Persistent burden and management gaps of hypoglycemia in pediatric type 1 diabetes: insights from the Epi-GLUREDIA Study

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Highlights

- **Why did we undertake this study?**

Hypoglycemia remains a major but incompletely characterized burden in pediatric type 1 diabetes despite advances in diabetes technologies.

- **What questions did we want to answer?**

We assessed, in real-world practice, the frequency, awareness, management, and daily-life impact of hypoglycemia and severe hypoglycemia.

- **What did we find?**

Hypoglycemia is frequent in pediatric type 1 diabetes, with marked interindividual variability in symptom thresholds and predominantly cognitive and functional symptoms. Over one-third of participants identified hypoglycemia as their dominant disease burden. Severe hypoglycemia was often unexplained and inconsistently managed, with post-event behavioral adaptations that may adversely affect glycemic control.

- **What are the implications?**

These findings identify persistent gaps in hypoglycemia awareness and care, supporting integrated strategies combining education, behavioral support, optimized technologies, and improved guideline implementation.

Persistent burden and management gaps of hypoglycemia in pediatric type 1 diabetes: insights from the Epi-GLUREDIA Study

Deep hypoglycemia analysis in pediatric T1D

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Summary

Hypoglycemia remains frequent and impactful in pediatric type 1 diabetes, with variable symptom thresholds, unexplained severe hypoglycemia, management gaps, and post-event adaptations that may impair glycemic control.

Abstract

Background/Objectives. - Despite advances in automated insulin delivery, hypoglycemia remains a major challenge in pediatric type 1 diabetes. We aimed to characterize, in real-world practice, the burden, awareness, and daily-life impact of hypoglycemia and severe hypoglycemia (SH), and to identify gaps in perception and management.

Methods. - We conducted a prospective, descriptive, multicenter study using the new GLUREDIA questionnaire, administered during routine pediatric diabetes visits across six centers in Belgium and Luxembourg. This structured, study-specific, semi-quantitative tool assessed hypoglycemia frequency, symptom severity, perceived glycemic thresholds, SH history and management, and post-SH behavioral adaptations. Hypoglycemia awareness was evaluated using items aligned with Clarke score domains.

Results. - Among 232 participants, 55.9% reported hypoglycemia at least weekly, with moderate-to-high symptom severity. Cognitive and daily-life symptoms (impaired focus, fatigue, hunger, tremor) were reported by >60% and interfered with activities. Hypoglycemia was identified as the dominant disease burden by 39.7% of participants. Hypoglycemia-related symptom burden remained substantial and was not fully explained by CGM-derived metrics. SH was reported by 45.7%, without clear cause in 29.1%. Recommended management, including glucagon use, was inconsistently applied, even in recurrent SH. Following SH, participants reported insulin dose reductions (27.4%), increased sugar intake (21.1%), and avoidance of physical activities (22.1%), as adaptations. The Epi-GLUREDIA questionnaire demonstrated promising discriminative ability against the Clarke score (AUC = 0.84), supporting its construct validity.

Conclusions. - Despite advances in diabetes technology, hypoglycemia remains highly prevalent, impactful, and often poorly anticipated in pediatric type 1 diabetes. Gaps in SH management and hypoglycemia awareness, together with post-event adaptations, highlight the need for integrated strategies combining education, behavioral support, optimized use of technologies, and improved implementation of guidelines, including appropriate glucagon use, to improve hypoglycemia safety, recognition, and long-term outcomes in pediatric type 1 diabetes.

Keywords: Adolescents/Children; Glucagon; Hypoglycemia; Hypoglycemia Awareness; Pediatric Diabetes; Severe Hypoglycemia; Type 1 Diabetes

Type 1 diabetes is a heterogeneous disorder involving the destruction of pancreatic β cells, which results in varying degrees of insulin deficiency. Type 1 diabetes accounts for 5%-10% of total diabetes cases worldwide [1]. After achieving partial remission, a progressively growing dependence on exogenous insulin induces an increase in glycemic variability and a rise in the risk for hypoglycemia [2]. In fact, achieving near-normoglycemia in children and adolescents with type 1 diabetes using multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) is inherently associated with hypoglycemia risk due to the limitations of exogenous insulin delivery and imperfect glucose monitoring [3–8]. This is particularly the case in younger children who may not recognize or communicate symptoms, in those without access to advanced technologies or with hypoglycemia unawareness (HUA) [9]. Currently, although severe hypoglycemia (SH) rates have declined over time, time spent below range (TBR, <7 0 mg/dl) remains present in most pediatric cohorts, with average values of 3–11% reported in real-world studies [8,10,11].

Hypoglycemia encompasses a spectrum of acute clinical conditions that can be classified according to severity and associated risk [12]. Level 1 hypoglycemia is defined as a measurable glucose concentration below 70 mg/dl. Level 2 hypoglycemia corresponds to a measurable glucose concentration below 54 mg/dl and is accompanied by symptoms of neuroglycopenia requiring action to resolve the hypoglycemic event. Level 3 hypoglycemia is defined as SH involving severe cognitive impairment (including coma and convulsions) and requiring assistance by another person for recovery [13]. As stated by the ISPAD as a level A recommendation, SH requires urgent treatment. In the ambulatory setting, subcutaneous (SC), intramuscular (IM) or intranasal (IN) glucagon should be given. In a hospital setting, intravenous glucose can be administered. Glucagon should be readily accessible to all caregivers. Education on the technique of administration of glucagon is essential [13].

However, proper treatment and glycemic surveillance require attention from patients or caregivers at all levels of hypoglycemia.

In addition to the burden of recurrent hypoglycemia, low glucose levels expose people with type 1 diabetes to SH including seizures, loss of consciousness, injury, and substantial psychosocial stress [13,17,18]. The prevalence of SH in children and adolescents with type 1 diabetes is approximately 5% in contemporary cohorts, with annual incidence rates ranging from 1.2 to 19 episodes per 100 patient-years depending on population, age, and treatment modality [14–16]. For some patients, hypoglycemia unawareness (HUA) and impaired counterregulatory responses (CRR) may increase vulnerability to recurrent SH episodes. Decreased glucagon secretion in response to hypoglycemia has been observed in pediatric and adult people with type 1 diabetes [19,20], and was recently mechanistically linked to an impaired beta-to-delta cell coupling [21]. In our Epi-GLUREDIA (GLUcagon Response to hypoglycemia in pediatric type 1 DIAbetes) study, we aimed to better understand how pediatric people with type 1 diabetes respond to hypoglycemia, and to provide a comprehensive, descriptive overview of the burden, awareness, and daily-life impact of hypoglycemia and SH events in real-world pediatric clinical settings. By integrating symptom perception, glycemic thresholds, SH etiology, management practices, and post-event behavioral adaptations within a single multicenter cohort, this study aimed to move beyond descriptive frequency estimates and provide clinically actionable insights into hypoglycemia vulnerability in pediatric practice.

1. Design and methods

The Epi-GLUREDIA study was part of the GLUREDIA consortium study (clinicaltrial.gov NCT06770621) and involved pediatric diabetes departments in Belgian (n=5) and Luxembourg (n=1) hospitals. The study was conducted in accordance with the Declaration of Helsinki and the General Data Protection Regulation (EU 2016/679), and ethical approval was granted by

the Hospital Faculty Ethics Committee (*Cliniques universitaires Saint Luc* – UCLouvain, 2022/02/FEV/043). Data were pseudonymized and processed in compliance with applicable Belgian data protection legislation. All participants provided informed consent for the use of their clinical data in the Epi-GLUREDIA study.

1.1 Primary and secondary objectives

The primary objective of the study was to describe the frequency, sensitivity, and perception of hypoglycemia symptoms, as well as how these parameters evolve over time in children and adolescents with type 1 diabetes. Secondary objectives included evaluating the impact of hypoglycemia on quality of life, providing an overview of SH and its causes and treatments in these people.

1.2 Design

This prospective, descriptive, non-interventional, multicentric, and questionnaire-based study was conducted during routine pediatric diabetes consultations. The study lasted 20 months. Patient enrollment began in April 2024 and ended in December 2025.

Participants in the research protocol were followed up during routine assessments within the diabetes convention of care. This includes a minimum of 4 visits per year to the clinical site, blood glucose self-monitoring equipment, and multidisciplinary management by the pediatric diabetology team. Interstitial continuous glucose monitoring (CGM) (Freestyle libre 3™, Dexcom One Plus™, Dexcom G7™, Medtronic Simplera (Plus)™) was recorded during each routine visit. Glycemic variability was evaluated by analyzing the following parameters: mean glucose level, glucose level standard deviation (SD), and glucose level coefficient of variation (CV), percentage of normoglycemia, insulin-dose-adjusted hemoglobin A1c, and glycemic-target-adjusted hemoglobin A1c. The analysis of physical activity and fear of hypoglycemia was based on the validated Physical Activity Questionnaire for Children/Adolescents (PAQ-

C/PAQ-A) [22,23] and Hypoglycemia Fear Survey (HFS-II) respectively [24]. During these consultations, attending physicians were available to answer patients' questions.

A GLUREDIA team member recruited participants and caregivers during routine visits to obtain informed consent for participation in Epi-GLUREDIA. Participants completed the Epi-GLUREDIA questionnaire at their next scheduled inpatient visit.

1.3 Population

The study population included male and female participants diagnosed with type 1 diabetes according to the criteria of the International Society for Pediatric and Adolescent Diabetes (ISPAD) and the American Diabetes Association [25]. These criteria were as follows: symptoms of hyperglycemia (polyuria, polydipsia, or ketoacidosis); fasting blood glucose ≥126 mg/dL and/or blood glucose ≥ 200 mg/dl at the 120th minute of an oral glucose tolerance test and/or HbA1c ≥ 6.5%, and/or a patient with symptoms of hyperglycemia/hyperglycemic crisis and random blood glucose ≥ 200 mg/dl; presence of one or more anti-islet autoantibodies (anti-insulin, anti-IA2, andti-GAD65, and anti-ZnT8). Participants must also have had type 1 diabetes for more than 2 years and be between 2 and 18 years old. All treatment modalities (i.e. MDI, CSII and hybrid closed loops (HCL)) were allowed.

The exclusion criteria were as follows: children under 2 years of age; participants taking treatments that interfere with insulin secretion and sensitivity (*e.g.,* sulfonylureas, diazoxide, somatostatin, methylxanthine derivatives, corticosteroids, biguanides, and incretins); participants with autoimmune/autoinflammatory disease (other than type 1 diabetes) or active malignant pathology present at inclusion; participants with a body mass index z-score superior to 3 standard deviations; participants with hepatic, renal, or adrenal insufficiencies; participants with a history of bone marrow allogeneic transplantation; participants with a history of diabetes post-hemolytic-hemolytic syndrome; epileptic participants; participants with dysmorphia and

suspected underlying genetic syndrome; participants in another study within the previous three months involving the administration of blood derivatives or immunomodulatory treatments.

Oral and written informed consent was obtained from each participant and/or legal guardian before enrollment.

1.4 Questionnaire completion

Participants and their caregivers completed the structured, study-specific Epi-GLUREDIA questionnaire. The full questionnaire is presented in the **Supplemental Material** section (**see Suppl. Data 1 associated with this article on line**). This tool includes several sections: hypoglycemia frequency, symptom perception and severity, hypoglycemia threshold, impact on daily activities and relative burden, as well as SH events and their management. Most questions assessed the preceding 3 months, while SH history covered up to 5 years of diabetes evolution. Post-event adaptations were assessed as self-reported changes in behavior or treatment following severe hypoglycemia events, without specification of timing, duration, or effectiveness. Participants also completed the Clarke questionnaire [26] to assess HUA and ensure clinical relevance and interpretability.

To further characterize hypoglycemia perception, we developed a composite hypoglycemia sensitivity score based on selected items from the Epi-GLUREDIA questionnaire. The score integrates multiple dimensions of hypoglycemia experience, including symptom frequency, symptom recognition, symptom intensity, number of symptoms, perceived glycemic threshold, and impact on daily activities. Individual items were assigned weighted scores according to their clinical relevance, and total scores were used to classify participants into three predefined categories: hypoglycemia-insensitive (HIS), hypoglycemia-normosensitive (NS), and hypoglycemia-hypersensitive (HHS).

To assess construct validity, the hypoglycemia sensitivity score was cross-validated against the Clarke score in participants with complete data for both instruments. Clarke classification was

used as the reference standard for impaired awareness of hypoglycemia. Agreement between classifications was assessed using Cohen's kappa coefficient and overall concordance. Discriminative ability of the hypoglycemia sensitivity score to identify impaired awareness was evaluated using receiver operating characteristic (ROC) analysis with calculation of the area under the curve (AUC). Sensitivity and specificity were estimated at predefined thresholds based on score distribution and clinical interpretability.

1.5 Data management and analyses

Data were entered into REDCap based on pseudo-anonymization. Personal identifiers were stored separately, and access to them was restricted to authorized study team members, and the GLUREDIA study team managed the database's content. Analyses were descriptive. Categorical variables are presented as counts and percentages, and continuous variables as appropriate. No formal hypothesis testing was performed, consistent with the descriptive design. Missing data were not imputed; analyses were performed on available data, and denominators are reported for each variable. Analyses were primarily descriptive. Exploratory statistical tests (including nonparametric and χ^2 tests) were performed to assess differences between groups, without prespecified hypotheses. Although CGM-derived metrics were collected as part of routine clinical care, the present analysis focuses on questionnaire-based outcomes, and CGM data were not included except for summary glycemic metrics (e.g., TBR) used for demographics and exploratory. Statistical analyses were conducted using GraphPad Prism 11 (Version 11.0.0[93], February 10, 2026). Figures were generated using GraphPad Prism, with minor graphical formatting supported by Napkin AI; no artificial intelligence tools were used for data analysis or statistical computations.

1.6 Data and resource availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

2. Results

A total of 232 participant records were analyzed. Demographic characteristics are summarized in **Table I**. Type 1 diabetes duration was two years for 12.6% (29/230), three years for 12.6% (29/230), four years for 15.7% (36/230), and more than five years for 59.1% (136/230). CGM measurements were available for 96.5% of participants.

2.1 Hypoglycemia frequency and symptom burden

More than half of the participants (55.9%) experienced symptoms of hypoglycemia at least weekly. Only a small percentage (9.2%) never or rarely experienced these symptoms (**Figure 1A**). The symptoms were moderate to severe in intensity for most with 6.6% of participants considering them as dangerous.

Cognitive and daily-life symptoms, such as impaired focus (69.6%, 160/230 participants), fatigue (70.0%, 161/230), hunger (63.9%, 147/230 participants), and tremor (63.5%, 146/230 participants), were reported by more than 60% of participants and were associated with substantial interference in daily functioning. Indeed, 57.0% (131/230) of participants reported a decline in performance, whether physical or cognitive (**Figure 1B**). Additionally, 30.9% (71/230) of participants reported discontinuing planned activities at least once a week due to hypoglycemia. Of note, over a third of participants (39.7%, 91/229) identified hypoglycemia as their dominant disease burden.

We found that TBR did not differ significantly between participants reporting very frequent symptoms and those reporting never/rare symptoms (Mann–Whitney $P = 0.74$), nor when analyzed using clinically relevant TBR categories (< 4%, 4–10%, >10%) (Fisher's exact $P = 0.39$). Similarly, hypoglycemia symptom frequency was not significantly associated with insulin regimen, including HCL use (Fisher's exact $P = 0.17$).

2.2 Glycemic threshold for symptom perception

The distribution of glycemic thresholds for hypoglycemia symptom perception showed substantial inter-individual variability: nearly one-quarter of participants (24.2%, 56/231) had a high glycemic threshold for experiencing symptoms of hypoglycemia (> 70 mg/dl; **Figure 1C**), whereas a third had a threshold between 60 and 69 mg/dl (34.6%, 80/231) and another third between 50 and 59 mg/dl (31.2%, 72/231). A smaller portion had glycemic thresholds between 40 and 49 mg/dl (6.1%, 14/231) and below 40 mg/dl (3.9%, 9/231). Glycemic thresholds were significantly associated with age, with higher thresholds observed in older participants (Kruskal-Wallis, $P = 0.03$). Mean age increased progressively across threshold categories, from 11.5 ± 3.0 years (< 40 mg/dl) to 14.7 ± 3.6 years (> 70 mg/dl) (**Figure 1D**). However, in exploratory multivariable analyses including age, diabetes duration, HCL use, HbA1c, and TBR, the unadjusted association between age and glycemic threshold category was no longer observed. A subgroup analysis was performed comparing participants reporting very regular hypoglycemia symptoms (i.e. more than once weekly) with those reporting rare or no symptoms. The distribution of glycemic thresholds for symptom perception differed significantly between the groups (χ^2 test, $P = 0.0007$). Participants reporting very regular symptoms of hypoglycemia were disproportionately represented in the higher glycemic threshold categories, whereas those reporting rare or no symptoms more frequently reported symptom onset at lower threshold range (**Figure 2**).

HbA1c was slightly but significantly lower in participants reporting very regular hypoglycemia symptoms compared with those reporting rare or no symptoms (7.0 ± 1.2% vs. 7.4 ± 1.2%, Mann–Whitney test, $P = 0.03$). No significant associations were observed between symptom frequency and insulin regimen, CGM-derived TBR, SH history, or other clinical variables (all $P > 0.05$). In particular, participants reporting very regular hypoglycemia symptoms did not

exhibit higher TBR values compared with those reporting rare or no symptoms (Mann–Whitney $P = 0.74$), and no association was observed using clinically relevant TBR categories (< 4%, 4–10%, > 10%) either (Fisher's exact $P = 0.39$).

When asked, the symptom perception over time, since diabetes primary onset, decreased for 20.3% (47/231) of participants, increased for 26.4% (61/231), and remained the same for 53.2% (123/231).

2.3 Severe hypoglycemia and etiology

Nearly half of participants (45.7%, 106/232) reported a history of severe hypoglycemia, with 46.6% (49/105) reporting three or more episodes. Among participants reporting SH, the median number of events was 2 (interquartile range 1–3) and the estimated incidence of SH was approximately 43 events per 100 patient-years. During severe hypoglycemia events, 53.4% (55/103) experienced loss of consciousness and 31.1% (32/103) reported seizures, consistent with established definitions of severe hypoglycemia and supporting the validity of event reporting. Among participants with SH, around 71.8% (74/103) were treated with MDI and 28.2% (29/103) with CSII; among those using CSII, six participants (20.6%) were treated with HCL systems, corresponding to 5.8% of the total SH subgroup.

As shown in **Figure 3A**, the reported etiology of SH was attributed to insulin in 32.0% (33/103) of cases, dietary errors in 24.3% (25/103), physical activity in 20.4% (21/103), and remained unknown in 29.1% (30/103). Other reported causes, including intercurrent illness or heat exposure, accounted for 9.7% (10/103) of episodes.

2.4 Management of severe hypoglycemia

Despite structured education on recognition and management of SH provided during routine diabetes follow-up visits, in accordance with international pediatric diabetes guidelines (e.g., from ISPAD [13]) and including training in glucagon administration, nearly half of participants

(49.0%, 48/98) reported use of oral carbohydrates rather than available IM or IN glucagon treatment options (**Figure 3B**). Among participants experiencing recurrent SH, this pattern of suboptimal rescue management did not improve over time, with oral carbohydrate use remaining frequent (49.0% at first episode vs. 54.5% at ≥ 5 episodes). In contrast, glucagon use increased from 30.6% at the first episode to 45.4% at ≥ 5 episodes, while overall emergency room visits and hospitalizations decreased from 39.7% to 27.3% (**Figure S1; see supplementary materials associated with this article on line**).

2.5 Post-event behavioral and therapeutic adaptations

Participants reporting SH also described several self-reported behavioral and therapeutic adaptations following these events. Approximately half of participants (51.6%, 49/95) reported increasing the frequency or quality of self-glucose monitoring, whereas 27.4% (26/95) reported reductions in total daily insulin dose. In addition, 21.1% (20/95) reported increased sugar intake, and 22.1% (21/95) reported avoidance of physical or social activities (**Figure 3C**). The questionnaire did not capture the precise timing, duration, or clinical outcomes of these adaptations.

2.6 Clarke Score cross-validation

Cross-validation of the hypoglycemia sensitivity score against the Clarke questionnaire was performed in 65 participants with complete data. The hypoglycemia sensitivity score demonstrated high overall concordance with Clarke classification (92.3%) and moderate agreement (Cohen's $\kappa = 0.62$). ROC analysis showed good discriminative ability for identifying impaired awareness as defined by the Clarke questionnaire (AUC = 0.84), with a sensitivity of 62.5% and specificity of 96.5% (**Table II, Figure S2; see supplementary materials associated with this article on line**).

3. Discussion

While strict glucose control in type 1 diabetes reduces the risk of chronic disease complications, it also increases the number of hypoglycemic events [27]. Despite major advances in glucose monitoring and insulin delivery, hypoglycemia remains a persistant clinical challenge in pediatric type 1 diabetes, contributing substantially to the lived burden for people with type 1 diabetes and their caregivers [17,28]. In this multicenter cohort, more than half of children and adolescents reported weekly symptomatic hypoglycemia, despite CGM use in over 95% of participants. In routine practice, these data extend beyond trial and registry observations, indicating that while CGM reduces TBR, particularly when combined with HCL systems, hypoglycemia remains frequent in youth [29–31]. Importantly, frequent symptomatic hypoglycemia was not associated with higher CGM-derived TBR in our cohort, suggesting that patient-reported hypoglycemia burden may persist despite apparently acceptable glucose metrics. Although numerically fewer participants using HCL reported very frequent symptoms, treatment modality alone did not explain symptomatic hypoglycemia burden. This reinforces that technological advances alone are insufficient to address the complex physiological, behavioral, and educational factors that predispose young people to recurrent hypoglycemia.

The symptomatic burden observed in this study was substantial and clinically meaningful. Moderate to severe symptoms were common, and impaired focus, fatigue, hunger, and tremor frequently interfered with both intellectual and physical activities. More than one-third of participants identified hypoglycemia as the dominant disease burden, exceeding insulin therapy and dietary constraints. From a clinical standpoint, these findings emphasize that hypoglycemia is not merely a metabolic complication but a major determinant of daily functioning and quality of life during critical developmental periods. Consistent with prior studies [32–34], the frequent interruption of activities and perceived performance impairment highlight how hypoglycemia is detrimental to day-to-day experiences in children and adolescents with type 1 diabetes and contributes substantially to disease burden.

A key contribution of this study is the detailed characterization of inter-individual variability in glycemic thresholds for symptom perception. Nearly one-quarter of participants reported symptom onset at glucose values > 70 mg/dl, whereas 10% reported markedly attenuated or absent symptoms at low glucose levels. This broad distribution provides real-world evidence of heterogeneous hypoglycemia awareness in pediatric type 1 diabetes. From a pathophysiological perspective, these patterns are consistent with progressive impairment of counterregulatory responses (CRR), including defective epinephrine and glucagon secretion, which characterize hypoglycemia-associated autonomic failure (HAAF) [18]. Importantly, these findings suggest that symptom thresholds and awareness phenotypes may serve as early markers of physiological vulnerability, even among people with access to advanced diabetes technologies. Moreover, although relative hypoglycemia —defined as the occurrence of hypoglycemic symptoms at glucose levels within or above the normal range (≥70 mg/dl) [35] —is more prevalent in people with poor diabetes control, it may also indicate an exacerbated autonomic status or deficient CRR.

The association between age and glycemic thresholds for hypoglycemic symptoms is well established [36] and further refines this interpretation. Although higher thresholds were associated with older age in unadjusted analyses, exploratory adjusted analyses did not identify independent associations with age or diabetes duration, suggesting that hypoglycemia awareness likely reflects a multifactorial phenotype shaped by interacting physiological, developmental, and behavioral factors.

Subgroup analyses showed that participants reporting very regular hypoglycemia exhibited a significantly different distribution of glycemic thresholds compared with those reporting rare or no symptoms. This suggests that symptom frequency is not merely a reflection of glycemic exposure but may be linked to distinct awareness phenotypes. Frequent symptomatic episodes

were associated with symptom onset at higher glucose levels, which may reflect heightened sensitivity or anticipatory awareness of falling glucose. Importantly, no significant differences were observed in insulin regimen or SH history between these groups, suggesting that awareness phenotypes may not be fully explained by treatment modality or prior severe events. This finding reinforces the concept that symptom perception represents an independent dimension of hypoglycemia vulnerability in pediatric type 1 diabetes.

The present study also introduces a multidimensional hypoglycemia sensitivity score (HSS) derived from the Epi-GLUREDIA questionnaire. The HSS demonstrated good discriminative ability and moderate agreement with the Clarke questionnaire, supporting the construct validity of this approach. Unlike the Clarke score, which primarily provides a binary classification of hypoglycemia awareness, the HSS captures multiple dimensions of hypoglycemia perception, including symptom frequency, intensity, and functional impact. This may allow a more granular characterization of hypoglycemia experience in pediatric populations. However, further validation in independent cohorts remains warranted.

SH remained alarmingly frequent in this cohort, with nearly half of participants reporting at least one event and a substantial proportion experiencing recurrent episodes. Although some degree of recruitment or participation bias toward individuals with greater hypoglycemia burden cannot be excluded, the observed incidence remains clinically concerning and aligns with the persistent vulnerability to SH reported in pediatric type 1 diabetes cohorts despite technological advances. Direct comparison with registry-based estimates should be interpreted cautiously, as the present study assessed cumulative self-reported SH history over multiple years of diabetes evolution, whereas national quality audits such as the Belgian IPQED reports generally capture SH occurrence over shorter predefined periods. Nevertheless, the observed burden remains substantial. The high rates of loss of consciousness and seizures

confirm the clinical severity of these events. Notably, the etiology of SH remained unknown in approximately one-third of cases. This proportion is clinically meaningful. Prior work by our team has shown that SH in pediatric type 1 diabetes does not consistently follow steep glucose declines and that glucose nadirs preceding SH may be modest, suggesting that a subset of episodes arises from atypical or physiologically unpredictable glycemic patterns [37,38]. When considered alongside the findings in the present study, this supports the concept that unrecognized defects in CRR or early HAAF may contribute to the "unexplained" SH category, rather than these events being caused solely by errors in insulin dosing, dietary intake, or physical activity.

The substantial proportion of unexplained SH is unlikely to be attributable to recall bias alone. In routine care, SH events are systematically reviewed at each follow-up visit, and parents typically recall these episodes with precise timing. Moreover, many SH events result in medical evaluation, allowing objective verification. Together, these considerations suggest that the observed proportion of unexplained SH reflects true underlying physiological and situational complexity, highlighting important limitations of current risk stratification approaches in pediatric diabetes.

Management patterns further revealed persistent implementation gaps. Despite structured education and access to glucagon, nearly half of participants reported treating SH with oral carbohydrates rather than guideline-recommended rescue therapy. Although increased glucagon use and fewer emergency department visits were observed over time in participants with recurrent SH, oral treatment remained the predominant response. This pattern points to a disconnect between education, access, and real-world implementation of recommended rescue strategies, with important implications for hypoglycemia safety.

Post-event adaptations illustrate how SH reshapes diabetes management in everyday life. Reductions in insulin dosing, increased carbohydrate intake, and avoidance of physical or social activities were frequently reported. While some of these adjustments may represent appropriate safety-oriented therapeutic optimization, others may reflect avoidance behaviors that could adversely affect glycemic stability. In practice, these patterns may contribute to a cycle of post-hypoglycemia reactive hyperglycemia [39], recurrent hypoglycemia, and increasing management complexity. However, the temporal relationship between SH events and reported behavioral adaptations could not be determined, as the questionnaire did not capture when these changes occurred or their duration. Similarly, the effectiveness of these adaptations in reducing subsequent hypoglycemia risk or improving glycemic control could not be assessed. These findings should therefore be interpreted as self-reported responses rather than demonstrated longitudinal outcomes. Importantly, such adaptations may reflect both appropriate safety-oriented strategies and potentially maladaptive behaviors, such as avoidance of physical activity or increased carbohydrate intake, which could contribute to glycemic instability.

Beyond quantifying burden, this study adds value by integrating symptom burden, glycemic thresholds for symptom perception, SH etiology, management practices, and post-event behavioral and therapeutic adaptations within a single real-world pediatric cohort. This integrated phenotyping approach moves beyond frequency estimates and provides clinically actionable insight into hypoglycemia vulnerability. In parallel, recent work by Harvengt *et al.* has shown that machine learning approaches can prioritize high-risk hypoglycemia events over milder episodes [38], further supporting the need for improved clinical risk stratification tools. Within this context, cross-alignment of the study-specific GLUREDIA questionnaire with the Clarke framework positions this tool as a pragmatic candidate for routine clinical phenotyping

of hypoglycemia awareness and risk, supporting future validation and potential implementation in pediatric diabetes care.

Taken together, these data indicate that pediatric hypoglycemia is a multifactorial clinical problem driven by interacting physiological, behavioral, and implementation factors. Meaningful reductions in hypoglycemia burden will likely require strategies that extend beyond technology alone to include early identification of physiological vulnerability, reinforcement of guideline-based rescue management, and targeted interventions addressing post-event behavioral responses.

This study has several limitations [40]. As a questionnaire-based study, findings rely on participant and caregiver reporting and may be subject to response and recall bias. Most questionnaire items assessed hypoglycemia experiences during the preceding 3 months, whereas SH history was collected over a longer retrospective period (up to 5 years of diabetes evolution), which may have introduced heterogeneity in recall accuracy. Nonetheless, SH events are generally memorable, clinically reviewed during routine visits, and often documented in medical records, which likely mitigates substantial misclassification. The multicenter cohort, drawn from Belgium and Luxembourg, may limit generalizability to other settings. However, the sample size was substantial (n=232) with minimal missing data. While the Epi-GLUREDIA questionnaire enables detailed assessment of symptom perception, it does not capture contextual or qualitative dimensions. Finally, although recruitment was prospective, the analyses presented here are cross-sectional in nature; therefore, temporal relationships and causality between hypoglycemia burden, treatment modality, and associated clinical factors cannot be inferred. Planned longitudinal follow-up within the broader GLUREDIA consortium will be required to assess underlying mechanisms.

In contemporary pediatric type 1 diabetes, hypoglycemia remains frequent, clinically severe, and disruptive, even in technology-rich care environments. Substantial heterogeneity in symptom perception, a high burden of severe and recurrent hypoglycemia—including a clinically meaningful proportion of unexplained events—and persistent gaps in guideline-based rescue management highlight important vulnerabilities in current care paradigms. By integrating symptom thresholds, awareness constructs, SH etiology, and post-event adaptations, the Epi-GLUREDIA study provides a comprehensive real-world framework for identifying pediatric people with type 1 diabetes at heightened risk. These findings support the need for multidimensional clinical strategies that address physiology, education, behavioral responses, and implementation of evidence-based management to meaningfully reduce hypoglycemia burden and improve long-term outcomes in children and adolescents with type 1 diabetes.

Appendix supplementary material

Supplementary materials (Figures S1-S2 and Data S1-S2) associated with this article can be found at http://www.scincedirect.com at doi . . .

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Questionnaire development: Maude Beckers, Philippe Lysy.

Methodology: Philippe Lysy

Investigation / Patient recruitment: Investigators at all participating centers (Saint-Luc, UZA, UZ VUB, CHU Namur, CHL).

Data collection: Local GLUREDIA investigators and study coordinators.

Data curation: Aline Van Maanen and the REDCap Statistical Support Unit.

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Writing – review & editing: All authors.

Supervision: Philippe Lysy.

Project administration: GLUREDIA study team.

Funding acquisition: Philippe Lysy.

Philippe Lysy is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The list of participating investigators is available in the **Supplemental Material** section (**Suppl. Data 2; see supplementary materials associated with this article on line**).

Prior Presentation

Partial results were submitted and accepted as a poster presentation at the 2026 ENDO Congress.

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Figure legends

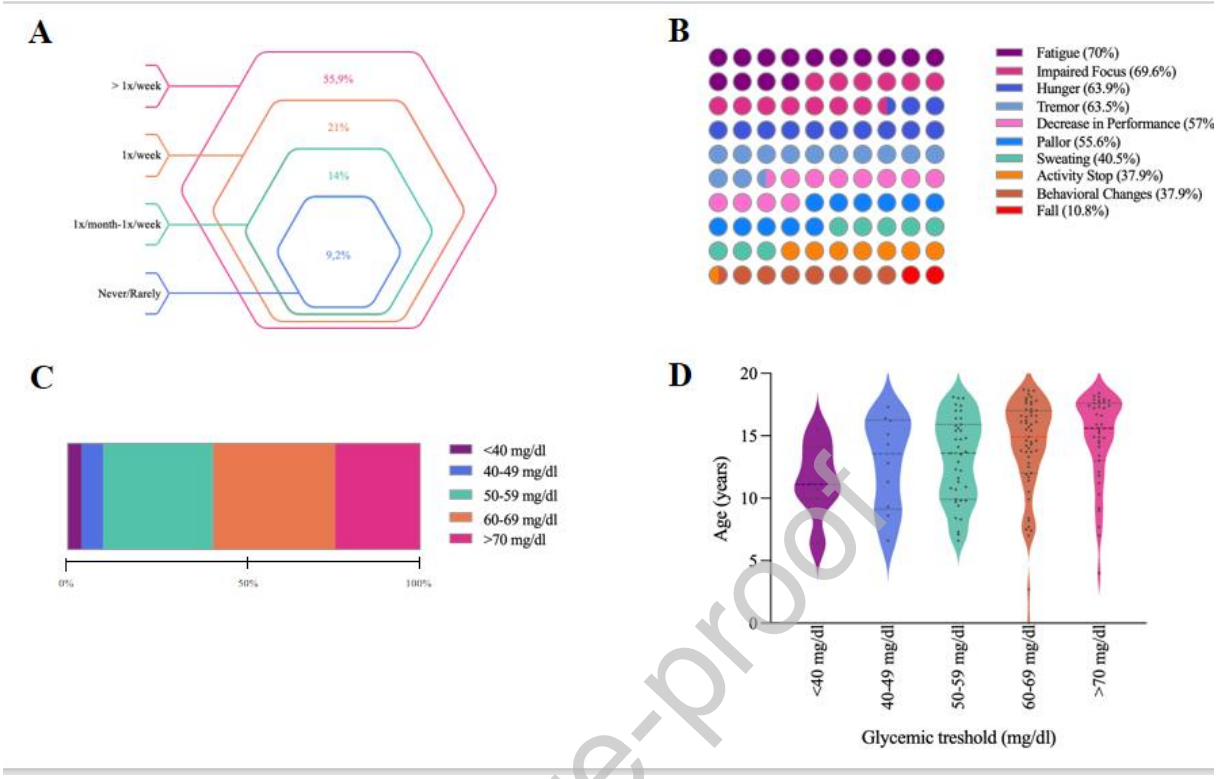


Figure 1. Hypoglycemia frequency, symptom profile, and glycemic thresholds for symptom perception

(A) Reported frequency of hypoglycemic symptoms among study participants. (B) Symptoms experienced during hypoglycemic episodes; participants could report multiple symptoms.

Reported hypoglycemia symptoms are ranked from most to least frequent. Colors indicate symptom categories (cognitive, autonomic, behavioral, and severe manifestations), while the number of dots reflects the relative frequency of reported symptoms.

(C) Self-reported glycemic thresholds for onset of hypoglycemia symptoms. Percentages represent the proportion of participants reporting symptom onset within each glycemic range. (D) Age distribution according to glycemic threshold categories for symptom perception. Violin plots represent the distribution of age within each category, with median and interquartile range indicated. Higher glycemic thresholds were observed in older participants (Kruskal–Wallis test, $P = 0.03$).

Data are expressed as n (%) unless otherwise indicated (n=232).

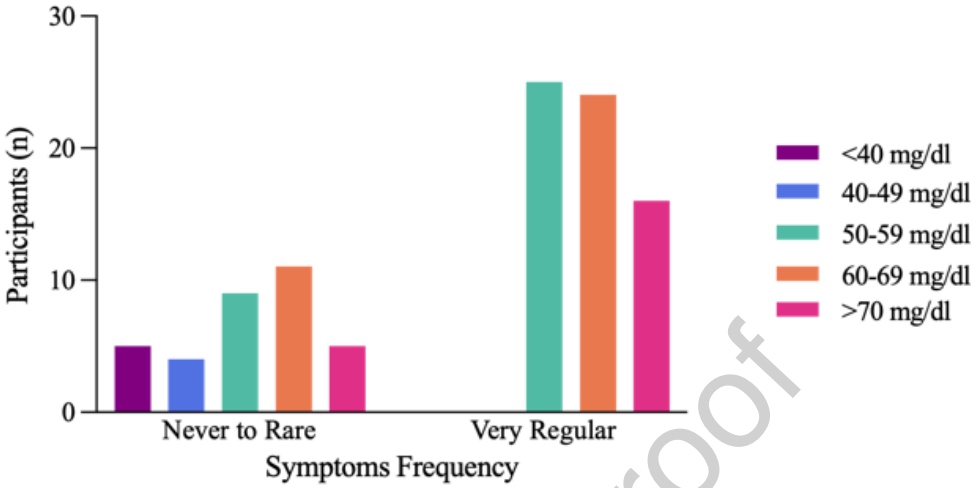


Figure 2. Distribution of glycemic thresholds for symptom perception according to hypoglycemia symptom frequency

Data are expressed as n (%) unless otherwise indicated (n=232).

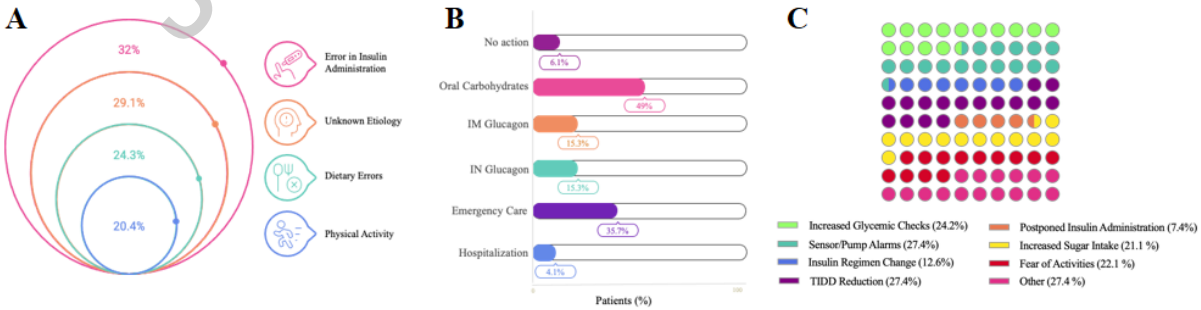


Figure 3. Severe hypoglycemia characteristics in pediatric type 1 diabetes

(A) Reported etiologies of severe hypoglycemia.

(B) Management strategies used during severe hypoglycemia episodes

(C) Behavioral and therapeutic adaptations following severe hypoglycemia.

Data are expressed as percentages of participants who reported a history of severe hypoglycemia (n = 106). Participants could select more than one response where applicable.

Table I. Demographic characteristics of the participants (n=232)

Variable	n	Mean (SD) / n (%)
Age at diagnosis (years)	232	7.8 (3.9)
Gender (male)	232	117 (50.4%)
DKA at diagnosis	215	79 (36.7%)
Age (years)	232	13.8 (3.8)
Diabetes duration (years)	232	6.1 (3.4)
BMI (Z-score)	208	21.6 (4.0) (+0.6 SD)
Puberty (Tanner ≥ 2)	185	141 (76.2%)
Insulin regimen	201	
• MDI		112 (55.7%)
• CSII		39 (19.4%)
• HCL		50 (24.9%)
TIDD (IU/kg/day)	230	0.9 (0.2)
HbA1c (%)	230	7.4 (1.4)
CGM metrics	201	
• TBR		6,6 (6.0)
• TIR		53.7 (17.3)

• TAR	40 (17.9)

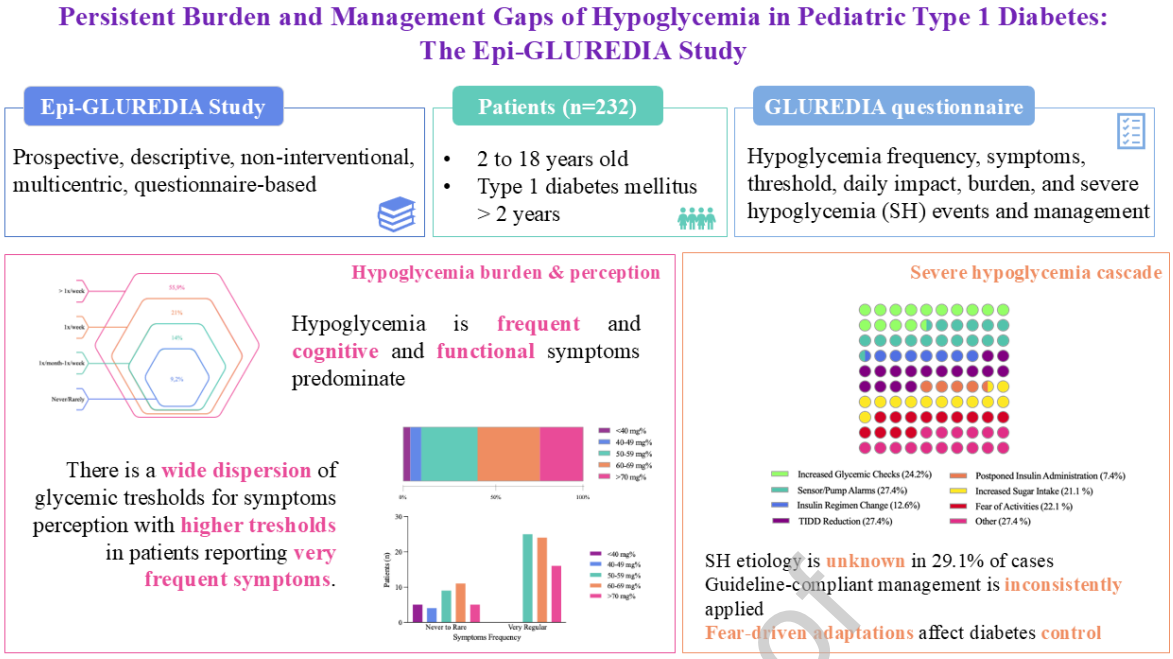
Valid cases (n) vary by variable due to missing data. Percentages are computed relative to n, not the total cohort (n=232).

Abbreviations: DKA, diabetic ketoacidosis; BMI, body mass index; MDI, Multiple Daily Injections; CSII, Continuous Subcutaneous Insulin Infusion; HCL, Hybrid Closed Loop; TIDD, Total Insulin Daily Dose; HbA1c, glycated hemoglobin; CGM, continuous glucose monitoring; TBR, Time Below Range; TIR, Time In Range; TAR, Time Above Range.

Table II. Cross-validation of the hypoglycemia sensitivity score against the Clarke questionnaire

Metric	Value
Participants with complete data	65
Raw agreement	92.3%
Cohen's κ	0.62
Sensitivity	62.5%
Specificity	96.5%
PPV	71.4%
NPV	94.8%
AUC	0.84

Graphical abstract



Declaration of interests

☐The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Philippe A. Lysy reports financial support was provided by The Leona M and Harry B Helmsley Charitable Trust. Maude Beckers reports financial support was provided by Fund for Scientific Research. Philippe A. Lysy reports financial support was provided by Saint-Luc Foundation. Willem Staels reports a relationship with Research Foundation Flanders that includes: funding grants. Willem Staels reports a relationship with Breakthrough T1D that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.