Diabetes Care
American Diabetes Association

Relationship Between Sensor-Detected Hypoglycemia and Patient-Reported Hypoglycemia in People With Type 1 and Insulin-Treated Type 2 Diabetes: The Hypo-METRICS Study

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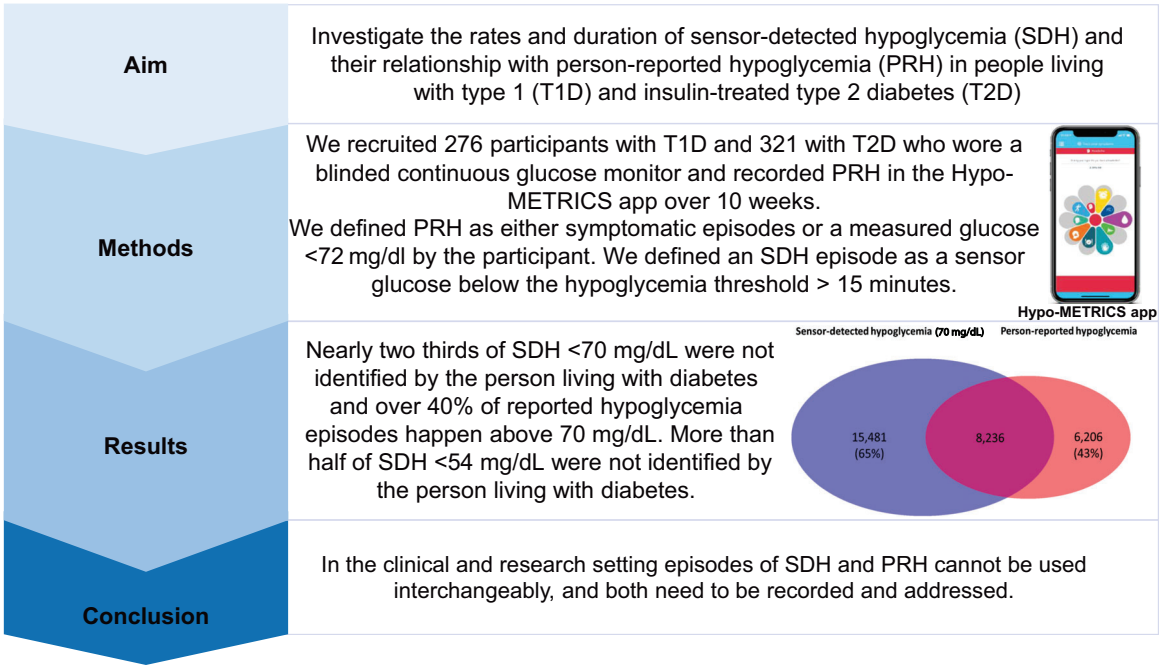
Diabetes Care 2024;47(10):1769–1777 | https://doi.org/10.2337/dc23-2332



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?**
  We sought to report the rates of hypoglycemia in type 1 and insulin-treated type 2 diabetes and the relationship between CGM hypoglycemia 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.

Relationship Between Sensor-Detected Hypoglycemia and Patient-Reported Hypoglycemia in People With Type 1 and Insulin-Treated Type 2 Diabetes: The Hypo-METRICS Study

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Diabetes Care 2024;47:1769–1777 | https://doi.org/10.2337/dc23-2332

OBJECTIVE

Use of continuous glucose monitoring (CGM) has led to greater detection of hypoglycemia; the clinical significance of this is not fully understood. The Hypoglycaemia–Measurement, Thresholds and Impacts (Hypo-METRICS) 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 diabetes (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 <70 mg/dL, SDH <54 mg/dL, and PRH were expressed as median episodes per week. Episodes of SDH were matched to episodes of PRH that occurred within 1 h.

RESULTS

Median [interquartile range] rates of hypoglycemia were significantly higher in T1D versus 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 SDH <54 mg/dL (47% vs. 25%) than in T2D.

CONCLUSIONS

The novel findings are 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.

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

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glucose concentrations more than when relying on intermittent capillary blood glucose (CBG) 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 (SH) and time spent in hypoglycemia are reduced in people using CGM (1,2).

Current consensus guidelines define three levels of hypoglycemia (3); level 1 or "alert" hypoglycemia of <70 mg/dL, level 2 or clinically significant hypoglycemia of <54 mg/dL, and level 3 or SH (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 min below a glucose threshold, with resolution of hypoglycemia above the threshold for 15 min (4). 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 threefold 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/dL (7).

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 impairment (8) and potentially harmful cardiac outcomes, with corrected QT interval prolongation and stimulation of proinflammatory proteins (9–11). Based on limited current evidence, asymptomatic SDH does not appear to have a negative effect on quality of life in type 1 diabetes (T1D) (12).

The Hypoglycaemia–Measurement, Thresholds and Impacts (Hypo-METRICS) study, part of the European Union Innovative Medicines Initiative Hypoglycaemia – Redefining Solutions for Better Lives (Hypo-RESOLVE) program (13), is a multicenter 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.

RESEARCH DESIGN AND METHODS

Hypo-METRICS was a 10-week multinational observational study taking place at nine sites in five countries in Europe (Austria, Denmark, France, the Netherlands, and U.K.). The trial protocol was approved by ethics committees in each country (South Central Oxford B Research Ethics Committee [U.K.], Ethikkommission der Medizinischen Universität Graz [Austria], Videnskabsetisk Komite for Region Hovedstaden [Denmark], Comité De Protection Des Personnes SUD Mediterranne IV [France], and Commissie Mensgebonden Onderzoek Regio Arnhem-Nijmegen [the Netherlands]. 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 type 2 diabetes (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 of <30 mL/min/1.73 m^2 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 published (14).

Study Procedure

After informed written consent, we collected clinical data, demographics (based on self-identification), and blood samples for hemoglobin A1c (HbA_{1c}) 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 min and was blinded to the participant. The sensor also stored up to 8 h of 15-min data that were used if the 5-min data were not available because of the reader being out of Bluetooth range. During this time, participants continued to use their usual glucose monitoring (either CBG readings or their personal CGM devices) for their diabetes self-management. Participants used the bespoke Hypo-METRICS app (15) to report on various 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 2, 4, and 6. Data from the study devices were downloaded after 10 weeks of collection. Because of coronavirus disease 2019 (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).

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Received 5 December 2023 and accepted 2 July 2024

Clinical trial reg. no. NCT04304963, ClinicalTrials.gov

This article contains supplementary material online at https://doi.org/10.2337/figshare.26359831.

This article is featured in a podcast available at diabetesjournals.org/care/pages/diabetes_care_on_air.

Data Analysis

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

Shapiro-Wilk tests were used to assess the normality of the data set. χ^2 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).

SDH

Blinded study sensors collected CGM data at 5-min intervals and were interpolated for 1-min data. SDH <70 mg/dL and SDH <54 mg/dL were defined according to Advanced Technologies and Treatments for Diabetes consensus guidelines as 15 min below the threshold with resolution occurring when glucose levels were above the defined threshold for >15 min (4). We also reported SDH ≤ 40 mg/dL for >15 min duration. SDH <70 mg/dL includes SDH <54 mg/dL and SDH ≤ 40 mg/dL in this analysis. SH was defined as per International Hypoglycemia Study Group guidelines (3), and all SH were independently adjudicated by experienced clinicians.

PRH

The study team took input from experts and the patient advisory council for Hypo-RESOLVE 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 subdivided into symptomatic (those detected by the participant because of symptoms) or technology detected (those detected because of an alert or a chance check of capillary or CGM glucose but without symptoms).

PRH where the participant had not recorded a time for the event were excluded from the matching analysis. Multiple PRH episodes within 1 h 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 subanalysis, 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 because of missing CGM data or nonengagement 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 1 h of the PRH. We defined SDH as "matched" if a PRH occurred within 1 h of an SDH. If an 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, 5 had less than 14 days of CGM data, leaving 276 T1D and 321 T2D participants. 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%), and 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 percent (IQR) of time in range 70–180 mg/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 an SDH <54 mg/dL of greater than 120 min, 26% having an SDH ≤ 40 mg/dL, and 3% having an SDH ≤ 40 mg/dL of greater than 120 min. 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 min, and 12% had at least one SDH ≤ 40 mg/dL, with 1.2% having an SDH ≤ 40 mg/dL of greater than 120 min. All participants with T1D and 95% of those with 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 2 h (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 2 h. There was a total of 22 episodes adjudicated as SH 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 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) min and 59 (43–84) min in T2D ($P = 0.99$). For SDH <54 mg/dL, the median (IQR) duration was 38 (28–50) min in T1D and 38 (27–55) min in T2D ($P = 0.66$). For SDH ≤ 40 mg/dL, the median (IQR) duration was 27 (19–39) min in T1D and 27 (19–45) min 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) episodes per week in T2D. For PRH detected through technology, the median (IQR) rate

Table 1—Baseline characteristics

Baseline characteristics	T1D, *n* = 276	Insulin-treated T2D, *n* = 321	*P* value
Age, years (IQR)	47 (30–56)	63 (55–69)	<0.001
Duration of diabetes, years (IQR)	21 (10–35)	19 (13–25)	0.12
Ethnicity, % (*n*)			0.52
White	88 (243)	90 (289)	
Not defined or of other ethnicity	12 (23)	10 (32)	
Gender, % (*n*)			<0.001
Female	54 (148)	37 (119)	
Male	45 (126)	63 (202)	
Other	1 (2)	0 (0)	
Country, % (*n*)			<0.001
U.K.	56 (154)	40 (129)	
Netherlands	13 (35)	31 (98)	
Austria	12 (33)	16 (52)	
Denmark	11 (30)	12 (38)	
France	9 (24)	1 (4)	
Employment, % (*n*)			<0.001
Employed	69 (191)	36 (115)	
Retired	17 (47)	52 (166)	
Full-time education	5 (15)	2 (5)	
Unemployed	8 (23)	11 (35)	
Highest level of education achieved, % (*n*)			<0.001
Primary school	2 (4)	11 (36)	
Secondary school	24 (66)	32 (102)	
College-undergraduate degree	44 (121)	35 (112)	
Postgraduate degree: Masters/PhD/MBA	25 (70)	11 (36)	
Other	5 (15)	11 (35)	
Glucose monitoring, % (*n*)			<0.001
CBG monitoring	24 (67)	59 (190)	
Flash/CGM	76 (209)	41 (131)	
Monitoring frequency			
CBG, 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, % (*n*)			<0.001
Multiple daily injections	64 (176)	63 (201)	
Mixed insulin	0 (0)	12 (37)	
Insulin pump	36 (98)	3 (9)	
Other	1 (2)	23 (74)	
HbA_{1c}			0.02
Percent, 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 (*n*)	1.4 (4)	0.3 (1)	

was 0.6 (0.2–1.4) episodes per week in T1D and 0.1 (0.0–0.4) episodes per week in T2D. The rates and durations of hypoglycemia are summarized in Fig. 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 1 h window of the SDH), with 61% of SDH <70 mg/dL not matched in T1D and 76% of SDH <70 mg/dL not matched in T2D (Fig. 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]; $P < 0.001$) (Fig. 3). When adjusted for age, gender, and 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 h) (Fig. 2). This equated to 43% of total PRH (37% in T1D and 58% in T2D). This analysis using only symptomatic PRH is available in Supplementary Fig. 1.

Of the unmatched PRH, 80% were reported as symptomatic and 20% as technology detected (in the absence of symptoms), with similar proportions in T1D and T2D. Unmatched PRH episodes were not associated with higher HbA_{1c} when adjusted for age, gender, and total PRH and CGM usage in either T1D ($P = 0.5$) or T2D ($P = 0.7$).

CONCLUSIONS

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 data set and allows us to analyze the relationship between SDH and PRH. 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 data (6), the rates in T2D were significantly higher than those seen in the literature (2). 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

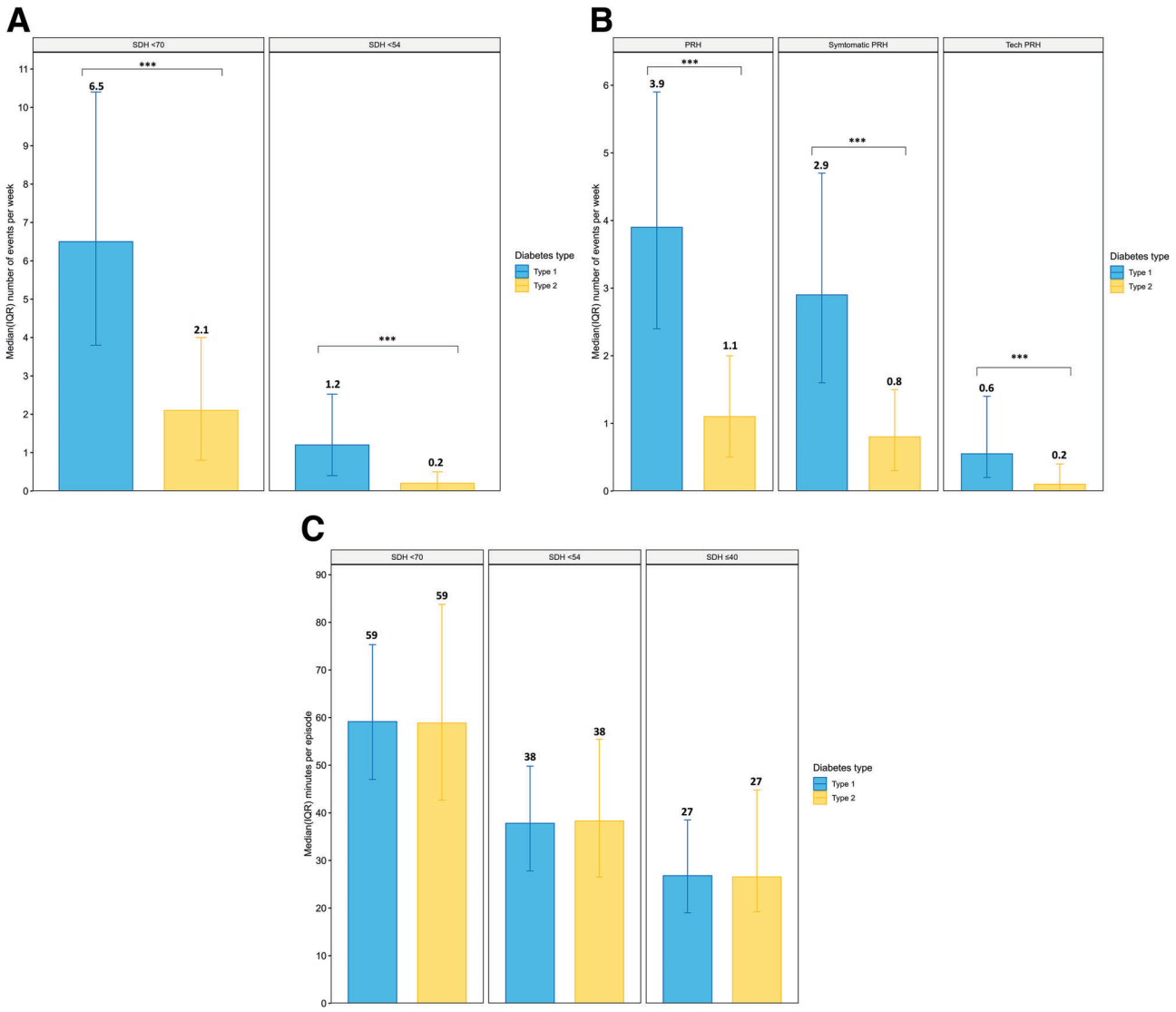

Figure 1—*A*: Median rates of SDH in T1D and T2D. *B*: Median rates of PRH in T1D and T2D. *C*: Median duration (*P* value <0.001) of SDH in T1D and T2D.

hypoglycemia during the current study was high compared with other real-world data (22,23). However, our rate of SH during the study is consistent with real-world data (21) and, indeed, lower than in similar observational studies (20). Also, out of the nearly 29,000 recorded SDH, we recorded only 302 SDH ≤40 mg/dL, with only 16 of these lasting longer than 2 h, the equivalent of 0.14 episodes per person-year.

Rates of PRH were higher in our study than in 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 underreporting of hypoglycemia from recall bias.

A key finding was that less than 40% of 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 T1D (5) and lower detection when using CBG monitoring (24), 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 raise questions about the clinical significance of asymptomatic SDH, which need urgent investigation.

Lower identification of SDH in T2D as compared with 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 counterregulatory response (25). 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 hypoglycemia are generated at between 60 and 65 mg/dL

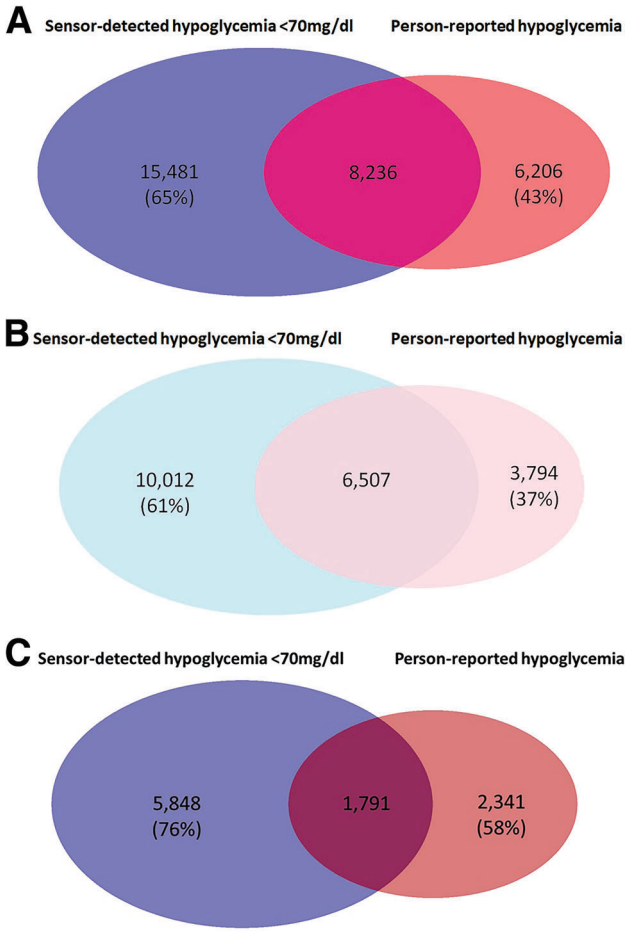

Figure 2—*A*: The proportion of matched and unmatched SDH <70 mg/dL and PRH in all participants. *B*: The proportion of matched and unmatched SDH <70 mg/dL and PRH in T1D. *C*: The proportion of matched and unmatched SDH <70 mg/dL and PRH in T2D.

(8), and so it is not surprising if many episodes 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 were asymptomatic in T2D. An episode below 54 mg/dL can potentially lead to acute neurological, cardiovascular, inflammatory, and procoagulant effects (8,11,26). The lack of identification of these episodes, particularly those below 54 mg/dL, is therefore of clinical concern.

An important finding was that many episodes recognized and treated by participants as hypoglycemia were not associated with an SDH. We can speculate on some possible explanations. There is anecdotal and some published evidence for counterregulatory responses to occur above hypoglycemic glucose concentrations in people accustomed to chronic hyperglycemia and no previous hypoglycemia (27); however, we did not see any association between HbA_{1c} 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; that is, 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 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 involving 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 min recommended for reporting by the Advanced Technologies

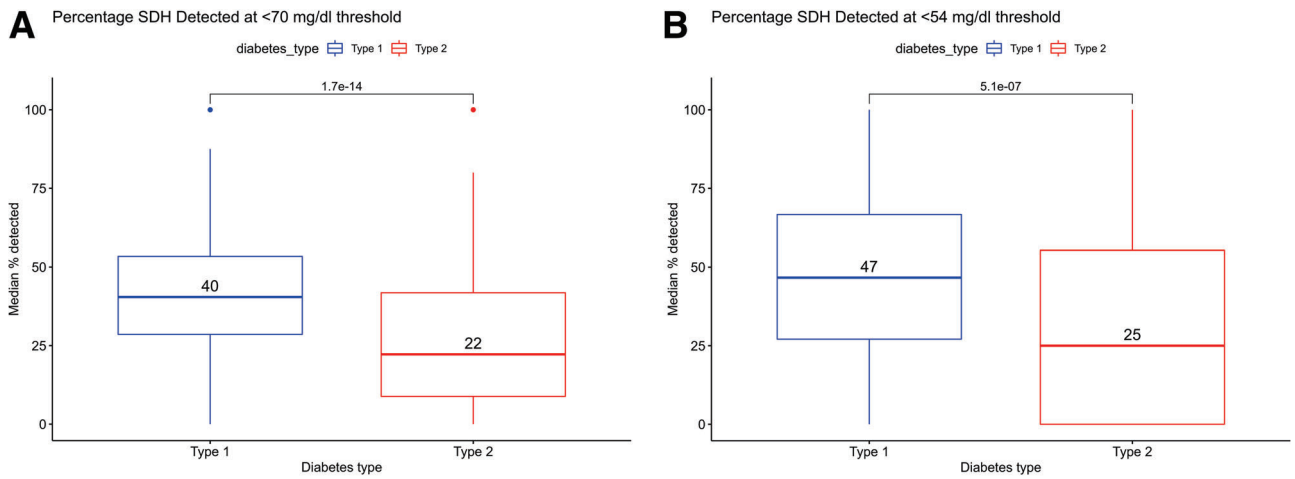

Figure 3—Median percentage of SDH detected by individuals with T1D and T2D (*A*) at SDH <70 mg/dL and (*B*) at SDH <54 mg/dL.

and Treatments for Diabetes consensus guidance document (28). 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 1 million h of CGM data and over 100 years' worth of patient experience accumulated. Analysis has shown that the usability of the app across the participant spectrum was high (29). 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 3 months may have enriched our sample, particularly in the T2D insulin-using population, where previous data show a smaller proportion of the population experiences hypoglycemia (20). 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% [30]), 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 with those using CBG only. This analysis does not address the biological consequences of symptomatic or asymptomatic hypoglycemia. In some study locations, people living with diabetes recognize 72 mg/dL (4 mmol/L) as the threshold for hypoglycemia, and this was the cutoff 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 used, the proportion of unmatched PRH would be largely unchanged. The study was also conducted during the COVID-19 pandemic, which meant significant changes to daily life and changes in glycemic outcomes (31), with these changes most pronounced in the older age-groups (32). 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 hypoglycemia 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 individual (33), which does not occur with unrecognized SDH. Rates of SDH and, in particular, rates of values below 54 mg/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. Therefore, 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 they are seen even in people without diabetes, with 28% of people without diabetes having SDH $<$54 mg/dL over a 10-day period (34). Given that more than half of SDH episodes are asymptomatic, and almost half of reported hypoglycemia occurs at sensor glucose concentrations above 70 mg/dL, we cannot assess the impact or burden of hypoglycemia from CGM metrics alone. The biological implications of asymptomatic level 1 SDH need 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 that 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 into 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.

Acknowledgments. We thank the Hypo-RESOLVE Patient Advisory Committee for their support in the development of the Hypo-METRICS study. We thank all participants in the Hypo-METRICS study. We acknowledge the hard work and dedication of all staff at the study sites, in particular, Andrew Pernet, Amy Aldridge, Marcia Henderson-Wilson (Kings College London), Pernille Banck-Petersen, Rikke Carstensen, Charlotte Hansen (Nordsjællands Hospital Hillerød), Sharon Caunt, Sue Hudson, Chloe Husband, Fahad Arshad (University of Sheffield), Anne Farret, Anne-Marie Marteil-Oudrer, Manal Shbat, Lisa Crespy, Jenny Constanza Thibout (University of Montpellier), Anja Rasing, Jesper Walburgh Schimidt, Daniel Loewenstein, Renate Huijsmans, Pieter Drijver (Radboud University Medical Centre), Daniel Chapman, Jane Kennet (University of Cambridge), Anna Barnett, and Jackie Lindsay (University of Dundee).

Funding. This work was supported by the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement 777460. JU receives support from the European Union's Horizon 2020 Research and Innovation Programme and European Federation of Pharmaceutical Industries and Associations and T1D Exchange, Juvenile Diabetes Research Foundation, International Diabetes Federation, and The Leona M. and Harry B. Helmsley Charitable Trust. The industry partners supporting JU include Abbott Diabetes Care, Eli Lilly, Medtronic, Novo Nordisk, and Sanofi-Aventis. G.M.-E.'s position at King's College London is funded by a grant from Novo Nordisk. The University of Cambridge has received salary support for M.E. through the National Health Service in the East of England through the Clinical Academic Reserve and work supported by the National Institute for Health and Care Research (NIHR) Cambridge Biomedical Research Centre and carried out in the NIHR Cambridge Clinical Research Facility/Translational Research Facility. This study represents independent research supported by the NIHR King's Clinical Research Facility and the NIHR Biomedical Research Centre at South London and Maudsley National Health Service Foundation Trust and King's College London. The University of Cambridge has

received salary support for M.E. through the National Health Service in the East of England through the Clinical Academic Reserve. Abbott Diabetes Care provided the continuous glucose monitors used in the study.

The views expressed are those of the author(s) and not necessarily those of the National Health Service, NIHR, the Department of Health and Social Care or the JU.

Duality of Interest. P.D. has spoken at an educational symposium sponsored by Novo Nordisk. S.A.A. has served on advisory boards for Novo Nordisk and Medtronic and has spoken at an educational symposium sponsored by Sanofi. M.E. has served on advisory boards and/or received lecture fees and/or research support from Novo Nordisk, Eli Lilly, AstraZeneca, Medtronic, Dexcom, Ypsomed, Abbott Diabetes Care, Roche, NGM Pharma, Zucara, Pila Pharma, and Sanofi. U.P.-B. has served on advisory boards for Novo Nordisk, Sanofi, and Vertex and has received lecture fees from Novo Nordisk and Sanofi. J.K.M. is a member of the advisory boards of Boehringer Ingelheim, Eli Lilly, Medtronic, Novo Nordisk AS, Prediktor A/S, Roche Diabetes Care, and Sanofi-Aventis Deutschland GmbH and received speaker honoraria from Abbott Diabetes Care, Astra Zeneca, Dexcom, Eli Lilly, Medtronic, MSD, Novo Nordisk AS, Roche Diabetes Care, Sanofi, Servier, and Takeda. She is shareholder of decide Clinical Software GmbH and elyte diagnostics. E.R. has served as consultant/advisor for Abbott, Air Liquide SI, AstraZeneca, Boehringer-Ingelheim, Dexcom, Eli Lilly, Hillo, Insulet, Medirio, Novo Nordisk, Roche, Sanofi-Aventis Deutschland GmbH, and Tandem and received research support from Dexcom, Insulet, and Tandem. P.C. has received personal fees Abbott Diabetes Care, Insulet, Dexcom, Novo Nordisk, AstraZeneca, Medtronic, Roche Diabetes Care, and Sanofi Diabetes and research funding support from Abbott Diabetes Care, Medtronic, and Novo Nordisk. R.J.M. has served on advisory boards and/or received lecture fees and/or research support from Sanofi and Novo Nordisk. F.P. has received funding for research from Novo Nordisk, Eli Lilly, and Sanofi-Aventis Deutschland GmbH. S.H. has served on advisory boards for Zealand Pharma and Zucara Pharma, and received research support from Dexcom and lecture fees from Novo Nordisk and Medtronic. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. P.D., N.Z., G.M.-E., S.A.A., and P.C. developed the plan for the manuscript, with input and advice from the remaining coauthors. G.M.-E. advised on the analysis plan, and P.D. conducted all analyses with G.M.-E.'s assistance. P.D. prepared the manuscript draft, with critical feedback from N.Z., G.M.-E., S.A.A., and P.C. P.D. prepared subsequent revisions with feedback from all authors. All authors approved the final draft of the manuscript. P.D. 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.

Prior Presentation. Parts of this study were presented in abstract form at the 83rd Scientific Sessions of the American Diabetes Association, San Diego, CA, 23–26 June 2023.

Handling Editors. The journal editors responsible for overseeing the review of the manuscript were Steven E. Kahn and Jennifer B. Green.

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