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Direct and indirect health economic impact of hypoglycaemia in a global population of patients with insulin-treated diabetes



Ronnie Aronson^{a,*}, Gagik Galstyan^b, Margalit Goldfracht^{c,1}, Saud Al Sifri^d, Lisa Elliott^e, Kamlesh Khunti^f

^a LMC Diabetes and Endocrinology, Toronto, Canada

^b Endocrinology Research Center, Moscow, Russian Federation

^c Clalit Health Services, The Technion, Haifa, Israel

^d Al Hada Military Hospital, Taif, Saudi Arabia

^e Novo Nordisk A/S, Søborg, Denmark

^f Diabetes Research Centre, University of Leicester, Leicester, UK

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ABSTRACT

Aims: The Hypoglycaemia Assessment Tool (HAT) study investigated the health economic impact of hypoglycaemic events in 24 countries, including countries without previously published data on hypoglycaemia.

Methods: Self-assessment questionnaires and patient diaries (4-week prospective period) were completed by adults with type 1 (T1D) or type 2 diabetes (T2D) treated with insulin for more than 12 months (N = 27,585).

Results: Direct economic impacts of hypoglycaemia during the 4-week prospective period, included increased blood glucose monitoring (reported by 69.7% [T1D] and 60.9% [T2D] of patients), hospitalisation (T1D 2.1%; T2D 3.4% of patients) and medical contact (clinic or telephone; T1D 3.8%; T2D 6.8% of patients). Regional variation in medical contact and hospitalisation was found, with the highest usage in Russia (T1D 17.1%; T2D 17.3%), and Latin America (T1D 5.2%; T2D 6.8%) respectively. Indirect economic impacts following hypoglycaemia included loss of productivity due to absence from work or study; 3.9% (T1D) and 6.2% (T2D) of patients. Regional differences in work productivity were noted among patients with T2D, with a low prevalence in Northern Europe and Canada (0.9%) and high in Southeast Asia (14.6%).

Conclusions: This study shows that hypoglycaemia has a significant but variable impact on the economics of diabetes healthcare globally.

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* Corresponding author at: LMC Diabetes & Endocrinology, Suite 106, 1929 Bayview Avenue, Toronto, ON M4G 3E8, Canada. E-mail address: ronnie.aronson@lmc.ca (R. Aronson).

¹ Prof. Goldfracht sadly passed away before completion of this manuscript.

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1. Introduction

Hypoglycaemia is an important concern for patients with diabetes who are treated with insulin, and also for physicians, who need to consider a patient's risk of hypoglycaemia when maintaining or adjusting insulin doses to individualised glycaemic targets. Consequently, clinical decisions on glycaemic control are often made according to the relative benefits of insulin therapy versus the risk of hypoglycaemia [1]. A large proportion of published data on the prevalence and incidence of hypoglycaemia comes from clinical trials, therefore caution should be exercised when extrapolating these findings to the real-world setting. A major limitation of these clinical studies is that the strict enrolment criteria – for example, the exclusion of patients who experience recurrent hypoglycaemia – may lead to underestimation of hypoglycaemia incidence in clinical practice. In addition, study design, frequent patient monitoring by healthcare professionals, and adoption of new treatment regimens, can reduce the external validity of observed rates in clinical trials [2]. Reports from observational studies of actual hypoglycaemia rates in patients with type 1 (T1D) or type 2 diabetes (T2D) have been few and have used varying clinical definitions of hypoglycaemia. Furthermore, observational studies have tended to rely on panels of internet volunteers to report rates and are retrospective in design, making them vulnerable to recall bias [1,3–6]. Although there is a lack of real world data on hypoglycaemia, a recent analysis of the existing literature has shown that hypoglycaemia is more common in clinical practice than clinical trials would suggest [7].

Hypoglycaemia is a significant contributor to total diabetes expenditure [8–11]. The health economic burden associated with hypoglycaemia can be divided into direct and indirect costs. Direct costs include ambulance attendance, hospital admission, additional contacts with healthcare professionals, and the need for medical supplies such as needles and blood glucose test strips. Indirect costs arise from factors such as work absenteeism and reduced productivity [12]. As a result of a lack of comprehensive data, particularly in developing countries, the economic impact of hypoglycaemia on patients and healthcare providers remains poorly understood, creating a need for additional studies to support the cost-effectiveness of future treatment strategies in the clinical setting.

The Hypoglycaemia Assessment Tool (HAT) study, the largest and most comprehensive study of its kind, assessed self-reported hypoglycaemic events and associated predictive factors in a global population of 27,585 patients with insulin-treated diabetes. The primary objective of the global HAT study was to investigate the prevalence of hypoglycaemia in patients with T1D and T2D and to compare among the different global populations affected by hypoglycaemia [13].

The aim of the present analysis was to assess the economic impacts of hypoglycaemia, both directly on healthcare providers and indirectly on patients, across different populations reported in the global HAT study.

2. Methods

2.1. Study design

The global HAT study was a non-interventional, multicentre, 6-month retrospective and 1-month prospective study of hypoglycaemic events, spanning 2004 sites in 24 countries (Argentina, Austria, Bulgaria, Canada, Croatia, Czech Republic, Denmark, Finland, Germany, Hungary, India, Israel, Lebanon, Malaysia, Mexico, the Netherlands, Poland, Romania, Russian Federation, Saudi Arabia, Serbia, Slovakia, Slovenia, and Sweden) [13]. Hypoglycaemia was recorded using self-assessment questionnaires (SAQs), and patient diaries (recorded for a prospective 4-week period). Start times varied by country; the study was conducted over a period of 1 year between 2012 and 2013. The study protocol was conducted in accordance with the Declaration of Helsinki (2004) and the International Conference on Harmonisation Guidelines for Good Clinical Practice (1996), and approved by country-specific regulatory agencies. All study materials were translated into local languages, and data obtained were translated back into English for analysis.

2.2. Study population

Consecutive patients were enrolled during a routinely scheduled clinical consultation with their healthcare provider. Eligible patients were at least 18 years of age at baseline, with T1D or T2D treated with insulin for more than 12 months, who had given informed consent to participate in the study. Exclusion criteria included non-ambulatory status and illiteracy or other issues resulting in an inability to complete a written questionnaire [13].

2.3. Assessments

A two-part SAQ were completed by patients. Part 1 was a cross-sectional assessment used to record baseline demographic and treatment information, as well as the history of severe hypoglycaemia over the past 6 months and non-severe hypoglycaemia over the previous 4 weeks in the lead-up to baseline study entry. Part 2, completed 4 weeks later, evaluated the occurrence of both severe and non-severe hypoglycaemia over the 4 weeks following baseline study entry. To assist recall, patients were provided with a diary, which was also used to prospectively record hypoglycaemic events anonymously. If a patient recorded more hypoglycaemic events using the patient diary than the Part 2 SAQ, the patient diary value was used to calculate prevalence of hypoglycaemia in the 4 weeks after baseline, to compensate for potential underestimates due to recall bias. The patient diary and Part 2 of the SAQ were also used to record the implications of hypoglycaemia which may translate to a health economic impact, such as increased healthcare utilisation, and the indirect impacts regarding patient workplace punctuality (arriving late or leaving early) and absenteeism. Patients

were asked if in the previous 4 weeks, they had an episode of hypoglycaemia that resulted in either a direct economic impact on HCPs or indirect impacts on themselves.

2.4. Hypoglycaemia definition

Hypoglycaemia was defined and classified using the following definitions. Non-severe hypoglycaemia, an event managed by the patient alone; severe hypoglycaemia, as per the American Diabetes Association definition (requiring third-party assistance) [14]; any hypoglycaemia, the sum of severe and non-severe hypoglycaemia; nocturnal hypoglycaemia, hypoglycaemia occurring between 00:00 and 06:00.

2.5. Data reporting

Data were reported using descriptive statistics (mean \pm SD) and percentages as appropriate. No imputation of missing data was performed.

3. Results

The patient population of the global HAT study has been previously reported [13]. Population differences between the six geographic regions (Northern Europe/Canada, Eastern Europe, Latin America, Middle East, Russia and Southeast [SE] Asia) are also of interest in the present study and are summarized briefly below, in addition to Table 1a and b, describing the baseline characteristics of patients with T1D and T2D respectively. A total of 27,585 patients (8022 T1D; 19,563 T2D) completed the Part 1 SAQ. Of these, 25,505 patients (7070 T1D; 18,435 T2D) completed the Part 2 SAQ and 23,627 patients (6822 T1D; 16,805 T2D) completed the patient diary. Mean glycated haemoglobin (HbA1c) at baseline was fairly consistent (between 7.7% and 8.2% [60.7 and 66.1 mmol/mol]) in patients with T1D or T2D across all regions, apart from in SE Asia where HbA1c values were 8.9% and 8.7% (73.8 and 71.6 mmol/mol), respectively.

Globally, the estimated annual incidence of any hypoglycaemia was higher in T1D (73.3 episodes per patient-year (PPY)) compared with T2D (19.3 episodes PPY). The rates of any hypoglycaemia in patients with T1D or T2D were similar across different global populations (Fig. 1a), with the exception of SE Asia where the rate of hypoglycaemia in T1D was lower than in other regions, and comparable with the rate in T2D. Rates of severe hypoglycaemia were also generally similar across geographical regions, although these were higher in patients with T1D from Latin America and lower in SE Asia, compared with other regions (Fig. 1b).

3.1. Health economic impact of hypoglycaemia

The direct and indirect economic impacts of hypoglycaemia are reported in Table 2. At a global level, the most prevalent direct impact of hypoglycaemia was increased blood glucose monitoring (reported by 69.7% [T1D] and 60.9% [T2D] of patients). Patients increased the frequency of blood glucose monitoring over the 4-week prospective period following an episode of hypoglycaemia, resulting in 7.9 ± 11.3 extra test

strips used by patients with T2D and 5.7 ± 8.4 extra test strips used by patients with T1D, per hypoglycaemic episode. Further, greater increases in the number of extra test strips used were found in patients with a greater prior experience of hypoglycaemia (Supplementary Table 1). When comparing those with no pre-baseline history of hypoglycaemia with those with over 30 prior events, the mean number of additional test strips used following any subsequent hypoglycaemia event was approximately three-fold higher (T1D, 6.4 ± 8.7 vs. 19.7 ± 24.0 ; T2D, 4.7 ± 6.9 vs. 12.5 ± 9.3).

Other direct economic impacts during the 4-week prospective period included a marked increase in medical contact following a hypoglycaemic episode – as measured both for clinic visits and for telephone contacts with the patients' HCPs. Globally, the prevalence of seeking extra HCP contact following hypoglycaemia was 3.8% for T1D, needing a mean of 1.6 ± 1.0 visits each, and 6.8% for patients with T2D, who needed a mean of 1.5 ± 1.1 visits each. Interestingly, there was a wide regional variation in HCP contact – for example, among patients with T2D the highest rates were seen in Russia, Latin America, SE Asia and Middle East. Similarly, there was a variable impact of hypoglycaemia on hospitalisation when comparing across regions, with hospitalisation highest in Latin America and the Middle East and lowest in Russia. Globally, hospitalisation occurred in 2.1% of patients with T1D and 3.4% of patients with T2D. Admission duration following hypoglycaemia in the 4-week prospective period was quite consistent across types of diabetes: 1.7 ± 2.5 days (T1D) and 1.8 ± 2.3 days (T2D). Among patients with T2D, there was a tendency for regions with a higher prevalence of hospitalisation to also have a higher prevalence of HCP contacts (telephone contact or clinic appointment), and vice versa. While these regional patterns in direct economic effects were generally consistent, exceptions included Russia, which showed the highest rates of HCP contact and lowest rate of hospitalisation.

The indirect costs of hypoglycaemia can be seen in its impact on absenteeism and its inferred impact on presenteeism. Globally, 3.9% of patients with T1D and 6.2% of patients with T2D took days off work because of hypoglycaemia in the 4-week prospective period. For those who took at least 1 day off work, the mean number of days lost from work during the 4-week prospective period were 2.0 ± 2.3 days (T1D) and 1.8 ± 2.1 days (T2D). Of note, the regional impact of hypoglycaemia on loss of work productivity was highly variable – using patients with T2D as an example, the results ranged from a prevalence as low as 0.9% in Northern Europe/Canada to as high as 6.1% in Latin America, 8.2% in the Middle East and 14.6% in SE Asia. Further impacting workplace productivity, the proportion of patients arriving late or leaving early following a hypoglycaemic episode was up to 5.9% for T1D and up to 7.1% for T2D, at the global level, with similar patterns of prominence in the regions of Latin America, Middle East and SE Asia. All the above measures of work/study absenteeism showed a consistent decline in prevalence with advancing age (Supplementary Table 2) and increasing duration of diabetes (Supplementary Table 3), likely a reflection of the highest participation in the work force among the younger patients, or those with the shortest duration of diabetes.

Table 1 – Baseline characteristics of patients with (A) T1D and (B) T2D across the HAT study populations.

Characteristic	Global (n = 8022)	Northern Europe/Canada (n = 2388)	Eastern Europe (n = 3135)	Latin America (n = 531)	Middle East (n = 1124)	Russia (n = 618)	SE Asia (n = 226)
A							
Age, years (SD)	42.1 (15.1)	46.3 (15.3)	42.0 (14.0)	40.1 (16.1)	38.0 (15.7)	37.5 (13.1)	36.8 (14.3)
Male/female, %	48.0/52.0	49.6/50.4	48.3/51.7	39.8/60.2	50.6/49.4	42.4/57.6	48.2/51.8
Duration of diabetes, years (SD)	17.6 (12.0)	21.3 (13.7)	16.8 (11.2)	16.6 (11.7)	15.3 (10.5)	14.5 (9.5)	11.6 (8.0)
Duration of insulin use, years (SD)	17.0 (12.1)	20.7 (13.8)	16.3 (11.2)	15.7 (11.8)	14.2 (10.3)	14.3 (9.5)	9.9 (8.3)
HbA1c, mmol/mol (SD)	62.8 (16.2)	62.3 (14.5)	61.0 (15.7)	65.6 (19.2)	65.6 (16.4)	64.6 (18.5)	73.3 (21.0)
HbA1c, % [*]	7.9	7.9	7.7	8.2	8.2	8.1	8.9
Characteristic	Global (n = 19,563)	Northern Europe/Canada (n = 3877)	Eastern Europe (n = 6369)	Latin America (n = 1660)	Middle East (n = 3073)	Russia (n = 737)	SE Asia (n = 3847)
B							
Age, years (SD)	60.8 (10.9)	65.6 (10.5)	62.5 (9.3)	61.2 (11.9)	58.0 (11.5)	60.3 (8.9)	55.3 (10.4)
Male/female, %	52.5/47.5	56.3/43.7	48.7/51.3	43.6/56.4	56.5/43.6	28.4/71.6	60.5/39.5
Duration of diabetes, years (SD)	13.7 (8.2)	15.4 (8.9)	13.6 (7.9)	14.6 (9.0)	14.9 (8.3)	12.5 (7.3)	10.9 (6.9)
Duration of insulin use, years (SD)	6.4 (5.6)	8.3 (6.7)	7.1 (5.8)	5.7 (5.3)	5.6 (5.3)	6.1 (4.7)	4.0 (3.5)
HbA1c, mmol/mol (SD)	64.2 (16.3)	60.3 (14.5)	60.9 (15.0)	64.9 (18.8)	68.6 (16.0)	64.3 (15.2)	71.8 (17.0)
HbA1c, % [*]	8	7.7	7.7	8.1	8.4	8	8.7

Analyses based on full analysis set. n is defined as the total number of participants.

^{*} Calculated, not measured. HbA1c, glycated haemoglobin; SD, standard deviation; SE, Southeast; T1D, type 1 diabetes; T2D, type 2 diabetes.

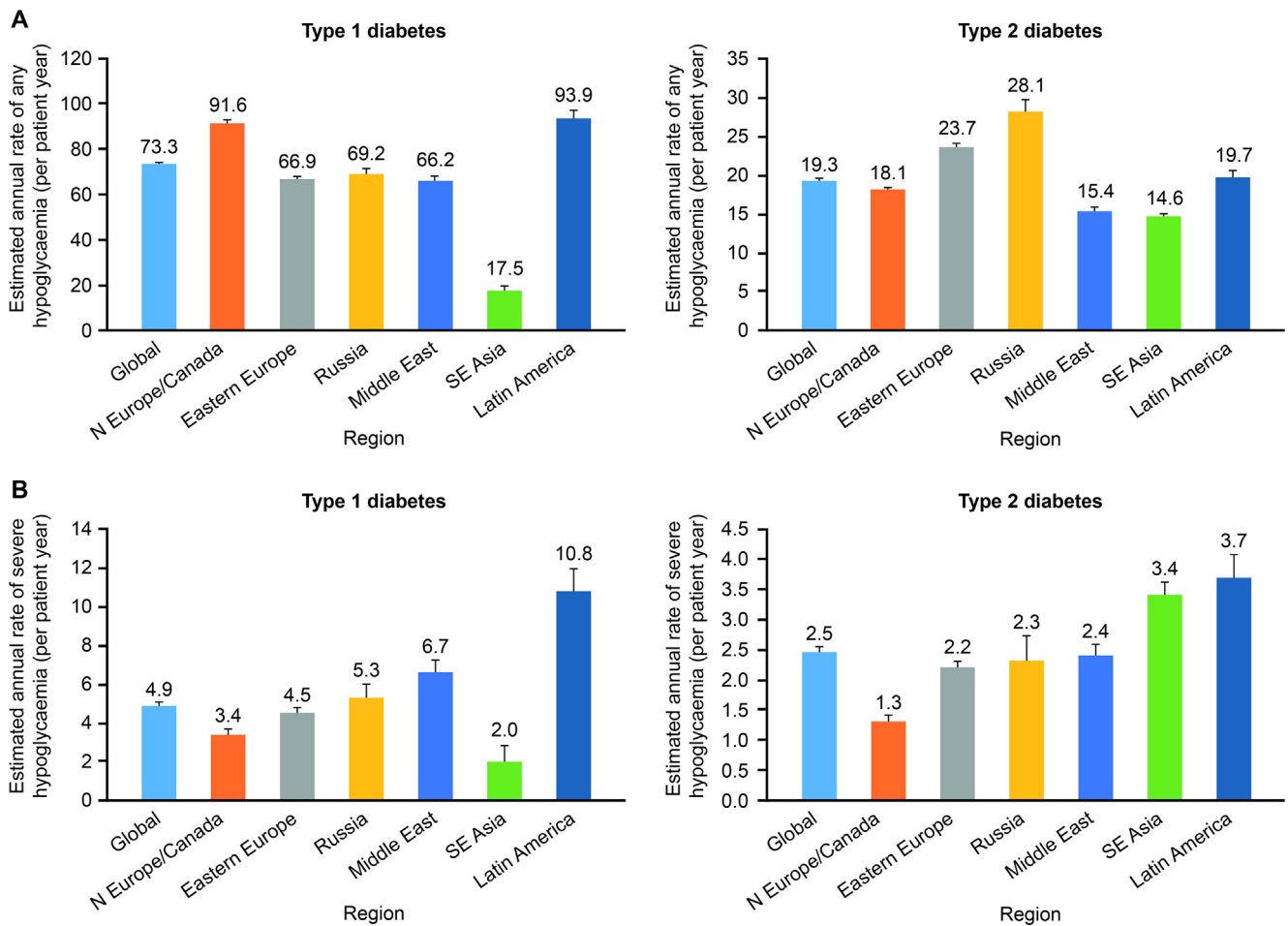


Fig. 1 – Estimated annual rates of any (A) and severe (B) hypoglycaemia during the prospective period by geographical region in the HAT study population in patients with type 1 and type 2 diabetes. Data are presented as mean (SD). N, Northern; SE, Southeast.

4. Discussion

These data from the global HAT study confirm that hypoglycaemia results in an increase in healthcare utilisation, contributing to an increased economic burden of diabetes management on healthcare payers in those countries where costs are not borne solely by patients. The global healthcare expenditure on diabetes in 2014 was estimated to be at least USD 612 billion, although large variations exist in expenditure per person between different regions [15,16] – at 87% lower than the global average, the SE Asia region had the lowest expenditure per person [15]. In general, the direct costs of diabetes tend to be greater than the indirect costs, particularly in high-income countries [17]; in the USA, hospital inpatient care accounted for 43% of total diabetes-related medical costs [18]. The global HAT study shows that following a hypoglycaemic episode, there is an increase in direct costs through increased use of self-management supplies and accelerated healthcare resource utilisation. Indirect costs are increased through resulting increases in workplace absenteeism and reduced productivity through presenteeism, given the documented late arrivals and early departures. Regional variations

in the economic impact were observed and these may have important implications for expenditure at national level.

Healthcare utilisation following a single episode of hypoglycaemia was similar across most regions; however, the increased number of HCP contacts and hospital admissions in Latin America (T1D and T2D) and SE Asia (T2D), compared with the global average, may reflect the higher proportion of severe hypoglycaemia versus non-severe hypoglycaemia in these populations. It may also reflect regional differences in healthcare organisation and delivery, as well as cultural differences in healthcare-seeking behaviour. In developing countries, a substantial amount of diabetes-related healthcare costs are paid by the patient, particularly for people with low-income and no healthcare coverage [17], which may account for differences in healthcare-seeking behaviours in comparison with high-income countries. In regards to self-assessed health there are inequalities between socioeconomic groups and the degree of inequality varies between countries [19], furthermore, in some regions it is estimated that only 45% of patients are aware of their diabetes status and while lower levels of education are associated with increased odds of developing diabetes, there is no association

Table 2 – Economic effects in response to hypoglycaemia in patients with T1D and T2D across the global HAT study population.

Patient response to hypoglycaemia		Global	Northern Europe/ Canada	Eastern Europe	Latin America	Middle East	Russia	SE Asia
<i>Direct economic effects</i>								
Increased blood glucose monitoring, %	T1D	69.7	62.1	75.7	65.2	61.2	80.9	53.2
	T2D	60.9	57.2	71.9	53.5	57.3	75.6	37.5
Admitted to hospital, %	T1D	2.1	2.1	1.2	5.2	3.6	1.3	3.6
	T2D	3.4	2.9	2.1	6.8	3.8	1.2	6.2
Mean extra number of clinic visits (SD); %	T1D	1.6 (1.0); 3.8	1.5 (1.1); 2.4	1.3 (0.7); 3.0	1.6 (0.9); 2.8 [*]	1.9 (1.2); 7.9	1.5 (1.0); 6.0	2.3 (0.6); 5.7 [*]
	T2D	1.5 (1.1); 6.8	1.4 (1.1); 3.2	1.3 (0.6); 5.1	2.9 (2.2); 5.7	1.5 (0.8); 7.0	1.4 (0.9); 12.3	1.4 (0.6); 12.6
Mean number of extra telephone contact with medical personnel (SD); %	T1D	2.0 (1.8); 8.8	1.5 (0.9); 3.6	2.0 (2.0); 9.2	2.0 (1.5); 10.7	1.8 (0.9); 11.7	2.3 (2.0); 17.1	1.8 (0.8); 8.6 [*]
	T2D	1.7 (1.2); 16.0	1.5 (0.8); 7.3	1.6 (1.0); 14.2	1.7 (1.1); 21.4	1.9 (1.0); 21.4	2.1 (1.7); 17.3	1.9 (1.3); 22.3
<i>Indirect economic effects</i>								
Mean days taken sick leave from work or studies (SD); % of patients in work/study	T1D	2.0 (2.3); 3.9	2.6 (4.3); 2.5	2.3 (2.2); 2.5	2.8 (2.7) 3.3 [*]	1.7 (1.1); 10.1	2.0 (NC); 0.3 [*]	1.4 (0.5); 25.9
	T2D	1.8 (2.1); 6.2	1.0 (0.0); 0.9 [†]	2.8 (5.0); 2.5 [*]	3.0 (2.5); 6.1 [*]	1.5 (1.0); 8.2	NC; 0	1.6 (1.0); 14.6
Mean days arrived late to work or studies (SD); % of patients in work/study	T1D	1.6 (1.1); 5.9	1.6 (1.5); 4.5	1.5 (0.9); 4.3	1.7 (1.2); 7.8 [*]	1.8 (1.3); 11.2	1.3 (0.7); 5.8	1.1 (0.3); 19.8 [*]
	T2D	1.4 (1.2); 6.6	1.6 (1.0); 2.7	1.2 (0.5); 2.7 [*]	1.9 (2.8); 7.1 [*]	1.5 (1.1); 10.3	1.3 (0.5); 4.5 [*]	1.3 (0.7); 11.8
Mean days left work or studies early (SD) days; % of patients in work/study	T1D	1.5 (1.0); 4.6	1.3 (1.0); 2.3	1.5 (0.9); 4.0	1.6 (1.0); 5.3	1.6 (1.1); 7.7	1.4 (0.8); 5.0 [*]	1.6 (1.2); 19.0 [*]
	T2D	1.5 (1.6); 7.1	1.0 (0.0); 0.6	1.8 (3.1); 4.9 [*]	1.1 (0.4); 6.6 [*]	1.6 (1.3); 8.3	1.4 (0.7); 10.0 [*]	1.3 (0.7); 12.4

^{*} n < 20; Data are prevalence of patient response to hypoglycaemia in the 4-week prospective period of the study; percentages are based on the number of patients with evaluable data; NC, not calculated; SD, standard deviation; SE, Southeast; T1D, type 1 diabetes; T2D, type 2 diabetes.

between education level and awareness of diabetic status [20]. Avoidance of severe hypoglycaemic episodes through optimisation of insulin treatment, better patient education, or improved access to blood glucose testing has the potential to reduce the economic impact of hypoglycaemia, particularly when severe.

There were wide differences in the pattern of indirect costs between regions. The mean number of days of work lost to hypoglycaemia were highest in the Middle East, SE Asia and Latin America. The structure of local healthcare services and other societal and cultural factors may in part be responsible for variations in the level of work absenteeism following a hypoglycaemic episode. For example, in countries without paid sick leave, being absent from work can mean the loss of wages, or in extreme cases termination of employment, which could push individuals to work even when they have not fully recovered from the hypoglycaemic episode. Conversely, some healthcare systems inadvertently incentivise hospitals to retain patients for an unnecessarily long duration as a result of remuneration provided by the state [21].

Although non-severe hypoglycaemia may incur a lower cost per episode compared with severe hypoglycaemia, its higher frequency implies a substantial impact on cost to healthcare payers/individuals. Similarly, although the frequency of hypoglycaemia is higher in T1D, the greater, and increasing, prevalence of insulin-using patients with T2D make the total cost of hypoglycaemia in T2D an important health economic consideration for healthcare payers [22]. Ultimately, the cost borne by healthcare providers following a single episode of severe hypoglycaemia is high regardless of diabetes type or country (T1D: Germany, €441; Spain, €577; UK, €236; T2D: Germany, €533; Spain, €691; UK, €537) [8]. Depending on the structure of the healthcare system, these costs may be borne by the government, private insurers or by the patients themselves. However the costs are dealt with, it is clear that hypoglycaemia presents a substantial economic burden.

4.1. Strengths and limitations

The global HAT study is the largest observational study of hypoglycaemia in insulin-treated patients with diabetes, and provides a large patient cohort within which to assess the indirect and direct economic impacts of an episode of hypoglycaemia on healthcare providers and employers. As a result, this study adds significantly to the literature, with few international studies investigating the economic impact of hypoglycaemia and those that do either utilising only retrospective surveys [3,10,23,24] or aggregating data in a meta-analysis from multiple small studies of differing design [9].

This study is subject to several limitations, the foremost being the observational study design and short duration of assessment. However, these characteristics facilitated the enrolment of a large patient population from which meaningful observations regarding the real-life rate and impact of hypoglycaemia could be made. Patients' willingness to participate and local literacy rates are likely to have affected the participant characteristics, thereby introducing selection bias into the study population. No data were collected on the

educational and or socioeconomic level of patients or their history of education related to diabetes management and hypoglycaemia. These factors could play a role in both the occurrence of hypoglycaemic episodes and the utilisation of healthcare services. The subjective definition of hypoglycaemia represents both a strength and a limitation of the study: a strength because it reduces the risk of missed events where patients forgot, or were unable, to test their blood glucose; and a limitation as a result of the potential for confounding. The study did not capture data on ambulance callouts, which can be an additional significant contributor to the cost of treating hypoglycaemia [10,25]. In addition, the 4-week limit of prospectively collected data may introduce uncertainty around extrapolated annual rates. Further, as the economic impacts were measured in response to hypoglycaemia during the previous 4-weeks, any episodes occurring close to the prospective cut-off period may have had impacts beyond this point that were not captured.

4.2. Conclusion

In summary, this study reveals that in addition to higher rates of hypoglycaemia in the real world setting, hypoglycaemia has significant direct and indirect economic consequences for healthcare payers across the globe, the burden of which can fall on the healthcare system or the patients themselves, depending on the country. Efforts to prevent both severe and non-severe hypoglycaemia, through optimisation of insulin treatment, better patient education, or improved access to blood glucose testing may help patients more effectively meet their treatment goals, while alleviating some of the costly impacts of hypoglycaemia on healthcare providers.

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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. Prof. Goldfracht sadly passed away prior to the completion of this manuscript. She played a significant role in the study and this manuscript as acknowledged by her co-authors.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.diabres.2018.01.007>.

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