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Title: The relationship between sensor-detected hypoglycemia and patient-reported hypoglycemia in people with type 1 and insulin-treated type 2 diabetes: The Hypo-METRICS study

Running title: Relationship between SDH & PRH in T1D & T2D

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Twitter Summary “Hypo-METRICS study highlights that most hypoglycemia on CGM is asymptomatic and >40% of hypoglycemia reported by people living with diabetes is when sensor read >3.9mmol/l (70mg/dl)”

Word count (excluding words in tables, table legends, figure legends, title page, acknowledgments, and references) = 3806 words

PD 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

Abstract

Objective: Use of continuous glucose monitoring (CGM) has led to greater detection of hypoglycemia, the clinical significance of this is not fully understood. The HypoMETRICS study was designed to investigate the rates and duration of sensor-detected hypoglycemia (SDH) and their relationship with person-reported hypoglycemia (PRH) in people living with type 1 (T1D) and insulin-treated type 2 diabetes (T2D) with prior experience of hypoglycemia.

Research Design and Methods: We recruited 276 participants with T1D and 321 with T2D who wore a blinded CGM and recorded PRH in the Hypo-METRICS app over 10-weeks. Rates of SDH <70mg/dl, SDH <54 mg/dl and PRH were expressed as median episodes/week. Episodes of SDH were matched to episodes of PRH that occurred within 1 hour.

Results: Median [Interquartile range] rates of hypoglycemia were significantly higher in T1D vs. T2D; for SDH <70 mg/dl (6.5 [3.8-10.4] vs 2.1 [0.8-4.0]), SDH <54 mg/dl (1.2 [0.4-2.5] vs 0.2 [0.0-0.5]) and PRH (3.9 [2.4-5.9] vs 1.1 [0.5-2.0]). Overall, 65% of SDH <70 mg/dl was not associated with PRH, and 43% of PRH had no associated SDH. The median proportion of SDH associated with PRH in T1D was higher for SDH <70 mg/dl (40% vs 22%) and <54 mg/dl (47% vs 25%) than T2D.

Conclusion: The novel findings that at least half of CGM hypoglycemia is asymptomatic, even below 54 mg/dl, and many reported symptomatic hypoglycemia episodes happen above 70 mg/dl. In the clinical and research setting these episodes cannot be used interchangeably, and both need to be recorded and addressed.

Abstract Word count: 250 words

Keywords: CGM, hypoglycemia, asymptomatic

Article Highlights

- Why did we undertake this study? With use of continuous glucose monitoring (CGM) more hypoglycemia is revealed, with many of these episodes not identified by people living with diabetes
- What is the specific question(s) we wanted to answer? To report the rates of hypoglycemia in type 1 and insulin treated type 2 diabetes and the relationship between CGM hypoglycaemia and person-reported hypoglycemia
- What did we find? The majority of hypoglycemia on CGM is not identified by people living with insulin-treated diabetes, and >40% of hypoglycemia episodes reported by people living with diabetes have no corresponding CGM hypoglycemia
- What are the implications of our findings? CGM hypoglycemia and person reported hypoglycemia need to be individually assessed in the clinical and research setting.

Introduction

Insulin therapy carries with it the risk of hypoglycemia. With the advent of continuous glucose monitoring (CGM), people living with diabetes have access to their glucose concentrations more than when relying on intermittent capillary blood glucose measurements. This allows for earlier intervention to prevent hypoglycemia and can facilitate behavior and therapeutic changes to avoid future episodes of hypoglycemia. Rates of severe hypoglycemia and time spent in hypoglycemia are reduced in people using CGM^{1,2}.

Current consensus guidelines define 3 levels of hypoglycemia³; level 1 or “alert” hypoglycemia of <70 mg/dl, level 2 or clinically significant hypoglycemia of <54 mg/dl and level 3, severe hypoglycemia (cognitive impairment requiring external assistance for recovery). CGM, which measures interstitial glucose, allows for the assessment of both the threshold and duration of hypoglycemia. By consensus, hypoglycemia recorded by CGM is defined using the same thresholds and importantly, with episodes defined as spending at least 15 minutes below a glucose threshold, with resolution of hypoglycemia above the threshold for 15 minutes⁴. This definition is based on expert opinion. Using it, a question of clinical significance of sensor-detected hypoglycemia (SDH) is raised since 60-80% of SDH are asymptomatic and 3-fold more SDH are reported than person-reported hypoglycemia (PRH)^{5,6}. We also know from clinical experience that people living with diabetes sometimes report hypoglycemic symptoms at glucose levels >70 mg/dl⁷.

While level 1 episodes are termed as “alert” level, level 2 hypoglycemia (<54 mg/dl) has important clinical and biological consequences. Glucose concentration <54 mg/dl can lead to neurocognitive impairment⁸ and potentially harmful cardiac outcomes, with corrected QT interval prolongation and stimulation of pro-inflammatory proteins^{9–11}. Based on limited current evidence, asymptomatic SDH does not appear to have a negative effect on quality of life in T1D¹².

The Hypo-METRICS (Hypoglycaemia-MEasurement, ThResholds and ImpaCtS) study, part of the EU-IMI Hypo-RESOLVE program¹³, is a multi-center observational study designed to explore the clinical, psychological and health economic impact of both symptomatic and asymptomatic hypoglycemia and provide an evidence-based definition of SDH, using prospective assessment of real-time recording of PRH and blinded CGM. In this analysis, we report the rates and duration of SDH and the relationship between SDH and PRH, using data from the Hypo-METRICS study.

Methods

Hypo-METRICS was a 10-week multinational observational study taking place at 9 sites in 5 countries in Europe (Austria, Denmark, France, the Netherlands, and the United Kingdom). The trial protocol was approved by ethics committees in each country. The trial is registered on ClinicalTrials.gov (NCT04304963). Written informed consent was obtained from all participants.

Study participants

Key inclusion criteria for the study were being an adult (aged 18–85 years), living with T1D or T2D, taking at least one insulin injection per day and experiencing at least one episode of hypoglycemia in the last 3 months. Key exclusion criteria were an estimated glomerular filtration rate <30 mL/min/1.73 m² and the use of automated insulin delivery systems. All participants were on stable therapy, including no changes to glucose monitoring, for 3 months prior to the study. The trial protocol including the full list of inclusion and exclusion criteria is published¹⁴.

Study procedure

After informed written consent, we collected clinical data, demographics (based on self-identification) and blood samples for hemoglobin A1c (HbA1c) and renal function. For the 10-week observation, participants wore Abbott Freestyle Libre 2 sensors that were connected by Bluetooth to a modified reader that collected glucose data every 5 minutes and was blinded to the participant. The sensor also stored up to 8 hours of 15-minute data that were used if the 5-minute data was not available due to the reader being out of Bluetooth range. During this time, participants continued to use their usual glucose monitoring (either capillary glucose readings (CBG) or their personal CGM devices) for their diabetes self-management. Participants used the bespoke Hypo-METRICS app¹⁵ to report on different aspects of daily functioning three times a day via “check-ins” (on waking, in the afternoon and before bed) and to report details of individual perceived hypoglycemia episodes at or near real-time, and/or during the morning and evening “check-in” with an estimated time of occurrence. Participants had support with study activities throughout the study with virtual visits at weeks two, four and six. Data from the study devices were downloaded after 10 weeks of collection. Due to COVID-19 restrictions, study visits could be performed remotely and in person, when deemed safe to do so by health authorities. Details of app development and content validity have been previously published^{15–17}.

Data analysis

Participants with less than 14 days of CGM data were excluded from all analyses. Results are expressed as median (intra-quartile range) and percentages unless otherwise stated.

Shapiro-Wilk tests were used to assess the normality of the dataset. Chi-squared and Mann-Whitney U tests were used to test for differences between groups. A p-value of <0.05 was considered statistically significant. Generalized linear regression models were used to control for variables in the adjusted analysis. Statistical tests were performed in R Studio version 2023.03.0^{18,19}.

Sensor-detected hypoglycemia

Blinded study sensors collected CGM data at 5-minute intervals and were interpolated for one-minute data. SDH <70 mg/dl and <54 mg/dl were defined according to ATTD consensus guidelines as 15 minutes below the threshold with resolution occurring when glucose levels

were above the defined threshold for > 15 minutes⁴. We also reported SDH ≤ 40 mg/dl for > 15 minutes duration. SDH <70 mg/dl includes SDH <54 mg/dl and SDH ≤ 40 mg/dl in this analysis. Severe hypoglycemia (SH) was defined as per International Hypoglycemia Study Group guidelines³ and all SH were independently adjudicated by experienced clinicians.

Person-reported hypoglycemia (PRH)

The study team took input from experts and the patient advisory council for HypoRESOLVE and defined PRH events as *“symptomatic episodes that resolved on ingestion of carbohydrate, or a measured glucose <72 mg/dl on routine glucose monitoring by either the participant’s clinical CGM or capillary glucose measuring device”*. Less than 72 mg/dl was selected instead of 70 mg/dl as many people living with diabetes at our study locations are educated clinically that less than 72 mg/dl is hypoglycemia requiring intervention. PRH was further sub-divided into symptomatic (those detected by the participant due to symptoms) or technology detected (those detected due to an alert or a chance check of capillary or continuous glucose monitoring glucose but without symptoms).

PRH where the participant had not recorded a time for the event were excluded from the analysis. Multiple PRH episodes within 1 hour of each other were treated as duplicate recordings and treated as the same PRH for calculation of the rates and matching.

Matching SDH and PRH

For this sub-analysis, we also excluded data from days where the CGM data capture was <70% or the Hypo-METRICS app had not been used at least once. This was to mitigate matching not occurring due to missing CGM data or non-engagement with the app. To allow for factors such as delays in recording of PRH, sensor lag and recall error of the time of events, we matched PRH to any SDH occurring within one hour of the PRH. We defined SDH as “matched” if a PRH occurred within 1 hour of an SDH. If a SDH did not have an associated PRH in this window it was deemed “unmatched”. As we saw no differences in rates of SDH and PRH based on hypoglycemic awareness, we included those with impaired awareness of hypoglycemia in this analysis. A further post-hoc analysis will be reported separately.

Results

A total of 602 participants (277 T1D, 325 T2D) completed the 10-week study. Of these, five had less than 14 days of CGM data, leaving 276 T1D and 321 T2D. The people living with T2D were older, but diabetes duration did not differ. The T1D group had a higher proportion of women (54 vs 37%), more people in employment (69 vs 36%). People living with T1D used more CGM (76 vs 41%) and insulin pumps (36 vs 3%) and did more self-monitoring of glucose, although the percent with impaired awareness of hypoglycemia (GOLD score ≥ 4) was not different (21 vs 27%). The baseline characteristics of the participants can be seen in Table 1.

In total, we recorded 37,386 days, equivalent to over 100 years of CGM data (17,117 days in T1D, 20,269 days in T2D). The median (interquartile range; IQR) app completion was 90% (84-95) in T1D and 91% (84-96) in T2D, with blinded CGM data capture being 95% (87-98) and 95% (89-98) in T1D and T2D respectively. The median % (IQR) of time in range 70-180mg/dl was lower in T1D than T2D, 60% (50-72) vs 67 (52-80); p -value <0.001 . The median (IQR) time below 70 mg/dl, 4.5% (2.5-7.9) vs 1.4% (0.5-3.3), and the time below 54 mg/dl, 0.6% (0.2-1.4) vs 0.1 (0.0-0.3), were higher in T1D than T2D ($p<0.001$). We recorded 28,999 SDH <70 mg/dl, (20,100 in T1D, 8,899 in T2D) and 6,711 SDH <54 mg/dl, (5,103 in T1D, 1,608 in T2D). Our participants reported 17,210 PRH, (12,375 in T1D, 4,835 in T2D). All participants with T1D had at least one SDH during the study, with 96% of participants having at least one SDH <54 mg/dl, 37% having a SDH <54 mg/dl of greater than 120 minutes, 26% having an SDH ≤ 40 mg/dl and 3% having an SDH ≤ 40 mg/dl of greater than 120 minutes. For T2D, 93% had at least one SDH <70 mg/dl, 73% had at least one SDH <54 mg/dl, 19% had an SDH <54 mg/dl of greater than 120 minutes, 12% had at least one SDH ≤ 40 mg/dl, with 1.2% having an SDH ≤ 40 mg/dl of greater than 120 minutes. All participants with T1D and 95% of T2D recorded at least one PRH during the study.

Of the SDH <54 mg/dl episodes, 558 (8.3%) had a duration of more than two hours (414 in T1D and 144 in T2D). There were only 302 episodes of SDH ≤ 40 mg/dl, with only 16 of these episodes lasting more than two hours. There was a total of 22 episodes adjudicated as severe hypoglycemia during the study in the combined population, a rate of 0.2 episodes per person per year.

The weekly rates of SDH at all thresholds were higher in the T1D population ($p<0.001$). The median (IQR) rate of SDH <70 mg/dl was 6.7 (3.9-10.8) episodes per week in T1D and 2.1 (1.0-4.3) episodes per week in T2D. The median (IQR) rate of SDH <54 mg/dl was 1.3 (0.5-2.8) episodes per week in T1D and 0.3 (0.0-0.6) episodes per week in T2D. The median (IQR) duration of SDH <70 mg/dl was 59 (47-75) minutes and 59 (43-84) in T2D ($p=0.99$). For SDH <54 mg/dl, the median (IQR) duration was 38 (28-50) minutes in T1D and 38 (27-55) in T2D ($p=0.66$). For SDH ≤ 40 mg/dl, the median (IQR) duration was 27 (19-39) minutes in T1D and 27 (19-45) in T2D ($p=0.98$).

The weekly rates of PRH, and PRH subtypes, were significantly higher in T1D than in T2D ($p<0.001$). The median (IQR) rate of all PRH was 3.9 (2.4-5.9) episodes per week in T1D and 1.1 (0.5-2.0) episodes per week in T2D. When we look at PRH identified by symptoms only, the median (IQR) rate was 2.9 (1.6-4.7) episodes per week in T1D and 0.8 (0.3-1.5) in T2D. For PRH detected through technology, the median (IQR) rate was 0.6 (0.2-1.4) episodes per week in T1D and 0.1 (0.0-0.4) in T2D. The rates and durations of hypoglycemia are summarized in Figure 1.

Relationship of SDH and PRH

For SDH <70 mg/dl episodes, 65% of episodes were not matched with PRH (i.e. had no PRH within a one-hour window of the SDH), with 61% of SDH <70 mg/dl not matched in T1D and 76% of SDH <70 mg/dl in T2D (Figure 2). For SDH <54 mg/dl, 59% of episodes were not matched with PRH, with 55% of episodes in T1D and 71% of episodes in T2D. For individuals, the median [IQR] proportion of matched SDH was higher in T1D than T2D, at both SDH <70 mg/dl (40% [29-53] vs 22% [8-42]; $p<0.001$) and SDH <54 mg/dl (47% [27-67] vs 25% [0-55]; $p<0.001$) (Figure 3). When adjusted for age, gender, rate of SDH and CGM usage, the differences in matched SDH between T1D and T2D were still significant, although the magnitude of differences was reduced to 13% for SDH <70 mg/dl and 12% for SDH <54 mg/dl ($p<0.001$).

After matching SDH to PRH, 6,206 PRH (3,794 in T1D and 2,341 in T2D) were unmatched (not associated with SDH within 1 hour) (Figure 2). This equated to 43% of total PRH (37% in T1D and 58% in T2D). This analysis using only symptomatic PRH is available in supplemental Figure 1.

Of the unmatched PRH, 80% were reported as symptomatic and 20% technology detected (in the absence of symptoms), with similar proportions in T1D and T2D. Unmatched PRH episodes were not associated with higher HbA1c when adjusted for age, gender, total PRH and CGM usage in either T1D ($p=0.5$) or T2D ($p=0.7$).

Discussion

The novel collection of 10 weeks' blinded CGM data and contemporaneous app-collected information of personal experiences of hypoglycemia from this large multinational study creates a unique dataset and allows us to analyze the relationship between sensor-detected and patient-reported hypoglycemia. Our main findings include a higher rate of SDH and PRH in people living with T1D than in those with insulin-treated T2D, a significant discrepancy between PRH and SDH, with many SDH not identified by people with either T1D or T2D, and many symptomatic episodes of PRHs not associated with hypoglycemic values on the sensors. This discrepancy in the relationship of PRH and SDH is more pronounced in T2D than T1D. The duration of SDH episodes did not differ by diabetes type.

While rates of hypoglycemia have previously been reported in multiple studies^{6,20–22}, most were done before CGM was widely used. The Hypo-METRICS study was performed during a time of transition from capillary glucose monitoring to CGM that may have impacted rates of SDH as well as PRH. While the rates of SDH for the T1D population were consistent with existing data⁶, the rates in T2D were significantly higher than those seen in the literature². This may be explained in part by the inclusion criterion of recent experience of hypoglycemia and increased interest in a study of hypoglycemia by people who experience more hypoglycemia. The proportion of people with T2D who had hypoglycemia and impaired awareness of hypoglycemia during the present study was high compared to other real-world data^{22,23}. However, our rate of severe hypoglycemia during the study is consistent with real-world data²¹ and indeed lower than in similar observational studies²⁴. Also, out of the nearly 29,000 recorded SDH, we recorded only 302 SDH ≤ 40 mg/dl with only 16 of these lasting greater than two hours, the equivalent of 0.14 episodes per person-year.

Rates of PRH were higher in our study than previous studies. This may be because a high proportion of those with T1D were using CGM, allowing higher detection of PRH related to increased frequency of glucose measurements and the availability of alarms which allows for increased detection of hypoglycemia. Another contributor to our higher rate of PRH may be the use of Ecological Momentary assessments or near real-time reporting of hypoglycemia using the bespoke Hypo-METRICS app that may have reduced under-reporting of hypoglycemia from recall bias.

A key finding was that less than 40% episodes of SDH < 70 mg/dl, were identified by participants. Even at a lower sensor glucose threshold of < 54 mg/dl, less than half the episodes were identified. While previous studies have shown some similar findings in a shorter duration study in T1D⁵ and lower detection when using capillary blood glucose monitoring²⁵, our data are novel in showing this finding in both T1D and T2D and that more of these episodes are unrecognized in T2D. These findings have implications for the use of CGM in defining or identifying those with impaired awareness of hypoglycemia and raises questions about the clinical significance of asymptomatic SDH, which need urgent investigation.

Lower identification of SDH in T2D as compared to T1D may be explained by several factors. We hypothesized that the lower detection of SDH in T2D could be explained by the differences in age or CGM use. Older people report lower symptom scores for hypoglycemia, despite intact counter-regulatory response²⁶. However, adjusting for these factors, as well as gender, we still saw significant differences in the proportion of reported hypoglycemia. The T1D population scanned more and performed more capillary blood glucose readings, which likely contributes to a confirmation bias in the identification of SDH.

Experimental studies have shown that adrenergic responses to hypoglycaemia are generated at between 60-65 mg/dl⁸, and so it is not surprising that many episodes between just below 70 mg/dl were asymptomatic. It was more surprising that at least half of episodes below 54 mg/dl were asymptomatic in T1D and nearly three-quarters in T2D. An episode below 54 mg/dl can potentially lead to acute neurological, cardiovascular, inflammatory and pro-coagulant effects^{8,11,27}. The lack of identification of these episodes, particularly those below 54mg/dl, is therefore of clinical concern.

An important finding was that many episodes recognized and treated by participants as hypoglycaemia were not associated with a SDH. We can speculate on some possible explanations. There are anecdotal and some published evidence for counterregulatory responses to occur above hypoglycemic glucose concentrations in people accustomed to chronic hyperglycemia and no previous hypoglycemia²⁸, however we did not see any association between HbA1c and the proportion of PRH that did not have matched SDH. Some of these episodes may be explained by participants who had their alarms set at levels above 70 mg/dl, and others may be explained by sensor lag – i.e. plasma glucose may have been low enough to generate symptoms, but sensor glucose may have been above 70 mg/dl. The clinical implications are that relying on time below range alone may not describe completely the patient experience of hypoglycemia.

We believe this is an important finding that suggests that many people have symptoms that they recognize and believe to be related to hypoglycemia. The proportion of these episodes were higher in T2D than in T1D, which again may be explained in part by the different characteristics of the population, both biomedical and also lower use of CGM in T2D.

With the increased use of CGM by people living with diabetes, the duration of hypoglycemia has become easily measurable and more clinically apparent. The median duration of hypoglycemia was significantly longer than the 15 minutes recommended for reporting by the ATTD consensus guidance document²⁹. There was no significant difference in the duration of episodes of hypoglycemia at any threshold between people living with T1D and T2D. Despite people living with T1D having significantly higher rates of hypoglycemia and time below range, once hypoglycemia occurred, the time taken for resolution of hypoglycemia was the same, suggesting that combined behaviors and biological responses to hypoglycemia across the diabetes spectrum led to resolution of hypoglycemia in a similar time frame.

The study has several strengths and some limitations. Hypo-METRICS was a large multinational multicenter study taking place in nine centers across five countries with detailed descriptions of participants using novel methods of reporting hypoglycemia. Data completion was over 90%, with just under one million hours of CGM data and over 100 years' worth of patient experience accumulated. Analysis has shown the usability of the app across the participant spectrum was high³⁰. The unique aspect of our study was the reporting of PRH in real time with the use of the Hypo-METRICS app, limiting recall bias seen with retrospective reporting. Our inclusion criteria of hypoglycemia in the previous three months may have enriched our sample, particularly in the T2D insulin-using population, where previous data show a smaller proportion of the population experiences hypoglycemia²⁴. We used the Libre 2 sensor, as this is the most widely used sensor system in Europe and has similar accuracy to other sensors (mean absolute relative difference 9.2%³¹), but sensor accuracy could account for a small proportion of the mismatch between SDH and PRH. While the study sensor was blinded, many participants had access to their own sensor during the study, which may have influenced their behaviors and/or treatment compared to those using CBG only. This analysis does not address the biological

consequences of symptomatic or asymptomatic hypoglycaemia. In some study locations, people living with diabetes recognise 72 mg/dl (4 mmol/l) as the threshold for hypoglycemia and this was the cut-off recognized by our patient advisory committee, in contrast to the SDH consensus definition of 70 mg/dl. This may have contributed to a proportion of the PRH not associated with SDH, however were only symptomatic episodes be used, the proportion of unmatched PRH is largely unchanged. The study was also conducted during the COVID-19 pandemic, which meant significant changes to daily life and changes in glycemic outcomes³² with these changes most pronounced in the older age groups³³. We acknowledge that this is a predominantly white European population and that these findings may not apply to other regions and ethnicities.

We believe that these data have important implications for the reporting of hypoglycemia in clinical trials. Given the proportion of PRH and SDH that were not matched, we believe that PRH and SDH should be reported independently in clinical studies, especially those where hypoglycaemia is a key primary or secondary outcome. Analysis from our data shows that PRH (regardless of the presence of SDH) has a measured negative psychosocial impact of hypoglycemia on the individual³⁴, which does not occur with unrecognized SDH. Rates of SDH and in particular rates of values below 54mg/dl are important given the potential cardiovascular and neurological impact of these episodes, but recording and reporting of hypoglycemia experience are important for their impact on daily functioning and quality of life and so in clinical trials it is important to accurately report both and one cannot substitute for the other.

These data also have implications for clinical practice. With over half of SDH being unrecognized, this suggests that it could be normal to experience some degree of asymptomatic hypoglycemia when reviewing CGM downloads of people living with diabetes. The presence of these episodes does not necessarily imply impaired awareness of hypoglycemia and are seen even in people without diabetes, with 28% of non-diabetic people having SDH <54 mg/dl over 10 days³⁵. Given that more than half SDH episodes are asymptomatic, and almost half of reported hypoglycemia occur at sensor glucose concentrations above 70mg/dl, we cannot assess the impact or burden of hypoglycemia from CGM metrics alone. The biological implications of asymptomatic level 1 SDH needs further investigation. Our data also suggest that in today's era of high CGM use, the most concerning biological hypoglycemia episodes, those of very low glucose for several hours, are thankfully rare.

In conclusion, this study highlights the high proportion of hypoglycemia on CGM which is not identified by people living with diabetes on insulin, and the high proportion of hypoglycemia reported by people living with diabetes without corresponding SDH. Given the discrepancy between SDH and PRH, the use of the Hypo-METRICS app provides insight to hypoglycemia that cannot be captured with CGM data alone. These findings will have a significant clinical impact when interpreting CGM data and have implications on how we define impaired hypoglycemic awareness and hypoglycemic research outcomes in the future.

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Conflict of Interest

PD has spoken at an educational symposium sponsored by Novo Nordisk

SAA has served on advisory boards for NovoNordisk and Medtronic and has spoken at an educational symposium sponsored by Sanofi

MLE has served on advisory boards and/or received lecture fees and/or research support from NovoNordisk, Eli Lilly, AstraZeneca, Medtronic, Dexcom, Ypsomed, Abbott Diabetes Care, Roche, NGM Pharma, Zucara, Pila Pharma and Sanofi

UPB has served on advisory boards for Novo Nordisk, Sanofi and Vertex and has received lecture fees from Novo Nordisk and Sanofi.

JKM is a member in the advisory board of Boehringer Ingelheim, Eli Lilly, Medtronic, NovoNordisk AS, Prediktor A/S, Roche Diabetes Care, Sanofi-Aventis and received speaker

honoraria from Abbott Diabetes Care, Astra Zeneca, Dexcom, Eli Lilly, Medtronic, MSD, NovoNordisk AS, Roche Diabetes Care, Sanofi, Servier and Takeda. She is shareholder of decide Clinical Software GmbH and elyte diagnostics.

ER has served as consultant/advisor for Abbott, Air Liquide SI, Astra-Zeneca, Boehringer-Ingelheim, Dexcom, Eli-Lilly, Hillo, Insulet, Medirio, Novo-Nordisk, Roche, Sanofi-Aventis, Tandem, and received research support from Dexcom, Insulet and Tandem.

PC has received personal fees Abbott Diabetes Care, Insulet, Dexcom, Novo Nordisk, AstraZeneca, Medtronic, Roche Diabetes Care and Sanofi Diabetes. Research funding support from Abbott Diabetes Care, Medtronic and Novo Nordisk.

RM has served on advisory boards and/or received lecture fees and/or research support from Sanofi, NovoNordisk.

FP has received funding for research from Novo Nordisk, Eli Lilly and Sanofi-Aventis.

SRH has served on advisory boards for Zealand Pharma, Zucara Pharma, research support from Dexcom, lecture fees from NovoNordisk and Medtronic.

Author Contributions and Guarantor Statement.

PD, NZ, GME, PC and SA developed the plan for the manuscript, with input and advice from the remaining co-authors. GME advised on the analysis plan, and PD conducted all analyses with GME assistance. PD prepared the manuscript draft, with critical feedback from NZ, GME, PC and SA. PD prepared subsequent revisions with feedback from all authors. All authors approved the final draft of the manuscript.

PD 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.

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Baseline Characteristics	Type 1 Diabetes N= 276	Insulin treated Type 2 Diabetes N= 321	p-value
Age, yrs (IQR)	47 (30-56)	63 (55-69)	<0.001
Duration of diabetes, yrs (IQR)	21 (10-35)	19 (13-25)	0.12
Ethnicity,			0.52
White people, % (n)	88 (243)	90 (289)	
Not defined or people of other ethnicity, % (n)	12 (23)	10 (32)	
Gender,			<0.001
Female, % (n)	54 (148)	37 (119)	
Male, % (n)	45 (126)	63 (202)	
Other, % (n)	1 (2)	0 (0)	
Country,			<0.001
United Kingdom, % (n)	56 (154)	40 (129)	
Netherlands, % (n)	13 (35)	31 (98)	
Austria, % (n)	12 (33)	16 (52)	
Denmark, % (n)	11 (30)	12 (38)	
France, % (n)	9 (24)	1 (4)	
Employment,			<0.001
Employed, % (n)	69 (191)	36 (115)	
Retired, % (n)	17 (47)	52 (166)	
Full-time education, % (n)	5 (15)	2 (5)	
Unemployed, % (n)	8 (23)	11 (35)	
Highest level of education achieved,			<0.001
Primary school, % (n)	2 (4)	11 (36)	
Secondary school, % (n)	24 (66)	32 (102)	
College- undergraduate degree, % (n)	44 (121)	35 (112)	
Postgraduate degree- Masters/PhD/MBA, % (n)	25 (70)	11 (36)	
Other, % (n)	5 (15)	11 (35)	
Glucose monitoring,			<0.001
Capillary blood glucose monitoring, % (n)	24 (67)	59 (190)	
Flash/Continuous glucose monitoring, % (n)	76 (209)	41 (131)	
Monitoring frequency,			
Capillary blood glucose, median (IQR) per week	5.0 (3.7-6.3)	2.0 (1.1-3.0)	<0.001
Flash glucose monitoring scans, median (IQR) per week	11 (8-16)	7 (5-10)	<0.001
Impaired awareness of hypoglycemia, % (n)	21 (58)	27 (87)	0.1
Insulin delivery,			<0.001
Multiple daily injections, % (n)	64 (176)	63 (201)	
Mixed insulin, % (n)	0 (0)	12 (37)	
Insulin pump, % (n)	36 (98)	3 (9)	
Other, % (n)	1 (2)	23 (74)	
HbA1c,			0.02
%, median (IQR)	7.3 (6.7-7.8)	7.5 (6.8-8.3)	
Mmol/mol, median (IQR)	56 (50-62)	59 (51-67)	
Missing data, (% of total)	4 (1.4)	1 (0.3)	

Table 1. Baseline characteristics

Figure 1

- a) Median rates of SDH in T1D & T2D
- b) Median rates of PRH in T1D & T2D
- c) Median duration of SDH in T1D & T2D

Figure 2.

- a) The proportion of matched and unmatched SDH <70 mg/dl and PRH in all participants
- b) The proportion of matched and unmatched SDH <70 mg/dl and PRH in T1D
- c) The proportion of matched and unmatched SDH <70 mg/dl and PRH in T2D

Figure 3. Median percentage of SDH detected by individuals with T1D and T2D (a) at SDH <70 mg/dl (b) at SDH < 54 mg/dl