)
Type 2 diabetes							
Normal	3.6 (0.83)	3.5 (0.79)	3.6 (0.82)	3.6 (0.80)	3.7 (0.87)	3.7 (0.85)	3.6 (0.91)
Impaired	3.6 (0.78)	3.5 (0.79)	3.6 (0.74)	3.6 (0.70)	3.6 (0.80)	4.0 (0.86)	3.8 (0.78)
Severely impaired	3.6 (0.85)	3.6 (0.83)	3.6 (0.86)	3.6 (0.76)	3.7 (0.81)	3.9 (1.00)	3.6 (0.87)

*The categories of 'hypoglycaemia awareness' correspond to answers given to the question 'Do you have symptoms when you have a low sugar level?', where 'Always' denotes normal, 'Usually' denotes impaired, and 'Occasionally' and 'Never' denote severely impaired awareness. Data are mean (SD).

ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; N/C, not calculable (0 participants in this group).

trend towards lower blood glucose definitions being used by people with Type 1 diabetes with severely impaired hypoglycaemia awareness, with the exception of Russia where the lowest blood glucose definition was used by those with Type 1 diabetes and normal hypoglycaemia awareness. There was no clear trend across the regions in the blood glucose definition used by people with Type 2 diabetes when stratified according to duration of diabetes or hypoglycaemia awareness.

To further investigate these regional differences and why, despite being familiar with the global hypoglycaemia definition, participants define their hypoglycaemia with a different blood glucose cut-off, the blood glucose level at which hypoglycaemia symptoms were perceived by participants was stratified according to HbA_{1c} and diabetes duration for three of the countries included in the study having different ethnic populations: India (considered to be a largely homogeneous population), Malaysia (considered to be a heterogeneous population) and Canada (which has a large Asian population) (Table 4). In these countries, there was no clear correlation between HbA_{1c} or diabetes duration with the hypoglycaemia blood glucose cut-off at which symptoms were perceived.

Discussion

In this analysis, a high proportion of participants involved in the global HAT study responded that they were familiar with the ADA/EASD definition of hypoglycaemia. However, there were regional variations in the way hypoglycaemia was typically defined by participants (symptomatic vs. blood glucose measurement) and in the blood glucose cut-off used. These differences can make comparing hypoglycaemia rates between countries difficult. Regional discrepancies between participant definitions and the consensus guidelines may highlight a need to redefine the criteria of hypoglycaemia

Table 4 Blood glucose levels at which hypoglycaemia symptoms are perceived, by country

	India		Malaysia		Canada	
Stratification	Type 1 diabetes (n = 112)	Type 2 diabetes (n = 2808)	Type 1 diabetes (n = 114)	Type 2 diabetes (n = 1039)	Type 1 diabetes (n = 183)	Type 2 diabetes (n = 315)
HbA_{1c}, no. of participants, mean mmol/l (SD)						
<53 mmol/mol (7%)	n = 2	n = 39	n = 14	n = 56	n = 32	n = 43
	2.9 (0.55)	3.4 (0.80)	3.2 (0.80)	3.4 (0.65)	3.6 (0.71)	3.7 (0.55)
53–64 mmol/mol (7–8%)	n = 15	n = 246	n = 20	n = 147	n = 69	n = 75
	3.6 (0.83)	3.8 (0.77)	3.0 (0.81)	3.8 (0.97)	3.6 (0.74)	3.6 (0.75)
>64 mmol/mol (8%)	n = 17	n = 395	n = 45	n = 275	n = 56	n = 95
	3.2 (0.75)	3.6 (0.80)	3.1 (1.33)	3.7 (0.96)	3.5 (0.69)	3.7 (0.92)
Duration of diabetes, no. of participants, mean mmol/l (SD)						
<5 years	n = 8	n = 93	n = 16	n = 46	n = 20	n = 17
	3.1 (0.74)	3.9 (0.88)	3.2 (0.50)	3.8 (0.88)	3.6 (0.53)	3.7 (0.60)
5–10 years	n = 9	n = 384	n = 17	n = 190	n = 28	n = 55
	3.5 (0.87)	3.7 (0.79)	3.1 (0.90)	3.8 (1.03)	3.6 (0.68)	3.6 (0.65)
>10 years	n = 24	n = 350	n = 52	n = 310	n = 121	n = 158
	3.3 (0.83)	3.5 (0.73)	3.0 (1.33)	3.6 (0.89)	3.5 (0.73)	3.6 (0.84)

Analysis based on participants who reported self-measured blood glucose and symptoms.

and/or the need to increase education. People with diabetes in developing countries may be less likely to have access to blood glucose-testing devices/materials, making them more reliant on diagnosis of hypoglycaemia by symptoms alone. This is supported by the lower reporting of hypoglycaemia in regions such as South East Asia and may also reflect lower levels of communication and/or reporting of hypoglycaemia to healthcare professionals. The study population in Northern Europe/Canada had a longer disease duration and had used insulin for longer than the other regions, which might influence the level of hypoglycaemia awareness. For the overall HAT study population, HbA_{1c} was not found to be a significant predictor of hypoglycaemia [13]. However, in people with Type 2 diabetes, the higher blood glucose cut-off for defining hypoglycaemia occurred in regions with a higher mean HbA_{1c} (Middle East, Russia and South East Asia), perhaps suggesting that these participants experience hypoglycaemia at higher blood glucose levels. Further understanding of these regional differences could help to better optimize therapies for particular populations. Regional differences may also be a consequence of physiological differences between ethnic groups regarding the level at which individuals experience the symptoms of hypoglycaemia, e.g. pseudohypoglycaemia; however, this needs further investigation. Furthermore, it is possible that there are additional between-country differences in the incidence and reporting of hypoglycaemia within the regions described here – this could be investigated in further analyses of these data.

The results provide important information on the incidence of hypoglycaemia in people with diabetes and show that rates are higher than many previous estimates, particularly those reported from randomized clinical trials [13]. The HAT study also provides regional data from many areas without previous information on hypoglycaemia and indicates that rates of hypoglycaemia vary considerably between countries. Furthermore, this analysis shows that the rates of any and severe hypoglycaemia were lower in the retrospective compared with the prospective study period, suggesting that hypoglycaemia may often be under-reported. This is supported by a previous European study, which showed that 65% of people with Type 1 diabetes and 50–59% of those with Type 2 diabetes frequently did not discuss hypoglycaemia with their physicians [18]. We observed the greatest differences between retrospective and prospective rates of hypoglycaemia in the Latin America cohort, suggesting under-reporting may be especially prevalent there.

The limitations of this study include potential participant-selection bias (due to participation in the observational study), the short duration of the prospective period and bias resulting from data collection based on participant recall, which may not be accurate, particularly for the retrospective period. A true rate of hypoglycaemia can only be obtained using continuous glucose monitoring, which was not possible in a study of this scale. Data were not available regarding the previous level of diabetes knowledge of the study participants, and this may have influenced the likelihood of recognizing and reporting retrospective hypoglycaemic events, prior to receiving information as a part of the study. During the prospective period, it is possible that participants were primed to look for hypoglycaemia, and therefore rates may be overestimated or differences over-interpreted, which may differ according to ethnicity. Data were not collected on the frequency of blood glucose testing during the prospective period, unless in connection with a hypoglycaemic event – this may introduce a further bias as access to blood glucose-testing devices/materials may vary, and those who test blood glucose more frequently may be more likely to notice and

report low blood glucose. Additionally, the definition of hypoglycaemia selected was subjective and, as nocturnal hypoglycaemia included any event occurring between midnight and 06:00 h, this may have included events when participants were not asleep (for example, in shift workers). The cohort size varied between regions and was, for example, smaller for South East Asia compared with the other regions, increasing the potential for selection bias. Within the geographical regions analysed, there was considerable population heterogeneity (nationalities/ethnicity). Data were not collected on the type of insulin used or the number of injections per day, both of which may impact upon the rate of hypoglycaemia.

There are also strengths to our study. The HAT study benefits from its size (it is the largest observational study of hypoglycaemia to date), global study population and observational design, meaning the participant population are likely to provide a better representation of clinical practice vs. clinical trials. Furthermore, HAT included countries/regions with little or no other previous data on hypoglycaemia and utilized an encompassing definition of hypoglycaemia (symptomatic episodes and those confirmed by a blood glucose measurement collected using participant diaries).

In conclusion, hypoglycaemia rates were higher than previous estimates, suggesting hypoglycaemia is underreported, particularly with retrospective recall. Although the rates of severe and non-severe hypoglycaemia differed between geographical regions, regional variations in the definition and reporting of hypoglycaemia may also contribute to the global variations reported in the HAT study. Discrepancies between participant definitions and guidelines highlight a need to redefine hypoglycaemia criteria. Indeed, a recent ADA/EASD position statement agreed that clinical trials should report a glucose level of < 3.0 mmol/l, which is sufficiently low to indicate serious, clinically important hypoglycaemia [10]; it remains to be seen whether this will be universally adopted.

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Competing interests

KK has acted as a consultant, advisory board member, and speaker for and has received research grants from Novo Nordisk, Eli Lilly, Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca, Sanofi, Boehringer Ingelheim, Servier and Roche. MCB has acted as a board member for Novo Nordisk and Novartis, and speaker for Novo Nordisk, Eli Lilly, Merck Sharp & Dohme, AstraZeneca, Sanofi, Boehringer Ingelheim and Novartis. BL has acted as an advisory board member and speaker for Amgen, Allergan, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Merck Serono KGaA, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Sanofi and Servier. EM has acted as a speaker for Novo Nordisk, Eli Lilly, Merck Sharp & Dohme, Sanofi and Boehringer Ingelheim. JA and HG are employees of Novo Nordisk. UP-B has acted as a consultant, advisory board member, and speaker for, and has received research grants from, Novo Nordisk, Eli Lilly, Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca, Sanofi, Boehringer Ingelheim and Roche.

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Author contributions

All authors had input into the data interpretation and preparation of the final manuscript for publication, and met the ICMJE criteria for authorship. The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1.
Table S2.
Figure S1. Study design.
Appendix S1. Patient self-assessment questionnaire and diary.