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Assessing awareness of hypoglycemia in children and adolescents with type 1 diabetes: evaluation of established questionnaires

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Assessing awareness of hypoglycemia in children and adolescents with type 1 diabetes: evaluation of established questionnaires

Running title: ***Evaluating pediatric hypoglycemia awareness***

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Abstract

Objective: To evaluate the use of two questionnaires assessing awareness of hypoglycemia, in a pediatric type 1 diabetes (T1D) population.

Methods: Prospective observational study with children (aged 9-18 years) and parents (for children aged 2-11 years) answering the Gold and Clarke questionnaires assessing awareness of hypoglycemia. Psychometric properties of the questionnaires were evaluated, and the most appropriate cut-off score to classify participants as having normal vs. impaired awareness of hypoglycemia (IAH) was determined by ability to recognize subsequent hypoglycemia and hypoglycemia severity, documented in a 4-week blood glucose diary. Questionnaires were re-administered at follow-up assessment approximately 1.5 years later.

Results: In total, 112 participants (51% male) with median (IQR) age 13.7 (11.1-15.8) years, T1D duration 4.7 (2.2-7.8) years, and HbA1c 62 (57-73) mmol/mol (7.8%) were included. Both questionnaires demonstrated acceptable psychometric properties. Using score ≥3 to classify IAH gave a prevalence of IAH of 41% (Gold) and 22% (Clarke). When classified using the Gold questionnaire, IAH participants had higher incidences of mild asymptomatic hypoglycemia, whereas with the Clarke questionnaire, they had higher incidences of clinically significant and severe hypoglycemia. Subgroup analyses confirmed these

associations only in participants aged ≥9 years. Follow-up was completed in 90% of the participants, and a change of awareness status was observed in 22-36%.

Conclusions: The Gold and Clarke questionnaires may be used to assess awareness of hypoglycemia in pediatric T1D in those ≥9 years of age, but the more detailed Clarke questionnaire has higher specificity and is superior in predicting risk of clinically significant hypoglycemia.

Key words: Hypoglycemia; impaired awareness of hypoglycemia; type 1 diabetes; pediatric diabetes

Introduction

Impaired awareness of hypoglycemia (IAH) is an acquired syndrome in people with insulin-treated diabetes, predominantly type 1 diabetes (T1D), and can be defined as a diminished or absent ability to perceive the onset of hypoglycemia[1]. It is associated with a 3 to 6-fold increase in the risk of severe hypoglycemia (SH) both in adult and pediatric populations with T1D[2-6], in which the prevalence of IAH is reported to be 20-25%[4] and 19-37%[5-8], respectively. The pathogenesis of IAH is associated with recurrent exposure to hypoglycemia, which modifies the glycemic thresholds for counterregulation and symptom generation in response to insulin-induced hypoglycemia[1]. Loss of awareness is not an 'all or nothing' process and IAH is recognized to be a dynamic clinical state, which can fluctuate in severity[1]. Awareness of hypoglycemia can be assessed by self-reported questionnaires, the most commonly used being those by Gold et al.[2] and Clarke et al.[3].

Originally developed and used in adults with T1D, the Gold and Clarke scoring systems have good concordance in identifying IAH[9]. However, when they were applied to a pediatric cohort with T1D, the concordance of IAH prevalence was low and the Gold questionnaire appeared to be less reliable in children[7]. Some studies have used a modified version of the Clarke questionnaire[5,6], and uncertainty remains as to what score is the most appropriate cut-off to determine when children have IAH[5,7]. Although these studies indicate that IAH is relatively common in children and adolescents with T1D, a thorough evaluation of these questionnaires has not been undertaken in the pediatric population. IAH should be identified as it is a major risk factor for SH, and is potentially reversible[10].

A prospective study was performed to validate the use of the Gold and Clarke questionnaires in assessing awareness of hypoglycemia in children and adolescents with T1D, and to determine the most appropriate cut-off score to identify IAH in this age group.

Methods

Subjects and setting

Between October 2014 and March 2015, 132 successive patients and their parents attending the pediatric outpatient clinic at St. Olavs Hospital, Trondheim, Norway, were invited to participate in a prospective study. Inclusion criteria were being aged between 2 and 19 years and having a duration of T1D for ≥6 months. Children prescribed medication that may affect autonomic function (i.e. beta-adrenoceptor blockers) were not included. A follow-up assessment was performed between April and December 2016. The study was approved by the Regional committee for medical and health research ethics in Norway (REC Central). Written consent was obtained from adolescents aged >12 years and from the parents of all participants aged <16 years.

Data collection

At inclusion, the participants and/or parent(s) answered the hypoglycemia awareness and fear of hypoglycemia questionnaires described below and subsequently completed a 4-week self-monitored blood glucose (SMBG) diary with assessment of all episodes with blood glucose (BG) ≤3.9 mmol/L (70 mg/dL). Whenever a child was suspected to have symptoms of hypoglycemia, BG was measured, and the child and/or parent(s) completed a questionnaire documenting symptoms, detection, treatment and severity of hypoglycemia, as well as the situation in which it occurred (i.e. during physical activity, sleep or alcohol consumption). Asymptomatic BG measurements ≤3.9 mmol/L (70 mg/dL) were similarly recorded. The questionnaires were re-administered after completion of the BG diary and approximately 1.5 years later (Figure 1). Demographic and clinical data were collected at inclusion (by a web-based system developed and administered by the Unit of Applied Clinical Research, NTNU) and at follow-up, and any history of SH (defined as an episode of hypoglycemia causing loss of consciousness, with or without seizure)[11] was obtained.

Questionnaires

Awareness of hypoglycemia was assessed with the Gold and Clarke questionnaires and fear of hypoglycemia with the Hypoglycemia Fear Survey (HFS) Worry subscale. The questionnaires were forward-backward translated to Norwegian[12], and the understanding

and interpretation of the questionnaires were piloted in three children and their parents before study start.

The Gold questionnaire is a single-item questionnaire asking 'Do you know when your hypos are commencing?' to which the participant responds on a 7-point Likert scale ranging from '1' (always aware) to '7' (never aware)[2]. The Clarke questionnaire consists of 8 specific items characterizing awareness of hypoglycemia giving a total score of '0' to '7', and a higher score indicates diminished awareness[3]. All items from the original questionnaire were used with no modifications.

In the HFS questionnaires a higher score relates to greater fear of hypoglycemia[13]. The parental version of the HFS Worry subscale (PHFS-W) has been validated in the Norwegian population[14], whereas the Worry subscale for children (CHFS-W) has been validated in the present study population (Hatle et al., manuscript in preparation).

Children aged ≥9 years completed the questionnaires by themselves. For children <9 years of age, one, or both, parents completed the questionnaires, and for the awareness questionnaire, the parents opined on their child's hypoglycemia awareness, based on their personal observations. In addition, the parents completed questionnaires expressing their opinion for the awareness status of the children aged 9-11 years, which allowed comparison to be made with the children's responses.

Data analyses

The Gold and Clarke scores were tested as scale measurements of hypoglycemia awareness, and the criterion and construct validity of the questionnaires were analyzed in addition to their reliability and responsiveness.

Criterion validity was evaluated by prediction of awareness status to hypothesized key characteristics of IAH from the prospectively collected BG data in the diary (episodes of SH, need for assistance to recognize and/or recover from the hypoglycemia, and frequent asymptomatic hypoglycemia episodes), as well as episodes of SH in the preceding year and between recruitment and follow-up. The most appropriate cut-off value to classify participants as having IAH was chosen based on ability to discriminate between these key

characteristics, the classification with this cut-off value was used in all other analyses, and the concordance between results of the Gold and Clarke questionnaires was investigated. Because the Clarke questionnaire includes SH in the preceding year as one of the items, sensitivity analyses were performed with this item excluded.

Evaluation of the *construct validity* includes examination of convergent, divergent and known-groups validity. *Convergent validity* was assessed by correlating Gold and Clarke scores, as well as the change in these scores between inclusion and follow-up. In addition, for both the Gold and Clarke methods, an expected modest correlation was evaluated between awareness score and fear of hypoglycemia score (CHFS-W and PHFS-W in children and parents, respectively), to demonstrate *divergent validity*. To evaluate *known-groups validity*, an expected higher awareness score (indicating participants who are less aware of hypoglycemia) in those who experienced SH the preceding year vs. those not, was examined for both scoring methods.

Test-retest reliabilities for the Gold and Clarke questionnaires were evaluated by examining responses at inclusion and after the 4-week BG diary. In participants aged 9-11 years, the *inter-rater reliability* between the parent and the child was investigated.

At follow-up, the *responsiveness* of the questionnaires was examined by examining the change in awareness scores in those who did, and those who did not, experience SH since inclusion, and the change in Clarke score between participants whose awareness score had 'worsened', 'improved' or remained 'stable' as categorized by a change in Gold score, and vice versa.

Subgroup analyses in children aged <9 and ≥9 years were performed because of the potential difference between self-report from children and parents, and the difficulty in identifying and interpreting symptoms of hypoglycemia in very young children.

Missing data

Three of 348 Clarke questionnaires (in the test-retest analysis), in which more than one item was missing, were excluded. Questionnaires were included if multiple or missing answers on one item occurred without an effect on scoring (n=5). If one item was completely missing,

the score was excluded in reliability analyses (n=8). For overall comparisons of the Gold and Clarke scores, an absent score in a child aged <12 years was assigned the score of their mother or father (in that order). Incomplete scores were used to classify participants as having IAH vs. normal awareness of hypoglycemia (NAH), except where the missing information could affect the classification. This was the case with two children (aged 10.5 and 11.0 years) who each had a score of '2'; classifying these as having IAH or excluding them from sensitivity analyses did not change the main results or conclusions of the study (data not shown). Therefore, they were classified as having NAH in the analyses, based on their parents' score and/or retest score.

For the Gold questionnaire, one parental response (child <9 years) was missing at inclusion, and one child gave an ambiguous response (both '2' and '3') on retesting. If an evident misinterpretation of the Gold score was discovered (test-retest difference ≥3 and a stable Clarke score), those participants (n=4) were excluded from the reliability analyses but were included in the sensitivity analyses.

The completion rate for the questionnaires was 99.5% (Gold) and 95% (Clarke).

Statistical procedures and sample size

In view of the non-normal distribution of the continuous variables, group differences were examined with the Mann-Whitney U-test, and the Kruskal Wallis test was used when comparing three groups. A chi-square or Fisher`s Exact test (independent samples) or McNemar`s test (related samples) were used for categorical data. All correlations were examined with the Spearman`s rank correlation (r_s). To examine the test-retest and inter-rater reliability the intraclass correlation coefficient ($ICC_{agreement}$) was used, which equals to the weighted kappa coefficient with quadratic weights[15]. All statistical analyses were performed with SPSS version 22.0 or higher. The sample size needed to validate questionnaires is not standardized, but guidelines and published reports advocate at least 50-80 participants[15,16].

Results

Study population and diary adherence

Of 132 eligible children and adolescents, 112 (85 %) consented to participate in the study. Of these, 102 (91%) completed the 4-week BG diary (Figure 1). The completers were similar to the non-completers with respect to all baseline characteristics (Table 1). They registered 12.1 (7.8) (mean (SD)) episodes with BG ≤3.9 mmol/L (70 mg/dL) during the 4-week diary period. At least one episode with BG <3.0 mmol/L (54 mg/dL) was experienced by 83 participants (81%). Only one participant reported no episodes of BG ≤3.9 mmol/L (70 mg/dL). During the diary recording period, they performed 6.0 (1.9) SMBG measurements daily vs. 6.6 (2.7) reported at inclusion (p=0.026) and used the same daily total insulin dose (0.88 (0.27) vs. 0.89 (0.28) U/kg, p=0.31). Follow-up data after median (IQR) 523 (491-578) days were complete in 101 (90%) of the participants (Figure 1). The proportion of participants using real-time continuous glucose monitoring (CGM) had increased from 33% to 51% during follow-up (p<0.001), with little evidence of difference in incident use between those classified as having IAH vs. NAH at study start (Clarke; 13 vs. 23%, p=0.388, and Gold; 19 vs. 23%, p=0.805).

Prevalence of IAH

At baseline, as classified by the Clarke questionnaire, 25 of 112 participants (22%) had IAH, which was associated with a statistically significant 4-fold higher prevalence of SH in the preceding year compared to those with intact awareness (20 vs. 5%, p=0.025). Using the Gold questionnaire, 45 of 111 subjects had IAH (41%), with a 2-fold higher frequency of SH in the preceding year (11 vs. 6%, p=0.481). Twenty participants identified as having IAH by the Clarke or Gold questionnaires were classified as having IAH by both scoring methods (χ^2=20.843, p<0.001). Clinical characteristics of patients classified as having IAH vs. NAH by the Clarke and Gold methods at baseline are shown in Table 2 and separately for those aged <9 and ≥9 years in a supplementary table (Suppl. tables: S1). In the younger age group (<9 years), the prevalence of IAH was 21% (n=4) with the Clarke questionnaire and 56% (n=10) with the Gold questionnaire.

Change of hypoglycemia awareness status with time

At follow-up, the prevalence of IAH was 20% and 37% with the Clarke and Gold questionnaires, respectively. Compared with baseline, 78% (Clarke) and 63% (Gold)

maintained their original awareness status, whereas a change from NAH to IAH was reported in 9% and 15%, and from IAH to NAH in 13% and 21% (Clarke and Gold, respectively). Consequently, 22-36% of participants reported that their awareness status had changed during the period of the study. At follow-up, a higher prevalence of IAH was seen in children aged <9 vs. ≥9 years for both the Clarke (36 vs. 18%) and the Gold (64 vs. 33%) scores.

Criterion validity

Criterion validity was evaluated by the ability of the questionnaires to predict the key characteristics of IAH. For both questionnaires, a cut-off score of ≥3 to classify participants as having IAH gave the best discrimination with respect to these key characteristics (Table 3). Subgroup analyses by age (<9 or ≥9 years) showed that these associations were preserved only in the older age group (Suppl. tables: S2). In participants ≥9 years, those with IAH by the Clarke score had more episodes of clinically significant hypoglycemia (BG <3.0 mmol/L; 54 mg/dL), more episodes with loss of consciousness or need for assistance, and a 2.5-fold higher number of asymptomatic hypoglycemic episodes. Those with IAH by the Gold score had more asymptomatic episodes with BG <3.0 mmol/L (54mg/dL) during sleep and more asymptomatic mild episodes (BG 3.0-3.5 mmol/L; 54-63 mg/dL) when awake. Data for the younger age group and for other cut-off values are given in supplemental tables (Suppl. tables: S2 and S3).

Sensitivity analysis using the Clarke score with item 4 excluded ('SH in the preceding year'), and with a cut-off score of '2' to classify IAH, showed similar associations to the key characteristics of IAH and a 5-fold higher prevalence of SH in the preceding year, but gave a 2-fold higher prevalence of IAH compared with the original Clarke score with '3' as the cut-off value (40% vs. 22%) (Suppl. tables: S3). The use of '3' as the cut-off score for this modified Clarke score was less able to discriminate on the key characteristics of IAH.

At follow-up, approximately 1.5 years after inclusion, only nine participants had experienced SH (one episode each), four of whom had been classified as having IAH (by the Clarke method) at recruitment. This corresponds to an incidence proportion of SH of 17% in participants with IAH compared to 6% in those with NAH (p=0.211). The respective

incidence proportions of SH were 7% vs. 9% in participants with IAH classified by the Gold method compared with those with NAH (p=0.728). Four of the nine SH events recorded at follow-up had occurred during sleep, and mainly in patients who had normal awareness at recruitment. Only one of the nine participants with SH during follow-up had reported SH the preceding year at inclusion.

Construct validity

The construct validity was evaluated by examining the correlation between the scores of methods measuring the same construct (convergent validity), or a different (divergent validity), as well as comparing the scores in predefined groups expected to have different scores (known-groups validity).

Convergent validity was demonstrated by the overall Clarke-Gold correlation for the whole study population with r_s=0.58 (p<0.001, n=108), with similar coefficients for both the children/adolescents and parents, as well as for parental gender (r_s=0.53-0.64) (Figure 2). Correlation with the parents' scores was stronger in the younger children (r_s=0.78, p<0.001, n=18 vs. r_s=0.57, p<0.001, n=62 in those aged <9 and ≥9 years, respectively). The change in awareness score between recruitment and follow-up correlated moderately between the questionnaires (r_s=0.46, p<0.001, n=98), but this relationship was stronger in the younger children (r_s=0.67, p=0.004 for those aged <9 years (n=16) vs. r_s=0.42, p<0.001 for age ≥9 years (n=82)).

Divergent validity was demonstrated by a modest correlation between fear of hypoglycemia and the Clarke score in parents (r_s=0.31, p=0.005, n=79) and children (r_s=0.34, p=0.001, n=88), whereas weaker correlations were observed for the Gold score (r_s=0.24, p=0.031, n= 81 and r_s=0.16, p=0.136, n=92 in parents and children, respectively). In parents, subgroup analyses by child age showed strong correlations between fear of hypoglycemia vs. Clarke and Gold awareness scores (r_s=0.58, p=0.009 (n=19) and r_s=0.71, p=0.001 (n=18), respectively) in children aged <9 years as opposed to weak correlations in children aged ≥9 years (r_s=0.24, p=0.065, n=60 and r_s=0.11, p=0.395, n=63).

Known-groups validity was demonstrated by a higher Clarke score in children with SH the preceding year than in those with no SH (3(2-3) vs. 1(0-2), median (IQR), p=0.006), with similar trends for the modified Clarke score with exclusion of item 4 (2(1.5-2) vs. 1(0-2), p=0.069), and for the Gold score (3(2-3.8) vs. 2(2-3), p=0.124).

Test-retest and inter-rater reliability.

The test-retest reliability, given as $ICC_{agreement}$ (95% CI), was 0.67 (0.55-0.77) for the Clarke questionnaire and 0.60 (0.46-0.71) for the Gold questionnaire (Table 4). Mothers and fathers scored their children similarly with $ICC_{agreement}$ of 0.68 (0.18-0.90) and 0.83 (0.46-0.96) for the Clarke (n=11) and Gold (n=10) questionnaires, respectively. For children aged 9-11 years, the questionnaire scores for parents and children showed good concordance with an $ICC_{agreement}$ of 0.77 (0.45-0.91) for the Clarke questionnaire (n=15), and 0.65 (0.27-0.86) for the Gold questionnaire (n=17) at inclusion. Median (IQR) time between test and retest was 38 (32-49) days. In children aged 9-11 years (n=17) the prevalence of IAH as assessed by parents' and the children's responses were 59% and 65% (Gold score) and 29% compared to 24% (Clarke score). In children aged ≥12 years the prevalence of IAH was 32% by the Gold questionnaire and 23% by the Clarke questionnaire.

Responsiveness

Responsiveness (i.e. a change in score in groups expected to have changed their score) was demonstrated by a median (IQR) change in Clarke score from inclusion to follow-up of 1 (0 to 2), 0 (-1 to 0) and -1 (-2 to 0) in participants who had 'worsened', remained 'stable' or had 'improved' their state of hypoglycemia awareness, as categorized by change in Gold score (p<0.001), and vice versa a change in Gold score of 1 (0 to 1.5), 0 (-1 to 1), and -1 (-2 to 0) across categories by change in Clarke score (p<0.001). Furthermore, four out of nine participants who experienced SH between inclusion and follow-up had an increase in Clarke score with ≥2 points (i.e. a greater increase than would be expected by simply scoring an extra point for the item asking for SH history). The remaining five participants had no change, or the Clarke score had decreased by one point, and four of these participants had been classified at baseline as having IAH.

Discussion

The present study is the first longitudinal investigation of the psychometric properties of the Gold and Clarke questionnaires in a large and unselected pediatric population with T1D. Overall, these questionnaires were found to be simple and useful methods to assess awareness of hypoglycemia in children and adolescents, with both methods showing good acceptability and satisfactory criterion and construct validity, as well as test-retest reliability and responsiveness. In addition, the present data suggest that a cut-off score of ≥3 is most appropriate to classify patients as having IAH when using these questionnaires in children and adolescents. This contrasts with adult studies in which a score of '3' indicates an indeterminate state of awareness[2,3], but it is difficult to state whether this implies IAH in children to be only partial, or represents a milder form of this clinical syndrome as no direct comparison could be made. This finding will need to be validated in a larger sample with more SH events to confirm the associated risk of such unequivocal clinically important events.

Differences in the criterion validity of IAH were observed between the Clarke and Gold questionnaires. The Clarke method was superior at identifying participants at risk of clinically significant hypoglycemia (BG <3.0mmol/l; 54mg/dL[17], and hypoglycemia with loss of consciousness or need for external help to effect recovery), whereas the Gold method was superior in identifying participants at risk of milder asymptomatic hypoglycemia episodes, including those occurring during sleep. The single-item Gold questionnaire might be more susceptible to day-to-day variations and misinterpretation, as reflected in the lower test-retest and inter-rater reliability in the present study. Score inflation by experiencing frequent non-significant hypoglycemia, or just a general uncertainty, may also drive the lower specificity of the Gold method, yielding a higher prevalence of IAH with a somewhat milder expression. The higher prevalence of IAH with the Gold scoring system that was observed in the present study was accentuated in the younger participants, and may indicate that young children do not comprehend the use of a Likert scale to score a subjective condition[18], as opposed to answering the more specific questions in the Clarke questionnaire. Discordance between the two questionnaires when assessing hypoglycemia awareness in a pediatric T1D cohort is supported by a Scottish study that showed a 3-fold increased prevalence of IAH with the Gold questionnaire compared with the Clarke

questionnaire, and where only the Clarke questionnaire could identify the patients at increased risk of SH[7]. However, in the present study, clinically significant episodes of hypoglycemia were more prevalent in patients classified as having IAH by both methods, consistent with previous findings in adults[9].

Several psychometric analyses were used to evaluate the validity of the Clarke and Gold questionnaires. The Gold questionnaire, being a single-item 7-point Likert scale, has good face validity, whereas the multi-item Clarke questionnaire includes the defining characteristics or 'composite indicators' of IAH (i.e. it is itself part of the definition of what is meant by IAH), which calls for a more clinimetric approach to evaluation, focusing on properties of prognosis and prediction of the characteristics of IAH[16]. However, as all items reflect awareness of hypoglycemia, treating the total Clarke score as a scale indicates good face validity and enables use of psychometric techniques as performed. A gold standard tool or questionnaire to determine the presence of IAH remains unavailable and cannot be determined by glucose clamp studies. The conditions in these experimental studies do not represent everyday life settings with their myriad distractions. It is therefore recommended that awareness status should be determined by self-report in specific questionnaires[1].

Participants in the present study were recruited successively from the pediatric diabetes outpatient clinic; the participation rate was 85%, and the clinical characteristics of the cohort are similar to those of the nationwide pediatric diabetes population registered in the Norwegian Childhood Diabetes Registry (Suppl. tables: S4). The prevalence of SH in the preceding year was slightly higher than in the nationwide registry, possibly influenced by the focus on registering hypoglycemia in the present study. The incidence of SH during the current study period was however low, and a larger sample size will be required to give adequate statistical power to determine whether IAH is predictive of future SH.

In the present study, more participants with IAH than NAH were using an insulin pump, and all children using CGM used an insulin pump. Both CGM and insulin pumps are associated with a lower risk of SH[10,19,20]. Interestingly, eight of the nine participants who experienced SH during follow-up were not using CGM when the study commenced. The use of CGM could potentially increase the incidence of identified asymptomatic hypoglycemia, and may help to prevent severe hypoglycemia. Few differences were observed in the key

characteristics of IAH in relation to use of CGM (data not shown), and the number of novel CGM users at follow-up did not differ between those with and without IAH. However, CGM data including the percentage of time in use were not available, and a detailed analysis of the role of CGM was not possible in the present study. Thus, we cannot state how the awareness scores relate to hypoglycemia detected by CGM, but a recent study in adults using blinded CGM found that a higher fraction of asymptomatic hypoglycemia was associated with IAH[21]. In the present study, the five children aged <9 years who used CGM were classified as having IAH by their Gold score. The use of CGM may have been initiated because of frequent or disabling hypoglycemia or to relieve fear of hypoglycemia, but CGM also informs the child and/or the parents about mild daytime and nocturnal hypoglycemia, which is common and frequently asymptomatic[22,23], and might have generated uncertainty about the child's ability to recognize hypoglycemia. The present data do however confirm that IAH is relatively common in children and adolescents, screening for which could identify individuals who might benefit from interventions to reduce the frequency of hypoglycemia.

Hypoglycemia awareness may be affected by sleep, alcohol, drugs, posture, and ongoing activities that cause distraction[1,24]. At recruitment, information on specific circumstances preceding SH episodes was not sought. However, at the follow-up assessment, it was observed that in the NAH participants most episodes of SH had occurred during sleep, when reduced awareness is a natural physiological state. Sleep is itself a recognized risk factor for SH which is not influenced by the state of awareness of hypoglycemia. The participants who were identified to have IAH by the Gold score experienced more asymptomatic episodes both when asleep and awake, indicating that their impaired awareness was not solely sleep-related. However, it is known that counterregulatory hormonal responses are attenuated during sleep, and it has been postulated that unrecognized recurrent nocturnal hypoglycemia may induce IAH[1].

Awareness of hypoglycemia is a dynamic process[1], and some of the participants in the present investigation reported a change in hypoglycemia awareness status during the course of the study, which may have influenced the accuracy by which IAH could predict SH events. Participants with IAH at baseline did receive education and/or changes in treatment regimen as part of their outpatient care. It is not possible to determine whether changes in awareness status preceded episodes of SH, or whether hypoglycemia awareness changed as

a consequence of alterations in glycemic control, treatment regimen, exposure to hypoglycemia, or other factors. Nevertheless, at follow-up, more participants reported a change in awareness status from impaired to normal than vice versa, suggesting a beneficial effect from study participation, which is consistent with previous studies in adults and adolescents aged <18 years[10,25].

The differences in the key characteristics of IAH between IAH and NAH participants were more pronounced in the participants aged ≥9 years and were absent in those <9 years, but there were few participants in the younger group, and their results should be interpreted with caution. Hypoglycemia symptomatology is challenging to determine in very young children and difficulties in acknowledging and interpreting symptoms in the youngest[26,27] limit the use of these questionnaires as a by-proxy-assessment in the <9 years age group. This difficulty may underlie a much higher prevalence of IAH in very young children than has generally been recognized. However, the strong correlation between parental fear of hypoglycemia and (parent-assessed) hypoglycemia awareness score in the younger age group suggests that their seemingly high prevalence of IAH may not constitute a genuine IAH syndrome but may reflect parental fear that their child is unable to recognize hypoglycemia. As parental fear of hypoglycemia may be associated with poor glycemic control[28], assessing this uncertainty is clinically important. Putative differences in mechanisms underlying IAH in pediatric as compared to adult populations are supported by previous studies in children that observed an association between younger age and IAH[5,7], in contrast to increasing age and diabetes duration being major risk factors associated with IAH in adults[1].

In summary, the Gold and Clarke questionnaires have been validated in a large and representative pediatric diabetes cohort with a high participation rate. The present study has shown that the Gold and Clarke questionnaires can be used in clinical and research settings to identify IAH in children aged ≥9 years. However, the Clarke questionnaire shows a higher specificity and is superior in predicting risk of clinically significant hypoglycemia. In children <9 years of age, parental-reported IAH may not represent a true IAH syndrome.

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Table 1. Characteristics of participants at inclusion in study and at follow-up.

	At inclusion	Completers of BG diary[†]	At follow-up
Participants, n	112	102	101
Males/Females, n (%)	57/55 (51/49)	50/52 (49/51)	50/51 (50/51)
Age, yr.	13.7 (11.1-15.8)	13.6 (11.0-15.7)	14.8 (12.2-16.8)
Age at diagnosis, yr.	7.7 (3.8-11.3)	7.7 (3.9-11.1)	7.3 (3.7-10.9)
Diabetes duration, yr.	4.7 (2.2-7.8)	4.4 (2.3-7.7)	6.1 (3.6-9.2)
HbA1c			
mmol/mol	62 (57-73)	62 (56-73)	65 (58-70)
%	7.8 (7.3-8.8)	7.8 (7.3-8.8)	8.1 (7.5-8.6)
Body mass index, kg/m^2	19.7 (17.5-23.3)	19.8 (17.5-23.5)	20.5 (17.8-23.5)
Insulin regimen, n (%)			
Pump	85 (76)	76 (75)	79 (77)
Multiple daily injections	27 (24)	26 (26)	22 (23)
Daily insulin dose, U/kg	0.85 (0.69-1.04)	0.85 (0.70-1.06)	0.83 (0.65-1.07)
RT-CGM, n (%)	34 (30)	28 (28)	51 (51) [§]
SMBG, measurements/day	6.0 (4.0-8.0)	6.0 (4.3-8.0)	-
≥ 1 SH in preceding year, n (%)	9 (8)	8 (8)	7 (7)
Clarke[‡] score	1.0 (0.3-2.0)	1.0 (0.0-2.0)	1.0 (0.0-2.0)
mean (SD)	1.5 (1.3)	1.5 (1.3)	1.5 (1.3)
Gold[‡] score	2.0 (2.0-3.0)	2.0 (2.0-3.0)	2.0 (2.0-3.0)
mean (SD)	2.5 (1.2)	2.5 (1.2)	2.5 (1.2)

Numbers are median (IQR) if not stated otherwise. BG = blood glucose. RT-CGM = real-time continuous glucose monitoring. SMBG = self-monitored blood glucose. SH = severe hypoglycemia (loss of consciousness with or without seizures).

[†] No statistically significant differences for completers vs. non-completers for any of the variables.

[‡] Questionnaires measuring hypoglycemia awareness, possible range for Clarke; 0-7 and Gold; 1-7.

[§] 21 were new users of RT-CGM and three had discontinued such use since inclusion ($p<0.001$, McNemars test).

Table 2. Characteristics of participants[†] by awareness status classified by the Clarke and Gold questionnaires for scoring hypoglycemia awareness.

	Clarke scoring system (n=112)			Gold scoring system (n=111)		
Awareness status	Impaired	Normal	p	Impaired	Normal	p
Prevalence, n (%)	25 (22)	87 (78)		45 (41)	66 (59)	
Sex, n males/females	12/13	45/42	.743	22/23	34/32	.786
Age, yr.	13.7 (11.6-14.7)	14.0 (11.0-16.3)	.509	12.4 (10.0-14.3)	14.7 (12.4-16.8)	.001
Age at diagnosis, yr.	6.5 (2.7-10.8)	8.2 (4.1-11.6)	.148	5.7 (3.2-10.6)	8.5 (5.2-11.8)	.045
Duration of diabetes, yr.	5.5 (2.0-9.7)	4.3 (2.3-7.3)	.650	3.9 (2.3-7.2)	5.5 (2.3-8.1)	.442
Body mass index, kg/m^2	19.2 (16.8-24.4)	19.8 (17.6-22.9)	.783	18.8 (16.8-20.6)	21.0 (18.4-23.8)	.003
HbA1c at inclusion						
mmol/mol	62 (56-68)	62 (57-76)	.520	62 (56-72)	62 (57-73)	.633
%	7.8 (7.3-8.4)	7.8 (7.4-9.1)		7.8 (7.3-8.7)	7.9 (7.4-8.8)	
Insulin pump users, n (%)	23 (92)	62 (71)	.033	41 (91)	43 (65)	.002
Daily insulin dose, U/kg	0.84 (0.72-1.04)	0.83 (0.67-1.04)	.569	0.78 (0.68-0.93)	0.88 (0.71-1.08)	.075
RT-CGM users, n (%)	9 (36)	25 (29)	.486	18 (40)	16 (24)	.077
≥1 SH in preceding year, n (%)	5 (20)	4 (5)	.025	5 (11)	4 (6)	.481
SMBG, measurements/day[‡]						
Reported at inclusion	7.0 (4.8-8.0)	6.0 (5.0-9.0)	.516	7.3 (5.0-8.8)	6.0 (5.0-8.0)	.113
Registered in diary	6.1 (5.0-7.4)	5.9 (4.6-7.5)	.724	6.3 (4.7-7.6)	5.5 (4.6-6.6)	.181

Numbers are median (IQR) if not stated otherwise. RT-CGM = real-time continuous glucose monitoring. SH = severe hypoglycemia (loss of consciousness with or without seizure). SMBG = self-monitored blood glucose.

[†] See supplementary material (table S1) for data on the <9 and ≥9 years age subgroups.

[‡] In addition to those 10 not completing the diary, 10 (of which 8 were CGM users) participants had predominantly recorded blood glucose values only at episodes of hypoglycemia and are excluded.

Table 3: Associations between hypoglycemia awareness status and key characteristics of impaired awareness[†].

	Clarke scoring system (n=102)			Gold scoring system (n=101)		
Awareness status[‡]	Impaired	Normal	p	Impaired	Normal	p
Prevalence, n (%)	22 (22)	80 (78)		41 (41)	60 (59)	
≥ 1 SH in preceding year, n (%)	5 (23)	3 (4)	.011	5 (12)	3 (5)	.264
Data from 4-week BG diary period						
≥ 1 SH, n (%)	2 (9)	0 (0)	.045	2 (5)	0 (0)	.162
≥ 1 hypoglycemia requiring help[§], n (%)	3 (14)	1 (1)	.031	2 (5)	2 (3)	>0.99
≥ 1 hypoglycemia recognized by others, n (%)						
BG 3.0-3.5	3 (14)	7 (9)	.446	7 (17)	3 (5)	.085
BG <3.0	6 (27)	6 (8)	.020	9 (22)	3 (5)	.013
Episodes of hypoglycemia, mean, median (IQR)						
BG 3.0-3.5	4.0, 3 (1-5)	4.8, 4 (2.3-6)	.218	5.7, 5 (2.5-9.5)	3.9, 3 (2-5)	.114
BG <3.0	4.2, 2.5 (1-7)	3.4, 3 (1-5)	.740	4.4, 3 (1.5-7)	3.0, 2.5 (1-4.8)	.054
Episodes of asymptomatic hypoglycemia						
BG 3.0-3.5, mean, median (IQR) episodes	1.5, 0 (0-2)	1.1, (0-1.8)	.614	1.6, 1 (0-2)	0.9, 0 (0-1)	.021
≥ 1 episode, n (%)	10 (46)	33 (41)	.724	23 (56)	19 (32)	.014
BG <3.0, mean, median (IQR) episodes	1.2, 0 (0-1.3)	0.4, 0 (0-0.8)	.187	0.9, 0 (0-1)	0.4, 0 (0-0)	.078
≥ 1 episode, n (%)	8 (36)	20 (25)	.290	15 (37)	13 (22)	.100
Mean, median (IQR) % of hypoglycemia that was asymptomatic[¶]						
BG 3.0-3.5	34, 0 (0-67)	22, 0 (0-41)	.216	33, 33 (0-50)	19, 0 (0-25)	.012
BG <3.0	25, 0 (0-50)	15, 0 (0-24)	.249	22, 0 (0-38)	14, 0 (0-18)	.179
≥ 1 asymptomatic hypoglycemia during sleep						
BG 3.0-3.5	7 (32)	17 (21)	.301	17 (42)	7 (12)	<0.001
BG <3.0	3 (14)	9 (11)	.718	10 (24)	2 (3)	.003

SH = severe hypoglycemia (loss of consciousness with or without seizure). BG = blood glucose (in mmol/L)

[†] See supplementary material (table S2) for data for those aged ≥9 and <9 years.

[‡] Impaired awareness defined as score ≥3 at inclusion in both the Clarke and Gold questionnaires. See supplementary material (table S3) for other cut-off scores.

[§] Episode of hypoglycemia with minor alteration of mental status, but with need of assistance to effect recovery.

[¶] Only participants having at least one hypoglycemic episode in given blood glucose (BG) range are included in this analysis (≥77% of participants included for each category)

Table 4: Intraclass correlation coefficients ($ICC_{agreement}$ (95% CI)) for test-retest reliability of the Gold and Clarke scoring systems.

	Clarke score	Gold score[‡]
Child/adolescent	0.67 (0.53-0.77), n=79	0.62 (0.47-0.74), n=79
Mother	0.70 (0.51-0.82), n=45	0.46 (0.21-0.66), n=45
Father	0.64 (0.26-0.85), n=17	0.46 (-0.06-0.79), n=14
Parents combined[†]	0.63 (0.45-0.75), n=66	0.43 (0.21-0.61), n=66
Overall[§]	0.67 (0.55-0.77), n=102	0.60 (0.46-0.71), n=97

[†] The mother`s score was used when both parents had completed the questionnaires.

[‡] Excluding three children, three mothers and one father due to evident misinterpretation of the scale. Sensitivity analyses including these yielded lower ICCs of 0.18-0.46.

[§] Parent`s score for children aged <9 years, the child/adolescent`s score in participants aged ≥9 years.

Figure legends

Figure 1. Study flow chart.

BG = blood glucose. †Median (IQR) time between inclusion and follow-up was 523 (491-578) days.

Figure 2. Median (IQR) Gold† score for given Clarke† score at inclusion‡.

† Higher scores indicate less awareness of hypoglycemia (Gold score range 1-7, Clarke score range 0-7).

‡ The overall score (parental response in children aged <9 and child/adolescents` response in those aged ≥9) is presented, with a corresponding correlation (r_s) between the Gold and Clarke score of 0.58 (n=107).

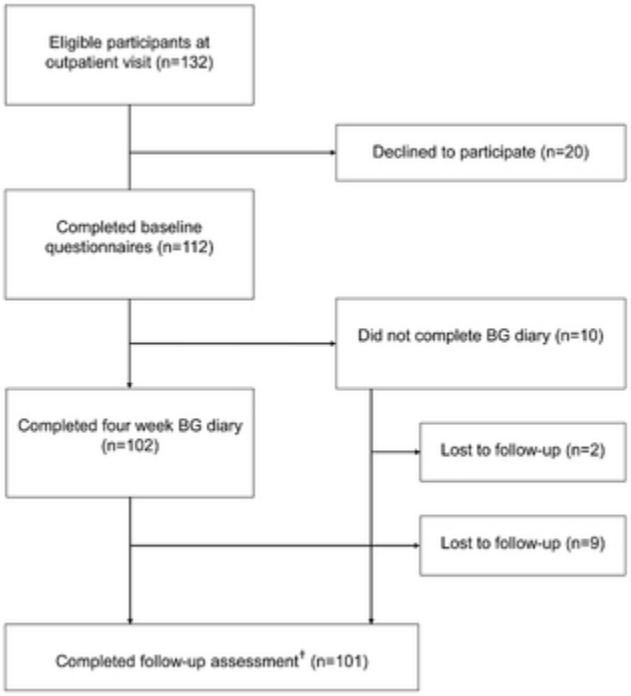

Figure 1: Study flow chart.

28x33mm (300 x 300 DPI)

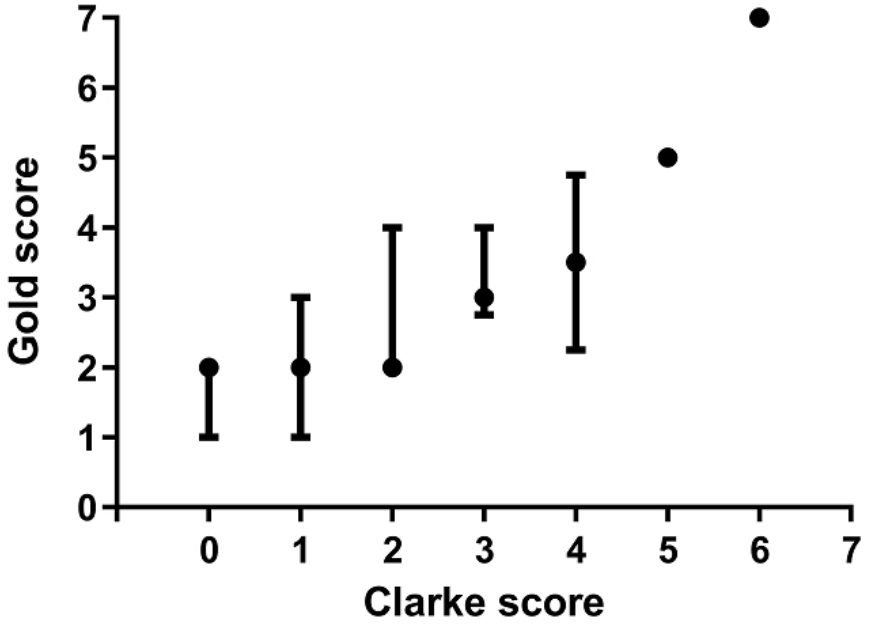

Figure 2: Median (IQR) Gold[†] score for given Clarke[†] score at inclusion[‡]

194x138mm (96 x 96 DPI)

Supplementary tables

Table S1. Characteristics in participants ≥9 (n=93) and <9 years (n=19) of age by awareness status as classified by the Clarke and Gold questionnaires.

		Clarke scoring system			Gold scoring system		
Awareness status		Impaired	Normal	p	Impaired	Normal	p
Prevalence, n (%)							
≥9 years		21 (23)	72 (77)		35 (38)	58 (62)	
<9 years		4 (21)	15 (79)		10 (56)	8 (44)	
Sex, n male/female							
≥9 years		9/12	41/31	.322	18/17	32/26	.726
<9 years		3/1	4/11	.117	4/6	2/6	.638
Age							
≥9 years		13.8 (12.6-15.0)	14.7 (12.5-16.7)	.330	13.0 (11.4-14.9)	15.1 (13.3-17.2)	.001
<9 years		7.4 (4.8-7.8)	7.3 (4.8-7.9)	.885	7.2 (5.1-7.9)	7.4 (5.2-8.4)	.762
Age at diagnosis							
≥9 years		7.3 (2.9-11.3)	9.0 (5.7-12.0)	.126	8.2 (3.8-11.3)	9.1 (6.6-12.0)	.142
<9 years		2.5 (1.1-5.7)	3.4 (2.1-5.1)	.530	3.3 (1.7-4.9)	3.8 (2.3-5.2)	.696
Duration of diabetes							
≥9 years		5.5 (2.2-10.8)	5.5 (2.4-8.3)	.547	5.3 (2.3-8.5)	5.9 (2.3-8.8)	.646
<9 years		3.6 (0.8-6.2)	2.8 (2.2-3.9)	.885	2.9 (1.9-4.6)	2.4 (2.1-5.3)	.829
Body mass index, kg/m^2							
≥9 years		20.1 (17.3-24.8)	20.7 (18.8-23.6)	.861	19.1 (17.4-22.0)	21.1 (19.2-23.8)	.013
<9 years		16.8 (16.4-19.1)	17.3 (16.5-17.8)	.961	16.8 (16.4-17.4)	17.5 (15.7-18.8)	.515
HbA1c at inclusion							
≥9 years	mmol/mol	63 (55-69)	64 (57-77)	.341	65 (55-74)	63 (57-76)	.880
	%	7.9 (7.2-8.5)	8.0 (7.4-9.2)		8.1 (7.2-8.9)	8.0 (7.4-9.1)	
<9 years	mmol/mol	61 (57-64)	58 (54-62)	.596	61 (55-63)	59 (57-62)	>0.99
	%	7.7 (7.4-8.0)	7.5 (7.1-7.8)		7.7 (7.2-7.9)	7.6 (7.4-7.8)	
Insulin pump users, n (%)							
≥9 years		19 (90)	51 (71)	.066	31 (89)	39 (67)	.021
<9 years		4 (100)	11 (73)	.530	10 (100)	4 (50)	.023
Daily insulin dose, U/kg							
≥9 years		0.86 (0.77-1.10)	0.87 (0.69-1.08)	.666	0.83 (0.68-0.97)	0.92 (0.73-1.09)	.111
<9 years		0.72 (0.57-0.96)	0.71 (0.53-0.81)	.961	0.73 (0.64-0.82)	0.74 (0.52-0.85)	.965
RT-CGM users, n (%)							
≥9 years		7 (33)	22 (31)	.809	13 (37)	16 (28)	.335
<9 years		2 (50)	3 (20)	.272	5 (50)	0 (0)	.036
≥1 SH preceding year, n (%)							
≥9 years		5 (24)	4 (6)	.025	5 (14)	4 (7)	.289

<9 years		0	0		0	0	
SMBG measurements per day[†]							
≥9 years	at inclusion	6.5 (4.9-7.6)	6.0 (4.3-8.0)	.929	7.0 (5.0-8.0)	6.0 (4.5-7.0)	.174
	in diary	6.1 (4.9-6.7)	5.4 (4.4-7.0)	.579	6.2 (4.5-7.5)	5.1 (4.4-6.6)	.230
<9 years	at inclusion	6.0 (2.0-10.0)[‡]	8.0 (6.0-10.0)	.654	8.0 (5.0-10.0)	8.0 (6.0-9.8)	.888
	in diary	8.2 (5.1-8.6)[‡]	6.6 (5.9-8.8)	.953	7.6 (5.5-8.7)	6.5 (6.1-7.8)	.963

Numbers are median (IQR) if not stated otherwise. RT-CGM = real-time continuous glucose monitoring. SH = severe hypoglycemia (loss of consciousness with or without seizure). SMBG = self-monitored blood glucose.

[†] Daily frequency reported at inclusion and registered in the 4-week diary period. In addition to those 10 not completing the diary, 10 (of which 8 were CGM users) participants had predominantly recorded blood glucose values at episodes of hypoglycemia and are excluded.

[‡] Data is from only three participants. Range of values in brackets.

Table S2. Associations between hypoglycemia awareness status and key characteristics of impaired awareness in participants aged ≥9 and <9 years.

	Clarke scoring system			Gold scoring system		
Awareness status[†]	Impaired	Normal	p	Impaired	Normal	p
Prevalence, n (%)						
≥9 years	19 (23)	65 (77)		32 (38)	52 (62)	
<9 years	3 (17)	15 (83)		9 (53)	8 (47)	
≥ 1 SH in preceding year, n (%)						
≥9 years	5 (26)	3 (5)	.013	5 (16)	3 (6)	.249
<9 years	0	0		0	0	
Data from 4-week BG diary						
≥ 1 SH, n (%),						
≥9 years	2 (11)	0 (0)	.049	2 (6)	0 (0)	.142
<9 years	0	0		0	0	
≥ 1 hypoglycemia requiring help[‡], n (%)						
≥9 years	3 (16)	1 (2)	.035	2 (6)	2 (4)	.633
<9 years	0	0		0	0	
≥ 1 hypoglycemia recognized by others, n (%)						
≥9 years						
BG 3.0-3.5	3 (16)	5 (8)	.373	6 (19)	2 (4)	.049
BG <3.0	6 (32)	3 (5)	.004	7 (22)	2 (4)	.024
<9 years						
BG 3.0-3.5	0	2 (13)	>0.99	1 (11)	1 (13)	>0.99
BG <3.0	0	3 (20)	>0.99	2 (22)	1 (13)	>0.99
Episodes of hypoglycemia, mean, median (IQR)						
≥9 years						
BG 3.0-3.5	4.3, 3 (1-5)	4.5, 3 (2-6)	.775	6.1, 5 (2.3-10)	3.5, 3 (1.3-5)	.041
BG <3.0	4.6, 3 (1-7)	3.3, 3 (1-5)	.415	4.7, 3.5 (1.3-7)	2.8, 2.5 (0.3-4)	.034
<9 years						
BG 3.0-3.5	1.7, 2 (0-2.5)	6.2, 5 (3-9)	.017	4.3, 4 (2.5-6)	7.0, 7 (3.3-9.8)	.200
BG <3.0	1.7, 2 (0-2.5)	3.8, 3 (1-6)	.309	3.4, 3 (1-5.5)	3.6, 2.5 (1-6.8)	.963
Episodes of asymptomatic hypoglycemia						
≥9 years						
BG 3.0-3.5, mean, median (IQR) episodes	1.6, 0 (0-2)	0.8, 0 (0-1)	.252	1.6, 1 (0-2)	0.6, 0 (0-1)	.010
≥ 1 episode, n (%)	9 (47)	24 (37)	.412	18 (56)	15 (29)	.013
BG <3.0 mean, median (IQR) episodes	1.4, 0 (0-2)	0.2, 0 (0-0)	.015	0.9, 0 (0-1)	0.3, 0 (0-0)	.057
≥ 1 episode, n (%)	8 (42)	12 (19)	.062	11 (34)	9 (17)	.075
<9 years						
BG 3.0-3.5, mean, median (IQR) episodes	0.7, 0 (0-1)	2.4, 2 (0-5)	.288	1.7, 2 (0-3)	2.8, 2 (0-5)	.541

	≥ 1 episode, n (%)	1 (33)	9 (60)	.559	5 (56)	4 (50)	>0.99
BG <3.0	mean, median (IQR) episodes	0	1.3, 1 (0-2)	.117	1.0, 0 (0-2)	1.3, 0.5 (0-3.3)	.888
	≥ 1 episode, n (%)	0	8 (53)	.216	4 (44)	4 (50)	>0.99
Mean, median (IQR) % of hypoglycemia that was asymptomatic[§]							
≥9 years							
BG 3.0-3.5		32, 33 (0-67)	18, 0 (0-32)	.118	30, 32 (0-50)	16, 0 (0-22)	.011
BG <3.0		28, 0 (0-54)	11, 0 (0-0)	.037	20, 0 (0-37)	12, 0 (0-0)	.159
<9 years							
BG 3.0-3.5		50, 50 (0-100)[¶]	39, 40 (0-71)	.824	46, 45 (0-95)	35, 25 (0-69)	.645
BG <3.0		0	32, 29 (0-54)	.229	31, 25 (0-67)	27, 33 (0-50)	>0.99
≥ 1 asymptomatic hypoglycemia during sleep							
≥9 years							
BG 3.0-3.5		6 (32)	13 (20)	.352	14 (44)	5 (10)	<0.001
BG <3.0		3 (16)	7 (11)	.687	8 (25)	2 (4)	.006
<9 years							
BG 3.0-3.5		1 (33)	4 (27)	>0.99	3 (33)	2 (25)	>0.99
BG <3.0		0	2 (13)	>0.99	2 (22)	0	.471

SH = severe hypoglycemia (loss of consciousness with or without seizure). BG = blood glucose (in mmol/L).

[†] Impaired awareness was defined as score ≥3 at inclusion for both the Clarke and Gold hypoglycemia awareness scoring systems.

[‡] Episode of hypoglycemia with minor alteration of mental status, but with need of assistance to effect recovery.

[§] Only participants having at least one hypoglycemic episode in given blood glucose (BG) range are included in this analysis (≥75% of participants included for each category, except only 67% in the category IAH identified by the Clarke method in children aged <9).

[¶] Data is from only two participants. Range of values in brackets.

Table S3: Key characteristics for all participants and the ≥9 years age subgroup with other score cut-offs for classifying participants as having impaired awareness of hypoglycemia (IAH)[†].

	Clarke, score ≥4 as IAH[‡]			Clarke score without item 4, score ≥2 as IAH[§]			Gold, score ≥4 as IAH		
Awareness status	Impaired	Normal	p	Impaired	Normal	p	Impaired	Normal	p
Prevalence, n (%)									
All	5 (5)	97 (95)		41 (40)	61 (60)		18 (18)	83 (82)	
≥9 years only	5 (6)	79 (94)		33 (39)	51 (61)		14 (17)	70 (83)	
≥ 1 SH in preceding year, n (%)									
All	0 (0)	8 (8)	>0.99	6 (15)	2 (3)	.058	2 (11)	6 (7)	.630
≥9 years only	0	8	>0.99	6 (18)	2 (4)	.052	2 (14)	6 (9)	.615
Data from 4-week BG diary									
≥ 1 SH, n (%)									
All	1 (20)	1 (1)	.096	2 (5)	0	.159	1 (6)	1 (1)	.326
≥9 years only	1 (20)	1 (1)	.116	2 (6)	0	.151	1 (7)	1 (1)	.307
≥ 1 hypoglycemia requiring help[¶], n (%)									
All	1 (20)	3 (3)	.185	4 (10)	0	.024	1 (6)	3 (4)	.550
≥9 years only	1 (20)	3 (4)	.221	4 (12)	0	.021	1 (7)	3 (4)	.525
≥ 1 hypoglycemia recognized by others, n (%)									
All									
BG 3.0-3.5	0	10 (10)	>0.99	5 (12)	5 (8)	.518	1 (6)	9 (11)	.686
BG <3.0	2 (40)	10 (10)	.104	7 (17)	5 (8)	.216	3 (17)	9 (11)	.444
≥9 years only									
BG 3.0-3.5	0	8 (10)	>0.99	5 (15)	3 (6)	.253	1 (7)	7 (10)	>0.99
BG <3.0	2 (40)	7 (9)	.087	7 (21)	2 (4)	.025	3 (21)	6 (9)	.168
Episodes of hypoglycemia, mean, median (IQR)									
All									
BG 3.0-3.5	3.2, 3 (1-5.5)	4.7, 4 (2-6)	.325	4.8, 4 (2.5-6.5)	4.5, 3 (2-6)	.547	4.1, 3 (1.8-6.3)	4.8, 4 (2-6)	.623
BG <3.0	4.4, 3 (1-8.5)	3.5, 3 (1-5.5)	.547	4.2, 3 (1-7)	3.1, 3 (1-5)	.210	3.7, 2.5 (1.8-6.3)	3.5, 3 (1-6)	.534
≥9 years only									
BG 3.0-3.5	3.2, 3 (1-5.5)	4.5, 3 (2-6)	.417	5.2, 5 (3-8.5)	3.9, 3 (1-5)	.082	4.1, 3 (1-7.3)	4.5, 3 (2-6)	.827
BG <3.0	4.4, 3 (1-8.5)	3.5, 3 (1-5)	.556	4.7, 3 (1.5-7)	2.8, 2 (0-4)	.021	3.9, 2.5 (1-7.3)	3.5, 3 (1-5.3)	.549
Episodes of asymptomatic hypoglycemia									
All									
BG 3.0-3.5, median (IQR) episodes	1.2, 1 (0.5-2)	1.2, 0 (0-2)	.243	1.4, 0 (0-2)	1.0, 0 (0-1)	.279	1.4, 0.5 (0-2.3)	1.1, 0 (0-2)	.381
≥ 1 episode, n (%)	4 (80)	39 (40)	.159	19 (46)	24 (39)	.483	9 (50)	33 (40)	.424
BG <3.0 median (IQR) episodes	1.0, 0 (0-2.5)	0.6, 0 (0-1)	.476	1.0, 0 (0-1)	0.4, 0 (0-0)	.064	0.7, 0 (0-1)	0.6, 0 (0-1)	.516

	≥ 1 episode, n (%)	2 (40)	26(27)	.613	15 (37)	13 (21)	.090	6 (33)	22 (27)	.570
≥9 years only										
BG 3.0-3.5,	median (IQR) episodes	1.2, 1 (0.5-2)	1.0, 0 (0-1)	.192	1.4, 0 (0-2)	0.7, 0 (0-1)	.151	1.0. 0 (0-2)	1.0, 0 (0-1)	.722
	≥ 1 episode, n (%)	4 (80)	29 (37)	.075	15 (46)	18 (35)	.352	6 (43)	27 (39)	.772
BG <3.0	median (IQR) episodes	1.0, 0 (0-2.5)	0.5, 0 (0-0)	.484	1.0, 0 (0-1)	0.2, 0 (0-0)	.018	0.5, 0 (0-1)	0.5, 0 (0-0)	.687
	≥ 1 episode, n (%)	2 (40)	18 (23)	.588	12 (36)	8 (16)	.038	4 (29)	16 (23)	.733
Mean, median (IQR) % of hypoglycemia that was asymptomatic[¥]										
All										
BG 3.0-3.5		50, 50 (38-63)	24, 0 (0-50)	.060	30, 22 (0-54)	21, 0 (0-33)	.207	35, 37 (0-50)	23, 0 (0-50)	.235
BG <3.0		31, 0 (0-79)	17, 0 (0-26)	.596	25, 0 (0-50)	12, 0 (0-17)	.066	28, 0 (0-62)	15, 0 (0-25)	.465
≥9 years only										
BG 3.0-3.5		50, 50 (38-63)	20, 0 (0-33)	.027	26, 11 (0-50)	18, 0 (0-25)	.190	23, 17 (0-50)	21, 0 (0-33)	.667
BG <3.0		31, 0 (0-79)	14, 0 (0-20)	.522	22, 0 (0-43)	10, 0 (0-0)	.061	24, 0 (0-54)	13, 0 (0-20)	.621
≥ 1 asymptomatic hypoglycemia during sleep										
All										
BG 3.0-3.5		1 (20)	23 (24)	>0.99	11 (27)	13 (21)	.519	6 (33)	18 (22)	.360
BG <3.0		1 (20)	11 (11)	.472	6 (15)	6 (10)	.537	3 (17)	9 (11)	.444
≥9 years only										
BG 3.0-3.5		1 (20)	18 (22.8)	>0.99	10 (30)	9 (18)	.176	5 (36)	14 (20)	.291
BG <3.0		1 (20)	9 (11.4)	.478	6 (18)	4 (8)	.181	3 (21)	7 (10)	.359

SH = severe hypoglycemia (loss of consciousness with or without seizure). BG = blood glucose (in mmol/L).

[†] See Table 2 in manuscript and S1 in supplementary material for cut-off ≥3.

[‡] No participants in the <9 years of age subgroup were classified as having IAH by this cut off.

[§] Original Clarke score (with item 4) and cut-off 2 yielded a prevalence of IAH of 44%, and with similar differences vs. those classified as having normal awareness of hypoglycemia as when using this modified Clarke score.

[¶] Episode of hypoglycemia with minor alteration of mental status, but with need of assistance to effect recovery.

[¥] Only participants having at least one hypoglycemic episode in given blood glucose range are included in this analysis (≥75% of participants included for each category)

Table S4. Population-based characteristics of children and adolescents with type 1 diabetes in Norway[†]

	N=2581
Males/Females, n (%)	1369/1212 (53/47)
Age, yr.	13.7 (10.4-16.1)
Age at diagnosis, yr.	7.4 (4.2-10.6)
Diabetes duration, yr.	4.8 (2.4-7.9)
HbA1c	
mmol/mol	62 (55-69)
%	7.8 (7.2-8.5)
Body mass index, kg/m^2	20.1 (17.7-22.9)
Insulin pump users, n (%)	1861 (72)
Daily insulin dose, U/kg	0.80 (0.66-0.98)
SMBG/day, mean (SD)	5.7 (2.8)
≥ 1 SH in preceding year, n (%)	113 (4.4)

Numbers are median (IQR) if not stated otherwise. SMBG = self-monitored blood glucose. SH = severe hypoglycemia (loss of consciousness with or without seizures).

[†] Data from annual controls in 2015 registered in the Norwegian Childhood Diabetes Registry (NCDR) in children with type 1 diabetes, age between 2-19 years, and diabetes duration ≥6 months. Courtesy of NCDR.