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Published in:

Diabetes, Obesity and Metabolism

DOI:

[10.1111/dom.13588](https://doi.org/10.1111/dom.13588)

Publication date:

2019

Document version

Publisher's PDF, also known as Version of record

Document license:




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Citation for published version (APA):

Pedersen-Bjergaard, U., Alsifri, S., Aronson, R., Berkovi, M. C., Galstyan, G., Gydesen, H., ... Khunti, K. (2019). Comparison of the HAT study, the largest global hypoglycaemia study to date, with similar large real-world studies. *Diabetes, Obesity and Metabolism*, 21(4), 844-853. <https://doi.org/10.1111/dom.13588>

ORIGINAL ARTICLE

Comparison of the HAT study, the largest global hypoglycaemia study to date, with similar large real-world studies

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Funding information

This review and the HAT study were sponsored by Novo Nordisk.

Aims: Optimal diabetes care requires clear understanding of the incidence of hypoglycaemia in real-world clinical practice. Current data on hypoglycaemia are generally limited to those reported from randomised controlled clinical trials. The Hypoglycaemia Assessment Tool (HAT) study, a non-interventional real-world study of hypoglycaemia, assessed hypoglycaemia in 27 585 individuals across 24 countries. The present study compared the incidence of hypoglycaemia from the HAT study with other similarly designed, large, real-world studies.

Materials and Methods: A literature search of PubMed (1995-2017) for population-based studies of insulin-treated patients with type 1 or type 2 diabetes (T1D, T2D), excluding clinical trials and reviews, identified comparable population-based studies reporting the incidence of hypoglycaemia.

Results: The 24 comparative studies, including more than 24 000 participants with T1D and more than 160 000 participants with T2D, varied in design, size, inclusion criteria, definitions of hypoglycaemia and method of recording hypoglycaemia. Reported rates (events per patient-year [PPY]) of hypoglycaemia were higher in patients with T1D than in those with T2D (overall T1D, 21.8-73.3 and T2D, 1.3-37.7; mild/non-severe T1D, 29.0-126.7 and T2D, 1.3-41.5; severe T1D, 0.7-5.8 and T2D, 0.0-2.5; nocturnal T1D, 2.6-11.3 and T2D, 0.38-9.7) and were similar to the ranges found in the HAT study.

Conclusions: The HAT data on hypoglycaemia incidence were comparable with those from other real-world studies and indicate a high incidence of hypoglycaemia among insulin-treated patients. Differences in rates among studies are mostly explained by differences in patient populations and study methodology. The goal of reducing hypoglycaemia should be a target for continued educational and evidence-based pharmacological interventions.

KEYWORDS

hypoglycaemia, insulin therapy, observational study, systematic review, type 1 diabetes, type 2 diabetes

1 | INTRODUCTION

The ultimate goal of glycaemic management in both type 1 (T1D) and type 2 diabetes (T2D) is achievement of individualized glycaemic goals

without hypoglycaemia, which remains a common and acute complication with antidiabetic medications, particularly exogenous insulin therapy. In T1D and T2D, hypoglycaemia can limit the glycaemic control that patients achieve and, therefore, undermine the goal of

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preventing long-term complications.^{1–5} Furthermore, hypoglycaemia has a well-established significant negative impact on well-being, productivity and quality of life (QOL).⁶ Recent studies have confirmed that, in addition to decreased overall health-related QOL, hypoglycaemia can negatively impact physical and mental well-being, limit mobility, lead to anxiety and depression, interfere with social activities, result in missed work (absenteeism), impair performance while at work (presenteeism) and decrease overall work productivity.^{7–12} In addition to an economic burden for patients, hypoglycaemia is associated with increased healthcare resource utilization and health-economic burden.^{7–9} Severe hypoglycaemia events frequently result in emergency/ambulance calls and hospital treatment and, hence, incur substantial healthcare costs.^{11–13}

It is important to have a clear understanding of the true incidence of hypoglycaemia in order to individually tailor glycated haemoglobin (HbA1c) targets, to provide optimal clinical care, to facilitate healthcare resource planning and to develop targeted hypoglycaemia prevention strategies.¹⁴ The incidence of hypoglycaemia is generally reported from randomized controlled trials, from which patients with comorbidities or frequent severe hypoglycaemia are typically excluded, and many of the studies have a treat-to-target design. Consequently, the application of findings to real-world settings may be limited, and the prevalence and incidence of hypoglycaemia in clinical trials may not reflect those in real-world clinical practice.¹⁴

The Hypoglycaemia Assessment Tool (HAT) study is one of the largest real-world global hypoglycaemia studies conducted to date. HAT is a large, international (27 585 patients with T1D or T2D in 24 countries across Europe, Asia, North America and South America), non-interventional, 6-month retrospective, 1-month prospective study to determine the extent of hypoglycaemia in both T1D and T2D in clinical practice.¹⁵ This literature review aimed to collate and evaluate the incidences of hypoglycaemia reported in current literature concerning real-world insulin-treated diabetes populations. Findings from similarly designed large observational studies identified in a literature search were to be compared with those of the HAT study with a view to explaining any observed differences.

2 | MATERIALS AND METHODS

2.1 | Search strategy

We conducted an electronic literature search of the PubMed database from January 1995 to December 2017 to identify population-based studies, excluding clinical trials and reviews, of individuals treated with insulin, with a design similar to that of the HAT study (clinicaltrials.gov NCT02240355), in which the proportion of individuals experiencing hypoglycaemia, or the rates of hypoglycaemic events, were reported by patient questionnaires, diaries or patient records.

The search terms used were “diabetes OR diabetic, AND hypoglycemia OR hypoglycaemia OR hypoglycemic OR hypoglycaemic, AND survey OR report OR questionnaire, AND rate OR incidence OR frequency OR risk.” We included observational studies in which the study population was a defined general population with T1D and/or

T2D. We did not apply any restrictions relating to language or classification, definition or measurement of hypoglycaemia.

Following removal of duplicate publications, titles and abstracts were reviewed to identify studies that met the inclusion criteria. Where it was unclear from the abstract whether the inclusion criteria were met, the full article was retrieved and reviewed. The reporting of data regarding the following criteria was used to determine study relevance: patient self-reported hypoglycaemia; incidence rates; observational studies and surveys; patient awareness of hypoglycaemia; fear of hypoglycaemia; experience of hypoglycaemia and its impact on QOL, productivity and healthcare utilization.

2.2 | Data extraction

Where data were available, we extracted the following for each study: country, number of participants (T1D and T2D), type of insulin therapy and duration of use, disease duration, HbA1c levels (% and mmol/mol), patient inclusion criteria, definitions of hypoglycaemia if available/documented and incidence of hypoglycaemia (overall, mild/non-severe, severe and nocturnal). Where data were not reported, no attempt was made to contact the authors of the individual publications to retrieve additional data.

2.3 | Data analysis

Relevant data were summarized and descriptive comparisons were made among studies, including the HAT study. The co-primary objectives of this literature review were to explore rates of hypoglycaemia (overall, severe and nocturnal) in individuals with T1D and/or T2D within population-based studies and compare the results with hypoglycaemia data from the prospective HAT study, both global and regional analyses.

3 | RESULTS

3.1 | Identification of studies

Results relating to the identification process for eligible studies are summarized in Figure 1. In summary, the PubMed search yielded 721 citations. Following abstract analysis of potentially relevant studies, 653 studies were excluded. Following assessment of 65 full text articles, 41 were excluded, leaving 24 studies, including HAT, that were eligible for inclusion in the analyses. Ten studies, DIALOG,¹⁶ GAPP2 UK,¹⁷ GAPP2 Canada,⁵ COMPASS,¹⁸ DSP China,¹⁹ PANORAMA,²⁰ JADE,²¹ survey of insulin adherence,²² the single centre study in India,²³ and the ICU study²⁴ primarily reported hypoglycaemia prevalence in terms of the proportion of participants reporting hypoglycaemia, rather than rates in events per patient-year (PPY); thus, these studies are reported separately.

3.2 | Summary of studies included in the analysis

An overview of the studies identified is provided in Table S1. All reported data are observational, with 13 studies being prospective, nine being retrospective and two, including the HAT study, using a

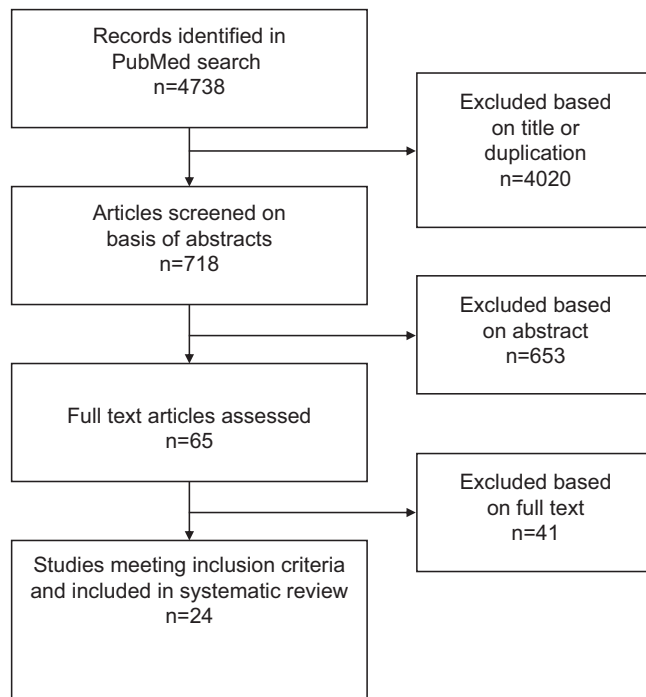


FIGURE 1 Flow chart of selection of studies for inclusion

mixed methods, prospective/retrospective design. In total, the studies included 24 468 participants with T1D and 160 046 participants with T2D. Studies were published from 2007 to 2017 inclusively. The number of participants within each study ranged from 77 to 66 726.^{25,26} Studies were conducted globally ($n = 4$), in Europe ($n = 12$), North America only ($n = 1$), South America ($n = 1$) and East/South East Asia only ($n = 6$). Study length ranged from 1 week (self-reported non-severe hypoglycaemic events in Europe³ and self-reported non-severe hypoglycaemic events in Germany²⁷) to 22 years (single centre survey in Germany²⁸). Studies variously reported rates of self-treated, overall, mild/moderate, mild/non-severe and nocturnal, mild/non-severe and severe, mild/non-severe and severe and nocturnal, overall and severe and nocturnal, overall and mild/non-severe and severe and nocturnal hypoglycaemia and severe hypoglycaemia. Definitions of hypoglycaemia varied among studies (Table S2).

3.3 | Evaluation of the HAT study and comparative real-world clinical study designs

Table S1 highlights differences in study design, type of insulin therapy, duration of prior insulin therapy, patient characteristics and inclusion criteria, definition of hypoglycaemia and reporting/documentation mechanism between the HAT study and real-world clinical studies identified for comparison.

Half (12/24) of the studies included only patients with T2D; three studies were specific to T1D only; and the remainder of the studies included patients with T1D or T2D ($n = 9$). Although the HAT study is one of the largest, real-world, global prospective hypoglycaemia studies with diaries conducted to date ($n = 27\ 585$), several other studies involved large numbers of participants. The Predictable Results and Experience in Diabetes through Intensification and Control to Target [PREDICTIVE] study included 7420 patients with T1D and 12 981

patients with T2D;²⁶ the A1chieve study included 66 726 patients with T2D;²⁹ and the JADE study included 18 589 patients with T2D.²¹

Patient selection and inclusion criteria for the HAT study were generally aligned with those of the other studies, that is, adult patients with T1D and/or T2D who were currently undergoing treatment with insulin.¹⁵ However, selected studies included patients less than 18 years of age (self-reported non-severe hypoglycaemic events in Europe,³ self-reported non-severe hypoglycaemic events in Germany,²⁷ the A1chieve study,²⁹ the UK self-reporting study,³⁰ and self-reported insulin adherence in Brazil²²) or they included only patients who were at least 40 years of age (the GAPP2^{6,16,31} and the PANORAMA²⁰ studies).

Similar to the HAT study, the duration of prior insulin therapies in these studies was generally more than 1 year, although some studies, such as SOLVE, examined patients for whom basal insulin was initiated. Some studies included patients with substantially longer exposure. For example, the GAPP2 study in the UK included patients with up to 20 years of insulin use.¹⁶ With the exception of the UK Hypoglycaemia study, which included patients with T1D duration of up to 40 years,³² the mean duration of diabetes (T1D: range, 16.4-30 years; T2D: range, 4.3-17.3 years) and baseline HbA1c levels (T1D: range, 60.5 mmol/mol to 83.3 mmol/mol; T2D: range, 52-80.3 mmol/mol) were also generally comparable.

The definitions of hypoglycaemia varied widely among studies (Table S2) and only the HAT,¹⁵ DIALOG¹⁶, survey of self-reported insulin adherence²² and HypoAna^{33,34} studies defined hypoglycaemia in accordance with ADA definitions.³⁵ Documentation was based primarily on symptoms, while a limited number of studies (a self-reported non-severe hypoglycaemia study in Europe,³ a self-reported non-severe hypoglycaemia study in Germany,²⁷ a single-centre study in Germany,²⁵ a basal insulin dose-timing study,²⁵ an ICU cohort study,²⁴ the PREDICTIVE²⁶ and HypoAna^{33,34} studies) required documentation with glucose thresholds defined.

The mechanisms used to report/document hypoglycaemic events also varied among studies and generally involved recall, making use of questionnaires, or patient diaries (the PREDICTIVE and A1chieve studies), with only one study (UK Hypoglycaemia study³²) using continuous glucose monitoring.

Data from real-world studies of patients with T1D were available for Europe (a self-reported non-severe hypoglycaemic events study in Europe,³ a self-reported non-severe hypoglycaemic events study in Germany,²⁷ the PREDICTIVE,²⁶ DIALOG¹⁶ and HypoAna studies,^{33,34} a study by Kristensen et al.,³⁶ the ICU cohort study,²⁴ the UK Hypoglycaemia study,³² and the UK self-reporting study³⁰), Japan²⁵ and Brazil.²²

Real-world studies of patients with T2D included global studies (GAPP2,³¹ A1chieve²⁹ and SOLVE³⁷), European studies (GAPP2 UK,¹⁷ a self-reported non-severe hypoglycaemic events study in Europe,³ a self-reported non-severe hypoglycaemic events study in Germany,²⁷ the PREDICTIVE²⁶ and DIALOG¹⁶ studies, the UK Hypoglycaemia study,³² a single-centre survey in Germany,²⁸ the UK self-reporting study,³⁰ the PANORAMA²⁰ and ICU cohort studies²⁴), Asian/South East Asian studies (Physicians' Routine Evaluation of Safety and Efficacy of NovoMix 30 Therapy [PRESENT],³⁸ COMPASS,¹⁸ Diabetes

Disease Specific Programme [DSP] China¹⁹, the JADE study²¹, a single-centre study in India,²³ a basal insulin dose-timing study in Japan²⁵) and one study from North America (GAPP2 Canada⁵).

Data on hypoglycaemia should be evaluated in the context of HbA1c. In many studies this was not reported, but there was very little variation across studies in the values that were reported (Table S1).

3.4 | Proportions and rates of hypoglycaemia in the HAT study vs other real-world studies

Data for hypoglycaemia rates in T1D and T2D are given in Tables 1 and 2, respectively, with the studies reporting rates, expressed here as events PPY, separated from those reporting only the proportion of patients affected. Both parameters were used in the HAT study. As expected, the rates of overall, mild/non-severe, severe and nocturnal hypoglycaemia in patients with T1D were higher than those in patients with T2D in all studies. Across studies, reported rates ranged as follows: T1D overall, 21.8 to 73.3 events PPY; mild hypoglycaemia, 29.0 to 126.7 events per PPY; severe hypoglycaemia, 0.7 to 5.8 events PPY; nocturnal hypoglycaemia, 2.6 to 11.3 events PPY and T2D overall, 1.3 to 37.7 events PPY; mild hypoglycaemia, 1.3 to 41.5 events per PPY; severe hypoglycaemia, 0.0 to 2.5 events PPY; nocturnal hypoglycaemia, 0.38 to 9.7 events PPY. In the dose-timing study in Japan, the frequency of hypoglycaemia (events/month) was 7.7 ± 9.9 in patients with T1D and 1.3 ± 3.3 in patients with T2D.²⁵ The data concerning proportions affected are potentially less informative, as these will be impacted by the time interval over which the evaluation was made; however, the proportions in the HAT study, given for the 4-week prospective interval, are broadly comparable to other studies, with a higher percentage of patients with T1D (83.0%) vs patients with T2D (46.5%) reporting hypoglycaemia. Proportions of hypoglycaemia reported in the HAT study are in line with other studies that reported hypoglycaemia prospectively. In the DIALOG study, 85.3% and 43.6% of patients with T1D and T2D, respectively, reported hypoglycaemia prospectively over 30 days.¹⁶ In the HypoAna study over 2 years,³³ 92.1% of patients with T1D reported hypoglycaemia. And in the DSP China study,¹⁹ 33.3% of patients with T1D reported hypoglycaemia over 1 year. Patients with T1D and T2D in the PREDICTIVE²⁶ study reported slightly lower proportions of hypoglycaemia over 4 weeks (21.8% and 3.1%, respectively). Among patients with T2D, 8.1% included in the JADE study over 10 years reported mild hypoglycaemia²¹ while, in the single-centre study in India, 95.9% of patients reported at least one symptom of hypoglycaemia.²³

3.4.1 | T1D: Overall and mild/non-severe hypoglycaemia

Rates of overall and mild/non-severe hypoglycaemia were comparable between the HAT study (77.3 events PPY) and the European T1D real-world studies (~20-125 events PPY) (Table 1). From European data in the global HAT study, Eastern and North European rates of non-severe hypoglycaemia were also within range at 66.9 PPY and 91.6 PPY, respectively. Overall rates in the PREDICTIVE trial were lower; however, in that study, the blood glucose definition of hypoglycaemia was less than 2.8 mmol/L (50 mg/dL), whereas, in the HAT study, various definitions were used and in the GAPP2 study, it was

undefined, and in other studies, such as HypoAna, it was less than 3.9 mmol/L (≤ 70.2 mg/dL).

3.4.2 | T1D: Severe hypoglycaemia

The rate of severe hypoglycaemia in the global HAT dataset was 4.9 events PPY, which is within the range of the other European studies (0.7-5.8 events PPY) (Table 1). According to global HAT data, patients in Europe had high rates of severe hypoglycaemia (Northern Europe, 3.4 PPY; Eastern Europe, 4.5 PPY). Rates were low in the European self-reported study (0.7 events PPY),³ which may be explained by selection bias, as this study used a web-based survey that may have precluded elderly and otherwise frail patients from participation. The relatively high rates in the HAT and Dialog studies may be explained by anonymous reporting, reducing bias, or by the fact that annual rates were calculated from shorter observation periods of 4 weeks. The PREDICTIVE study also reported lower rates than the HAT study, but used a more stringent definition of severe hypoglycaemia. While both the HAT and HypoAna studies defined severe hypoglycaemia as events requiring third-party assistance to administer carbohydrate, glucagon or other resuscitative action, the PREDICTIVE study required third-party intervention along with a blood glucose reading less than 2.8 mmol/L (50 mg/dL) or reversal of symptoms after food intake, glucagon or intravenous glucose.

3.4.3 | T1D: Nocturnal hypoglycaemia

Only three studies reported nocturnal hypoglycaemia in T1D. The rates in the HAT study (11.3 events PPY) were higher as compared with the HypoAna study (8.5 non-severe, 2.6 symptomatic and 3.3 asymptomatic events PPY) and the PREDICTIVE study (3.6 events PPY) (Table 1). According to the HAT study, nocturnal hypoglycaemia rates in Northern Europe were higher than those reported globally, at 12.9 PPY, and in Eastern Europe rates were lower, at 9.8 PPY.

3.4.4 | T2D: Overall and mild/non-severe hypoglycaemia

Rates of overall and mild/non-severe hypoglycaemia were similar, between 19 and 40 events PPY, in the HAT¹⁹ and GAPP2²¹ studies and in two European self-reported studies.^{4,29} According to the HAT study, Northern and Eastern Europe rates of non-severe hypoglycaemia were 18.1 PPY and 23.7 PPY, respectively. Other studies, such as PREDICTIVE²⁷, A1chieve²⁹ and SOLVE,³⁷ reported lower rates of 1.3 to 3.1 events PPY. These lower rates may reflect the fact that, in the A1chieve study, 67.2% of patients were insulin-naïve at baseline, whereas 100% of participants in the SOLVE study were insulin naïve at baseline. Hence, the lower rates of overall hypoglycaemia in those studies vs the HAT and GAPP2 studies may reflect different participant populations. As for the PREDICTIVE trial, the comparatively lower rates may reflect more stringent hypoglycaemia criteria as compared to the HAT and GAPP2 studies.

3.4.5 | T2D: Severe hypoglycaemia

Rates of severe hypoglycaemia in T2D were uniformly low across most studies, ranging from 0.0046 to 0.7 events PPY, and were highest in the HAT study, at 2.5 events PPY. In Europe, rates were high at 1.3 PPY (Northern Europe) and at 2.2 PPY (Eastern Europe). In the

TABLE 1 Reported rates and incidence of hypoglycaemia in type 1 diabetes

Study	Region/country	Method of hypoglycaemia reporting	Incidence of hypoglycaemia			
			Overall	Mild/non-severe	Severe	Nocturnal
Rates of hypoglycaemia, per patient year (PPY)						
HAT global ¹⁵	Global	Questionnaire and patient diary	73.3 events PPY	NR	4.9 events PPY	11.3 events PPY
Self-reported non-severe hypoglycaemic events in Europe ³	Austria, Denmark, Finland, Norway, Sweden, Switzerland, The Netherlands	Self-complete questionnaires (recall)	NR	91 events PPY	0.7 events PPY	NR
Self-reported non-severe hypoglycaemic events in Germany ²⁷	Germany	Self-complete questionnaires (recall)	NR	85.3 events PPY	NR	NR
PREDICTIVE ²⁶	Austria, Czech Republic, Denmark, Finland, Germany, Ireland, Israel, The Netherlands, Sweden, Turkey, UK	Patient records, recall and patient diaries	21.8 events PPY	NR	0.7 events PPY	3.6 events PPY
HypoAna ^{33,34}	Denmark	Patient diary	NR	55.5 events PPY	5.8 events PPY	Non-severe; 8.5 events PPY Symptomatic; 2.6 events PPY Asymptomatic 3.3 events PPY
UK Hypoglycaemia study ³²	UK	Self-reporting and continuous glucose monitoring	NR	<5 years; 35.5 events PPY >15 years; 29.0 events PPY	<5 years; 1.1 events PPY >15 years; 3.2 events PPY	NR
UK self-reporting study ³⁰	UK	Weekly, on-line questionnaires (recall)	NR	126.7 events PPY ^a	1.2 ^a	NR
Kristensen ³⁶	Denmark	Self-completed questionnaires (recall)	NR	114.4 PPY	1.21 ± 0.08	NR
Basal insulin dose-timing study ²⁵	Japan	Self-reporting of blood glucose during a 1-month period	7.7 ± 9.9 episodes per month	NR	NR	NR
Incidence of hypoglycaemia, % participants						
HAT global ¹⁵	Global	Questionnaire and patient diary	83.0%	NR	14.4%	40.6%
DIALOG ¹⁶	France	Patient records and self-administered questionnaire (recall)	85.3%	84.4%	13.4%	40.2%
Nationwide survey of self-reported insulin adherence ²²	Brazil	Questionnaire during a clinical visit	Adherence group: maximum, 67.5%; moderate, 74.8%; minimum, 75.3% ^b	NR	NR	NR
ICU cohort study ²⁴	The Netherlands	Blood glucose measurements	3.7% ^c	NR	NR	NR
Kristensen ³⁶	Denmark	Self-completed questionnaires (recall)	NR	NR	29.2%	NR

Abbreviations: ICU, intensive care unit; NR, not reported; PPY, per patient year.

^a Several rates reported depending on regimen.^b Experienced hypoglycaemia in the past month.^c Experienced at least one episode during ICU admission.

TABLE 2 Reported rates and incidence of hypoglycaemia in type 2 diabetes

Study	Region/country	Method of hypoglycaemia reporting	Incidence of hypoglycaemia		
			Overall	Mild/non-severe	Severe
Rates of hypoglycaemia, per patient year (PPY)					
HAT global ¹⁵	Global	Questionnaire and patient diary	19.3 events PPY	NR	2.5 events PPY
GAPP2 ³¹	Global	Online self-complete questionnaires	37.7 events PPY 36% ^a	NR	NR
Self-reported non-severe hypoglycaemic events in Europe ³	Austria, Denmark, Finland, Norway, Sweden, Switzerland, The Netherlands	Self-complete questionnaires (recall)	NR	BOT; 20.3 events PPYBB; 35.4 events PPYOther; 27.0 events PPY	BOT; 0.1 events PPYBB; 0.2 events PPYOther; 0.2 events PPY
Self-reported non-severe hypoglycaemic events in Germany ²⁷	Germany	Self-complete questionnaires (recall)	NR	BOT; 31.7 events PPYBB; 32.8 events PPYOther; 39.5 events PPY	NR
PREDICTIVE ²⁶	Austria, Czech Republic, Denmark, Finland, Germany, Ireland, Israel, The Netherlands, Sweden, Turkey, UK	Patient records, recall and patient diaries	3.1 events PPY	NR	0.1 events PPY
UK Hypoglycaemia study ³²	UK	Self-reporting and continuous glucose monitoring	NR	<2 years; 4.08 events PPY >5 years; 10.2 events PPY	<2 years; 0.1 events PPY >5 years; 0.7 events PPY
A1chieve ²⁹	China, South Asia, East Asia, North Africa, Middle East/Gulf, Latin America, Russia	Patient records, recall, patient diaries and laboratory measurements	Naïve; 1.33 events PPY Experienced; 1.83 events PPY 1.84 events PPY	Naïve; 1.33 events PPY Experienced; 1.83 events PPY	Naïve; 0.0 events PPY Experienced; 0.01 events PPY
PRESENT ³⁸	India	Data collection forms (recall)	1.5 events PPY	1.4 events PPY	0.05 events PPY
SOLVE ³⁷	Germany, Canada, China, Spain, Israel, Italy, Poland, Portugal, UK, Turkey	NR	NR	2.4 events PPY	NR
Single centre survey in Germany ²⁶	Germany	Patient records	NR	MIT; 0.3 events per week CT; 0.2 events per week	MIT; 0.04 events PPY CT; 0.01 events PPY
UK self-reporting study ³⁰	UK	Weekly, on-line questionnaires (recall)	NR	41.5	NR
Basal insulin dose timing study ²⁵	Japan	Self-reporting of blood glucose during a 1-month period	1.3 ± 3.3 episodes/month	NR	NR
Incidence of hypoglycaemia, % participants					
HAT global ¹⁵	Global	Questionnaire and patient diary	46.5%	NR	8.9%
GAPP2 UK ¹⁷	UK	Online self-complete questionnaires (recall)	84%	NR	NR

^a36% of events were severe

TABLE 2 (Continued)

Study	Region/country	Method of hypoglycaemia reporting	Incidence of hypoglycaemia			
			Overall	Mild/non-severe	Severe	Nocturnal
GAPP2 Canada ⁵	Canada	Online self-complete questionnaires (recall)	33%*	NR	NR	47%*
DIALOG ¹⁶	France	Patient records and self-administered questionnaire (recall)	43.6%	41.7%	6.4%	11.1%
COMPASS ¹⁸	China	Patient questionnaires (recall) and self-monitoring of blood glucose	58.9%	NR	NR	NR
DSP China ¹⁹	China	Physician report form and chart review	33%	NR	8.6%	16.2%
PANORAMA ²⁰	Belgium, France, Germany, Greece, Italy, the Netherlands, Spain, Turkey, and the UK	Medical record review, patient interview, and patient-self-completed questionnaires (recall)	NR	15.7% ^b	4.4% ^b	NR
Mild hypoglycaemia in JADE ²¹	Hong Kong	Self-recall		8.1% ^c		
Single centre study in India ²³	India	15-20 min questionnaire (recall) administered in an interview setting	95.9% ^b	78.7% ^b	23% ^b	NR
ICU cohort study ²⁴	The Netherlands	Blood glucose measurements	3.4% ^d	NR	NR	NR

Abbreviations: BB, basal bolus; BOT, basal-only; CT, conventional therapy; MIT, multiple insulin injection therapy; NR, not reported; UK, United Kingdom.

^a At least one event during previous 30 days.

^b At least one event during previous year.

^c At least once monthly over the previous 3 months.

^d Experienced at least one episode during ICU admission.

HAT study, only 0.237 events PPY required hospitalization. Differences among the rates of severe hypoglycaemia probably reflect the differences among studies, in the study populations and in the definitions of hypoglycaemia used, as discussed above.

3.4.6 | T2D: Nocturnal hypoglycaemia

Rates of nocturnal hypoglycaemia were higher in the HAT (3.7 events PPY) and GAPP2 (9.7 events PPY) studies than in the other studies that reported rates, including PREDICTIVE, A1chieve, PRESENT and SOLVE (0.4-0.7 events PPY). Rates were also high in European datasets from the HAT study; in Northern Europe, rates were 3.7 PPY and in Eastern Europe, rates were 4.0 PPY. This is perhaps not surprising, given the different populations included in the various studies. For example, the GAPP2 study,²¹ which had the highest rates of nocturnal hypoglycaemia, included participants who had undergone more than 5 years of insulin therapy, whereas studies with the lower rates, including the PRESENT and SOLVE studies, included insulin-naïve participants.

4 | DISCUSSION

This review of 24 real-world studies highlights the fact that reported rates of overall, mild/non-severe, severe and nocturnal hypoglycaemia are variable; however, most of this variability appears to be explained by the type of participants included and by differences among studies in the definitions of hypoglycaemia. Different data collection methods (questionnaires, diaries and patient records) also contribute to some variation in the level of detail available and to the reported rates of hypoglycaemia. Recently, attention has been focused on the different definitions that confound the ability to compare and translate study data. This has led to the release of a joint ADA/EASD statement from the International Hypoglycaemia Study Group calling for uniform definitions to be used in clinical trials.³⁹ Clearly, this approach would also contribute to the ability to draw meaningful comparisons across data from real-world and epidemiological studies. Another source of variation in reported rates may arise from differences between retrospective and prospective reporting, whereby retrospective reporting is potentially less accurate as the result of memory bias and inconsistency in methods of data collection. Global data, from studies such as GAPP2 and HAT, provide initial indications that rates of hypoglycaemia in some regions of the world may be higher than previously suggested, but further regional real-world studies are required to confirm this.

4.1 | Relationship to other literature

Other than the individual studies identified in this analysis, there is a paucity of literature focusing on hypoglycaemia rates among insulin-treated patients in real-world settings. However, a recent systematic review and meta-analysis of population-based studies involving patients with T2D concluded that hypoglycaemia is highly prevalent among insulin-treated patients with T2D. The meta-analysis described a high degree of heterogeneity among studies, and estimated an incidence of 23 events PPY for mild/moderate hypoglycaemia, and one

event PPY for severe hypoglycaemia. The rate for mild/moderate hypoglycaemia was comparable to that reported in the HAT study (19.3 overall events PPY) but the rate for severe hypoglycaemia was lower than that reported in the HAT study (2.5 severe events PPY).¹⁴

While the HAT study included a truly global population, no previous hypoglycaemia incidence data were available for many participants. A further finding of the literature review was the limited global reach of other real-world studies. Most studies, particularly in T1D, were focussed on Europe and North America. The exceptions were the GAPP2 (Global), A1chieve (Asia, North Africa, Middle East/Gulf, Latin America and Russia) and PRESENT studies, a single-centre study (India), the COMPASS and DSP China studies (China), the JADE study (Hong Kong), a basal insulin dose-timing study in T2D (Japan) and a self-reported insulin adherence study in T1D and T2D (Brazil). Therefore, in order to identify regional differences in hypoglycaemia rates, particularly in T1D, further real-world global studies are required to identify the explanation for variations among regions, and intervention studies are required to reduce the high rates of hypoglycaemia.

4.2 | Study limitations

Comparison of data from the component studies is not straightforward because of differences in inclusion criteria and definitions of hypoglycaemia, as well as differences in reporting/documentation mechanisms. There are multiple definitions of hypoglycaemia and conflicting data concerning the incidence of hypoglycaemia available in the scientific literature.⁴⁰ Combined with the fact that hypoglycaemic events often go undetected, for a number of reasons, studies with patient-reported data will unavoidably have variable outcomes if hypoglycaemia events are not confirmed with blood glucose measurements.⁴⁰ Recall is an often-used but potentially inaccurate mechanism to document hypoglycaemic events and a patient diary provides a more realistic mechanism to record the incidence of hypoglycaemia. A further confounding factor might be an unequal use of different insulin regimens (eg, insulin analogues vs more traditional products) and density of glucose measurement among studies. Limitations of the methodology of this literature review are that it includes only publications that are listed in PubMed and the fact that results were reviewed and included/excluded by multiple individuals.

4.3 | Implications of the study

The main clinical implication of this analysis is that hypoglycaemia is more prevalent in real-world insulin-treated diabetes cohorts than is indicated by data from randomized controlled trials. This is important because hypoglycaemia has a significant impact on glycaemic control and health-related QOL. Data from the HAT study broadly support other studies in highlighting this issue. Concerning T1D, the HAT study confirmed the seriousness of the hypoglycaemia challenge facing individuals, with overall rates of 73.3 events PPY, approximately six events each month, five severe events PPY and 11 nocturnal events PPY. Individuals with insulin-treated T2D will probably experience an average of 19 hypoglycaemic events overall annually, including 2.5 severe and 3.7 nocturnal events according to data from the HAT study.

The current study highlights the need for uniform definitions of hypoglycaemia, and for these uniform definitions to be used in real-world studies, in order to draw accurate conclusions from the literature base. Standardization of hypoglycaemia definitions would be particularly useful in making comparisons among regions, with a view to informing the construction of regional guidelines. However, a further implication of our literature review is that there is a need for further study of hypoglycaemia rates in cohorts beyond Europe and North America to support regional recommendations.

In conclusion, data from the HAT study contributes to the existing literature by demonstrating that the global incidence of hypoglycaemia is high in all insulin-treated patient groups. There are inconsistencies among studies in the rates reported, but these are explained mostly by patient characteristics and by study methodology, leaving an overall picture of a globally consistent clinical problem. We therefore suggest that the goal of reducing hypoglycaemia should be a target for continued educational and evidence-based pharmacological interventions.

ACKNOWLEDGMENTS

The authors wish to pay tribute to Associate Professor Margalit Goldfracht for her significant contributions to the field of diabetology, and notably, for her contribution to improving the treatment of diabetes and mental health in primary care. Her positive attitude, enthusiasm and kindness will be remembered by all those who were fortunate enough to have had the opportunity to work with her.

The authors thank Watermeadow Medical, funded by Novo Nordisk, for medical writing and editorial assistance.

K. K. acknowledges the support of the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care - East Midlands (NIHR CLAHRC - EM), and the NIHR Leicester Biomedical Research Centre.

CONFLICTS OF INTEREST

U. P. B. has served on advisory boards for, and has received lecture fees, from AstraZeneca, Bristol-Myers Squibb, Novo Nordisk and Sanofi-Aventis. S. A. has no conflicts of interest to disclose. R. A. has provided research support to, has acted as a consultant to and advisory board member for, and has received research grants from Novo Nordisk, Janssen, Sanofi, Medtronic, Bristol-Myers Squibb, AstraZeneca, Takeda, Becton Dickinson, Merck Sharp & Dohme, Boehringer Ingelheim, Regeneron, Eli Lilly, Abbot, Quintiles, ICON, Medpace and GlaxoSmithKline. M. C. B. has acted as a board member for Novo Nordisk and Novartis, and a speaker for Novo Nordisk, Eli Lilly, Merck Sharp & Dohme, AstraZeneca, Sanofi, Boehringer Ingelheim and Novartis. G. G. has served on advisory panels for and as a board member and speaker for Novo Nordisk, Eli Lilly, Merck Sharp & Dohme, AstraZeneca, Sanofi, Novartis and Takeda. H. G. and J. B. L. are employees of Novo Nordisk.

B. L. has been a consultant to, and a speaker and advisory board member for AstraZeneca, Boehringer-Ingelheim, Eli Lilly, MSD, Merck, Novartis, Novo Nordisk, Sanofi, Takeda, Roche and Servier. E. M. has served as a speaker for Novo Nordisk, Eli Lilly, Merck Sharp & Dohme,

Sanofi and Boehringer Ingelheim. A. R. has served as an advisory board member and speaker for AstraZeneca, Bristol-Myers Squibb, Novo Nordisk and Sanofi, and has received research grants from Novo Nordisk.

K. K. has been a consultant to, and a speaker and advisory board member for AstraZeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp and Dohme, Janssen and Boehringer Ingelheim, and he has received grants in support of investigator-initiated trials from AstraZeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim, Merck Sharp and Dohme and Roche.

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SUPPORTING INFORMATION

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

How to cite this article: Pedersen-Bjergaard U, Alsifri S, Aronson R, et al. Comparison of the HAT study, the largest global hypoglycaemia study to date, with similar large real-world studies. *Diabetes Obes Metab*. 2019;21:844-853. <https://doi.org/10.1111/dom.13588>