

# Descriptions of health states associated with increasing severity and frequency of hypoglycemia: a patient-level perspective

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**Aims:** We sought to develop descriptions of health states associated with daytime and nocturnal hypoglycemia in a structured fashion from the patient's perspective under different combinations of severity and frequency of hypoglycemic events.

**Methods:** An expert meeting followed by two patient focus groups was used to develop comprehensive descriptions of acute consequences of severe and non-severe, daytime and nocturnal hypoglycemia. Patients with diabetes (type 1 = 85, type 2 = 162) from a survey panel then validated these descriptions and assessed how often they worried and took different actions to prevent hypoglycemia. Severity and frequency of hypoglycemia were compared with respect to how often people worried and took actions to prevent an event. The effect of hypoglycemia on 35 different life activities was quantitatively compared for patients who had and had not experienced a severe hypoglycemic event.

**Results:** At least 95% of respondents agreed that the detailed patient-level descriptions of health states accurately reflected their experience of severe and non-severe, daytime and nocturnal hypoglycemia, thereby validating these descriptions. Respondents who had experienced a severe hypoglycemic event were generally more adversely affected in their worries and actions and life events than those who experienced only non-severe events; those who experienced nocturnal events were more affected than those who experienced only daytime events.

**Conclusion:** The negative psychosocial consequences and undesirable compensatory behaviors arising from hypoglycemia underscore the importance of preventing severe episodes, particularly severe nocturnal episodes. These validated descriptions for hypoglycemia from the patient's perspective may also help inform future qualitative and quantitative research.

**Keywords:** hypoglycemia, health states, diabetes, quality of life

## Introduction

Hypoglycemia is a common, unwanted adverse effect of glucose-lowering treatment in patients with type 1 or type 2 diabetes.<sup>1-8</sup> Hypoglycemia occurs when the plasma glucose becomes too low. Hypoglycemia can be divided into non-severe (minor) and severe (major) events, as well as according to daytime or nocturnal (during sleeping hours) occurrence. In non-severe events, the individual is able to take remedial action, whereas, in severe events, assistance by a third party is required. Traditionally, hypoglycemia has tended to be viewed as a more serious issue for patients with type 1 diabetes due to the greater frequency of events, and of severe events in particular.<sup>4,9</sup> There is, however, growing appreciation of the burden of hypoglycemia in people with type 2 diabetes.<sup>4,7,10-12</sup>

The scope of the acute symptoms of hypoglycemia, as well as the negative psychosocial consequences and compensatory health-related behaviors arising from fear

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of these symptoms, are well documented.<sup>1,10,13–21</sup> These result in reduced therapy adherence, poorer treatment satisfaction and reluctance to escalate blood glucose-lowering therapy.<sup>13</sup> As a result, hypoglycemia remains the critical treatment-limiting factor in diabetes management,<sup>10,14,22,23</sup> and represents a significant barrier to the achievement of optimal blood glucose control.<sup>24</sup>

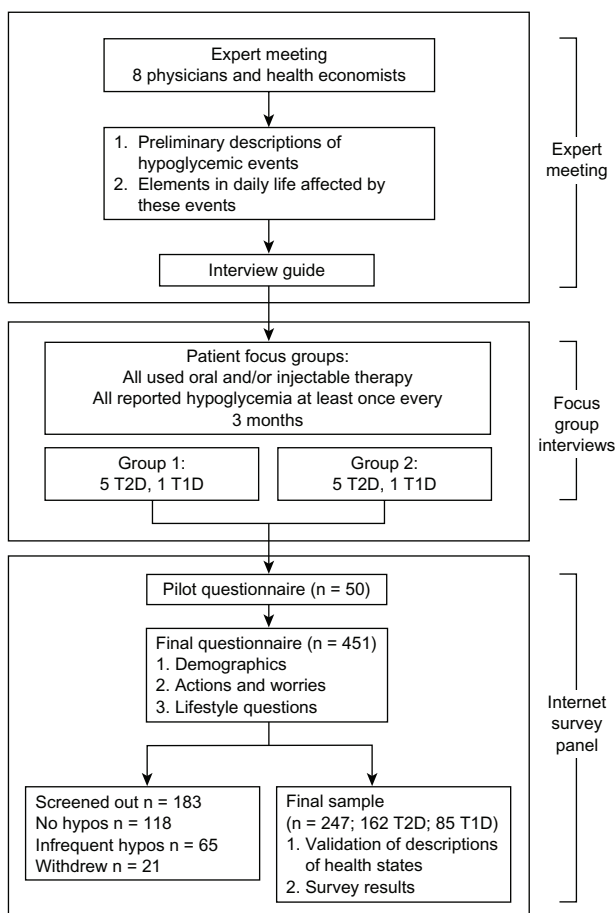
Qualitative and quantitative research has characterized how hypoglycemia and fear of hypoglycemia adversely affect a patient's health-related quality of life (HRQoL),<sup>15–17,19,21,25,26</sup> although there is no complete understanding of how different aspects of hypoglycemia affect particular aspects of patients' lives when describing health states.<sup>27</sup> Indeed, there is a dearth of information in the literature about the differentiation of health states between severe and non-severe hypoglycemia from the patient's perspective. Therefore, this study was conducted to generate and validate comprehensive descriptions of health states associated with non-severe and severe, daytime and nocturnal hypoglycemia, occurring from once yearly to three times weekly. Basing these descriptions on a patient's perspective was a prelude to incorporating them as health-state descriptions in a multinational time trade-off study.<sup>28</sup>

## Patients and methods

Since the goal of this study was to develop descriptions of health states associated with various severities and frequencies of hypoglycemia, the patients' experiences of acute symptoms of non-severe and severe, daytime and nocturnal hypoglycemia, as well as the effect of those symptoms on daily life, needed to be understood. A series of prospective, qualitative efforts, including an expert meeting, patient focus groups, and a self-administered questionnaire distributed to an internet survey panel, were conducted and administered sequentially. When combined, these were used to generate comprehensive descriptions of health states associated with hypoglycemia, from a patient's perspective. A flow chart explaining the sequence of activities in the study is shown in Figure 1.

### Expert meeting

An expert panel summarized preliminary symptomatic descriptions of daytime and nocturnal, severe and non-severe hypoglycemic events, and identified elements in the daily life of patients likely to be affected by experiencing these events. The results of this meeting were used to prepare an interview guide for subsequent patient focus groups.



**Figure 1** Study design.

**Abbreviations:** hypos, hypoglycemic events; n, number; T1D, type 1 diabetes; T2D, type 2 diabetes.

### Patient focus groups

Ten patients with type 2 diabetes and two patients with type 1 diabetes were recruited to participate in focus groups, the purpose being to further develop detailed descriptions of the experience (acute symptoms) of hypoglycemic events, and to explain how hypoglycemia influenced aspects of daily living such as working, driving, exercising, and socializing. The focus groups were administered by a subcontractor and participants were recruited from the subcontractor's existing panel (see Acknowledgments).

Two separate focus groups, each consisting of six patients who were gender-matched to support building commonalities between respondents, were conducted. All participants were using oral and/or injectable therapy and reported having hypoglycemic events at least once every 3 months. Five patients experienced nocturnal hypoglycemia and three had required medical assistance as a result of hypoglycemia. No definition of hypoglycemia was provided to patients at recruitment so as not to bias discussions. To ensure that all relevant aspects

of hypoglycemia were covered during the focus groups, the interview guide described on the previous page was used to shape the discussion.

## Internet-based survey panel

The questionnaire used for this survey was derived from the outcomes of the expert meeting and the patient focus groups, which also provided descriptions of the acute symptoms of health states. In order to investigate how hypoglycemia affected daily lives of patients with different degrees of hypoglycemic experience, 35 lifestyle questions were formulated about how and how frequently hypoglycemia affected activities such as traveling, driving, exercising, socializing, and study/work. Examples of these questions include: “How often do you plan your life around food and medicine?” and “How often do you worry about the risk of having a hypo [hypoglycemic event] when traveling?” Finally, the questionnaire also contained various items regarding the respondents’ backgrounds and diabetes characteristics.

The main data were obtained from randomly selected people with diabetes aged 18 and older who had previously agreed to be part of an internet survey panel in the UK. The panel comprised a representative sample of people with diabetes. Participants for this particular survey were recruited by an alert sent out to members requesting participation. However, for inclusion in the sample, the respondents must have experienced non-severe daytime (based on a description of a minor daytime hypo and answers to the questions: “Have you ever experienced a minor daytime hypo?” and “How often do you usually have a minor daytime hypo?”) or nocturnal hypoglycemic events (based on a description of a nocturnal hypo and answers to the questions: “Have you ever experienced a night-time [nocturnal] hypo?” and “How often do you usually have a night-time [nocturnal] hypo?” more often than once every 3 months, or have experienced at least one severe hypoglycemic event (based on a description of a major hypo and answers to the questions: “Have you ever experienced a major hypo?” and “How many major hypos have you had within the past year?”). Therefore, this sample should be viewed as representative of a population of people with diabetes who experience hypoglycemia, and not the general population of diabetes patients. Patients responded anonymously via an online self-administered questionnaire, an approach that has been successfully used by other groups.<sup>29–31</sup> As part of their response, patients also indicated whether or not (Yes/No) they agreed with the descriptions of minor daytime, minor nocturnal, and

major hypoglycemic events. Background information on the participants, including the generic HRQoL Instrument, EQ-5D,<sup>32–34</sup> and diabetes characteristics was also collected. EQ-5D is a standardized instrument for measuring health outcomes on a scale of 0–1, with a lower value indicating poor health (see [www.euroqol.org](http://www.euroqol.org)).

Before the main data collection was initiated, a pilot survey was carried out with an additional 50 respondents not included in the final analysis, to assess whether they understood the questions. When necessary, the questionnaire was modified to improve understanding.

## Statistical analysis

Basic descriptive statistics were calculated for patients overall, and for subgroups of patients with greater or lesser experience of hypoglycemia, using a statistical software package, SAS version 9.2 (SAS Institute Inc, Cary, NC, USA).

Spearman’s correlation coefficient was used to determine if the frequency of co-occurrence of different types of hypoglycemic events was statistically significant. In order to obtain health-state descriptions of a manageable number, length, and complexity, the results were grouped and frequencies averaged, and the most remarkable changes in actions and worries with changed frequencies and severity of hypoglycemia were identified. The scheme for describing patient actions and worries in response to various frequencies and severity of hypoglycemia is shown in supplementary material, Table S1.

Validation of health-state descriptions refined during the previously conducted patient focus groups was determined by assessing agreement with the proposed descriptions among members of the survey panel. The responses to each of the 35 questions about lifestyle consequences of hypoglycemia were given on a text-based Likert scale (Never, Rarely, Sometimes, Often, Always) and converted to numbers (1, 2, 3, 4, 5) for analysis. For each of the 35 questions, the chi-squared test was used to determine if actions and worries for respondents who had experienced severe hypoglycemia were significantly different from those who had only experienced non-severe events.

## Results

### Description of hypoglycemic events

Descriptions of acute symptoms for non-severe daytime, non-severe nocturnal and severe hypoglycemia, derived from expert panel and patient focus groups, are shown in Table 1.

**Table 1** Patient-level descriptions of acute symptoms in type 1 and type 2 diabetes for non-severe daytime, nocturnal, and severe hypoglycemia

**Minor daytime hypoglycemic event** – “A minor daytime hypo happens suddenly because of low blood sugar. You might feel shaky, dizzy, sweaty or irritable. You might also feel confused or sick, get a headache, or feel your heart pounding (have palpitations). These symptoms usually do not last long and will go away when you eat or drink something that contains sugar. After a minor daytime hypo, you might feel tired and not even remember what happened.”

**Minor night-time (nocturnal) hypoglycemic event** – “A night-time (nocturnal) hypo happens without warning during the night because of low blood sugar. You might wake up, feel shaky, hungry, irritable, extremely sweaty, confused, sick and feel your heart pounding (have palpitations). This can be treated by eating or drinking something that contains sugar. You may have difficulty in getting back to sleep. You might have nightmares and when you wake up in the morning you might have a headache or be unusually tired for the whole of the following day.”

**Major hypoglycemic event** – “A major hypo happens suddenly because of very low blood sugar. You will not be able to treat it yourself; you will need help from another person, possibly medical assistance. A major hypo may occur after a brief period of feeling shaky, dizzy, sweaty, irritable or confused. You may experience seizures, convulsions, further confusion, fainting or fall into a coma. In very rare cases it can be life-threatening.”

**Notes:** The abbreviation “hypo” was used in the questions to simplify reading instead of hypoglycemic event. These descriptions of how it feels (acute symptoms) to have a hypo were developed by an expert panel and two patient focus groups, and validated by a survey of 247 patients in a diabetes panel. The terms “minor” and “major” were the terms used in the actual patient survey. Complete descriptions of the health states, including impact on patients’ lives, can be found in the Supplementary material (Table S2).

## Response from internet survey panel

A total of 451 patients from the internet survey panel responded to the recruitment alert. Most of the respondents ( $n = 346/451$ , 77%) had type 2 diabetes, while 23% ( $n = 105/451$ ) had type 1 diabetes. Based upon their

hypoglycemia experience,  $n = 118/451$ , 26% ( $n = 5/105$ , 5% type 1 diabetes and  $n = 113/346$ , 33% type 2 diabetes) were screened out because they had not experienced any kind of hypoglycemia, and  $n = 65/451$ , 14% ( $n = 10$ , type 1 diabetes and  $n = 55$ , type 2 diabetes) were screened out because they had experienced only infrequent hypoglycemia. Twenty-one of these eligible participants dropped out after screening, leaving a final sample of 247 patients ( $n = 85$ , 34.4% type 1 diabetes and  $n = 162$ , 65.6% type 2 diabetes).

Demographic characteristics of the participants, by severity of hypoglycemia, are shown in Table 2. People with more severe hypoglycemic experience tended to have a longer duration of diabetes ( $P = 0.0223$ ) and be using insulin or other injectable therapy ( $P < 0.0001$ ).

## Severity and frequency of hypoglycemic events

As a result of the screening process, there was considerable experience with all types of hypoglycemia among the survey respondents. Nearly all ( $n = 243/247$ , 98%) experienced a non-severe daytime hypoglycemic event, and three-quarters ( $n = 185/247$ , 75%) experienced a non-severe nocturnal hypoglycemic event, including  $n = 71/85$ , 84% of those with type 1 diabetes and  $n = 113/162$ , 70% of those with type 2 diabetes. The frequency of non-severe events is further broken down by type of diabetes in Table 3. Severe events were less common than non-severe events. Nevertheless, within this pre-screened sample, over half ( $n = 133/247$ , 54%) experienced a severe hypoglycemic event (including 74% of respondents with type 1 diabetes and 43% of respondents with type 2 diabetes), the majority of which ( $n = 122/133$ , 91.7%) occurred

**Table 2** Demographic and diabetes characteristics of 247 patients from a diabetes panel, according to severity of hypoglycemic experience

	Severity of hypoglycemic experience <sup>a</sup>					Total	Test for trend <sup>b</sup>
	1	2	3	4	5		
N (%) in group	44 (18)	70 (28)	40 (16)	62 (25)	31 (13)	247 (100)	n/a
Mean age (years)	51	48	41	35	35	42	<0.0001 <sup>c</sup>
Female (%)	50	54	45	42	52	49	0.4690
Mean duration of diabetes (years)	5.3	6.0	6.4	7.0	7.6	6.4	0.0223 <sup>c</sup>
EQ-5D index <sup>32–34</sup>	0.64	0.59	0.63	0.59	0.53	0.59	0.2104
Diabetes therapy							
Tablets (%)	73	69	63	77	81	72	0.2575
Insulin (%)	16	33	50	66	68	45	<0.0001
Other injectable (%)	2	1	15	32	39	16	<0.0001

**Notes:** <sup>a</sup>(1) Only experienced non-severe daytime hypoglycemic events; (2) also experienced non-severe nocturnal hypoglycemic events; (3) have experienced severe daytime hypoglycemic events; (4) have experienced severe nocturnal hypoglycemic events; (5) have experienced >12 severe hypoglycemic events during the previous year.

<sup>b</sup>Test for trend shows the *P*-value from a two-sided Cochran–Armitage trend test in the case of categorical variables and an ANOVA test for linear trend in the case of continuous variables (age, duration of diabetes, and EQ-5D). <sup>c</sup>Indicates that the result is driven by people with type 2 diabetes. A test run on the sub-sample of people with type 1 diabetes yields *P*-values of 0.8434 and 0.3472 respectively. The *P*-value for the test run on the sub-sample of people with type 2 diabetes is <0.0001 and =0.0184 respectively.



**Table 3** Frequency of non-severe and severe daytime and nocturnal hypoglycemic events among 247 respondents from a diabetes panel, according to type of diabetes

	Daytime events				Nocturnal events			
	T1D		T2D		T1D		T2D	
	N = 85	(%)	N = 162	(%)	N = 85	(%)	N = 162	(%)
<b>Non-severe events</b>								
Have not experienced	1	(1)	3	(2)	14	(16)	49	(30)
Less frequent than once every 3 months	5	(6)	13	(8)	12	(14)	24	(15)
Once every 3 months	5	(6)	29	(18)	12	(14)	19	(12)
Once a month	26	(31)	44	(27)	16	(19)	23	(14)
Once a week	30	(35)	49	(30)	16	(19)	28	(17)
Three times a week	18	(21)	24	(15)	15	(18)	19	(12)
<b>Severe events</b>								
Have not experienced in the past year	32	(38)	100	(62)	38	(45)	122	(75)
Average per year in the past year (for patients having experienced in the past year)	52	6.0	57	8.4	47	6.7	38	9.1
Average per year in the past year (for all patients)	84	3.7	157	3.0	85	3.7	160	2.2

**Note:** Respondents to this survey were screened for having a minimal level of hypoglycemic experience, therefore frequencies should not be taken as reflecting the experience of the entire population of patients with diabetes.

**Abbreviations:** T1D, type 1 diabetes; T2D, type 2 diabetes.

in the daytime. Furthermore, over a third ( $n = 89/247$ , 36%) of the respondents had experienced a severe nocturnal event ( $n = 48/85$ , 56% among type 1 diabetes,  $n = 42/162$ , 26% among type 2 diabetes).

As would be expected in a sample of patients with documented experience of diabetes treatment-related hypoglycemia, the frequency of occurrence for the different types of hypoglycemic events was significantly correlated ( $r = 0.44$  [ $P < 0.0001$ ] for non-severe daytime and nocturnal events;  $r = 0.66$  [ $P < 0.0001$ ] for severe daytime and nocturnal events;  $r = 0.18$  [ $P = 0.004$ ] for non-severe and severe daytime events; and  $r = 0.47$  [ $P < 0.0001$ ] for non-severe and severe nocturnal events).

## Validation of descriptions of acute symptoms

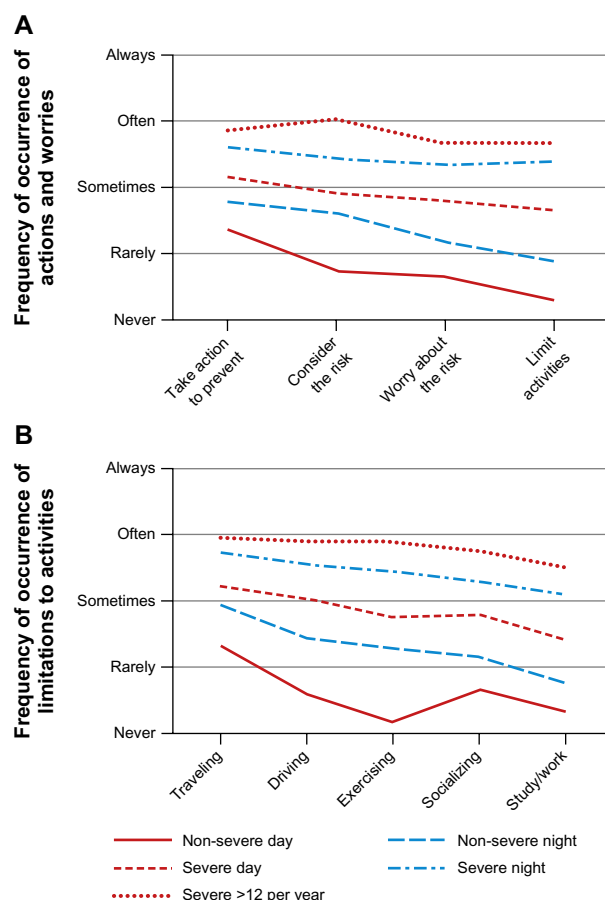
Between 95% and 98% of all respondents agreed, using a “Yes/No” dichotomous response, that the descriptions of acute symptoms from the expert panel and patient focus groups (Table 2) accurately described their experience with a particular type of hypoglycemic event ( $n = 232/243$ , 95%, for non-severe daytime hypoglycemia;  $n = 179/185$ , 97%, for nocturnal hypoglycemia; and  $n = 130/133$ , 98%, for severe hypoglycemia). Complete validated descriptions of health states are presented in the Appendix (available as supplementary material, Table S2).

## Differential impact of hypoglycemia on patients

In order to keep the descriptions of health states manageable, five respondent groups were constructed based upon

having incrementally more serious hypoglycemic experience (Group 1: Only experienced daytime non-severe hypoglycemia; Group 2: Also experienced non-severe nocturnal hypoglycemia; Group 3: Experienced severe daytime hypoglycemia; Group 4: Experienced severe nocturnal hypoglycemia; Group 5: Cumulative experience of  $>12$  severe hypoglycemic events during the previous year). The demographic and diabetes characteristics of these groups are shown in Table 3. Using the five groupings described above, the frequency of patient actions and worries associated with descriptions of incrementally worse health states due to hypoglycemia was evaluated. Categories of actions and worries included taking action to prevent the risk, considering the risk, worrying about the risk, and limiting activities due to the risk (Figure 2A). In general, the most frequent action was to prevent a hypoglycemic event.

These actions and worries showed a consistent pattern in that they tended to occur more frequently (eg, “often” versus “rarely” or “never”) for patients having more clinically serious hypoglycemic experience. For example, it appears that patients having experienced severe hypoglycemic events were affected more often in their daily lives than the groups having experienced only non-severe hypoglycemic events. With respect to specific parts of daily life, activities such as traveling and driving tended to be more affected than study/work for people with mostly non-severe hypoglycemic experience, but for people with severe hypoglycemia, all of the listed activities were impacted to a similar degree (Figure 2B).



**Figure 2** Frequency of actions and worries in response to hypoglycemia (A) and effect on daily life for 247 patients from a diabetes panel, (B) according to severity of hypoglycemic events.

Results for the 35 questions pertaining to impact of hypoglycemia on lifestyle are shown in Figure 3. To simplify reporting, the five groups of hypoglycemia experience were aggregated into two groups: “Non-severe: Have not experienced severe hypoglycemic events” ( $n = 114/247$ , 46%), and “Severe: Have experienced severe hypoglycemic events” ( $n = 133/247$ , 54%). The aggregate data indicate that respondents having experienced severe events were in general more affected in all aspects of their daily lives, compared with respondents having experienced only non-severe events. This difference between the two groups was statistically significant ( $P < 0.05$ ) for all actions and worries except for “closely follow a special diet in order to avoid a hypoglycemic event,” which is done equally frequently for both groups.

## Discussion

This study provides, for the first time, validated patient-level descriptions of health states arising from different frequencies of occurrence of non-severe, severe, and

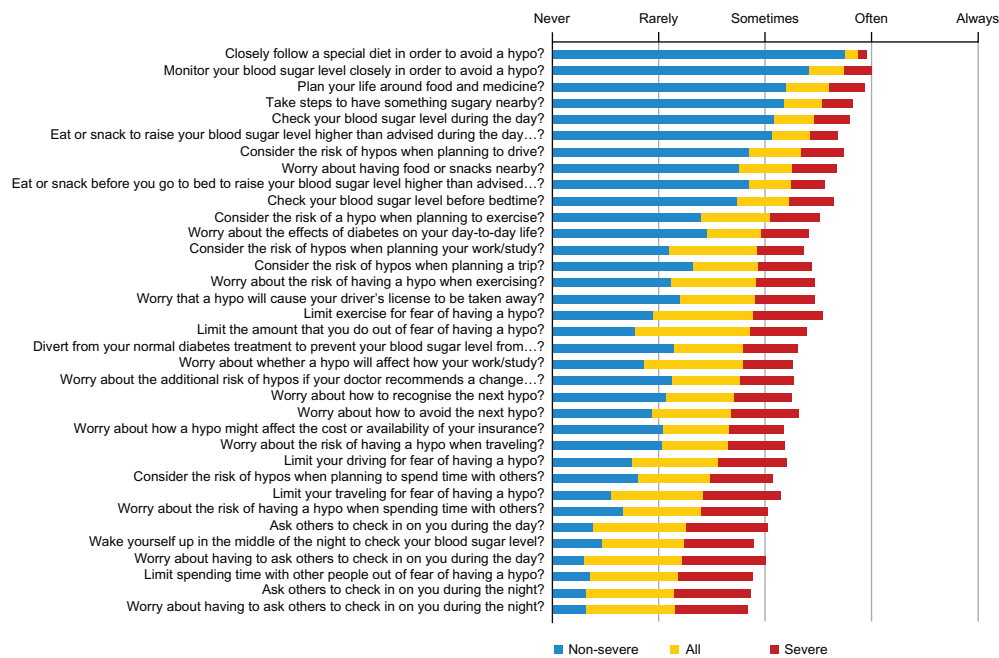
nocturnal hypoglycemia. Using such descriptions, the perceived health impact of experiencing a severe hypoglycemic event is clearly demonstrated, highlighting the value of preventing severe events. These data also reaffirm that severe hypoglycemia has a greater detrimental impact on perceived health status compared with non-severe events. Increasing frequency of events and events occurring during the nocturnal period were also identified as having a greater negative impact on health-related behavior. These results reinforce the detrimental effect of non-severe hypoglycemia on perceived health, which is an important consideration in routine clinical practice, since the frequency of non-severe hypoglycemia is many-fold greater than severe hypoglycemia.<sup>9</sup>

Based upon responses from 247 patients with type 1 and type 2 diabetes, this study has resulted in descriptions of health states associated with hypoglycemia from the patient’s perspective, including acute symptoms and the effect on their daily lives, for 12 combinations of severity (non-severe, severe, nocturnal, daytime) and frequency of events. The broad range of hypoglycemic experience among the respondents indicated ample familiarity with the symptoms of various forms of hypoglycemia, which speaks to the content validity of the descriptions. The low drop-out rate among the patients recruited for the internet survey is one indication that patients found the questionnaire understandable and relevant to their experience of hypoglycemia. These descriptions should prove helpful when a nuanced understanding of the experience of hypoglycemia and its effect on quality of life is needed. This could occur, for example, in time trade-off studies, in which it is important that participants fully understand the consequences of a health problem when communicating preferences for treatment.

The relationship demonstrated between increasing severity of hypoglycemia and decreased perceived health status was consistent with what has been reported in other health utility studies.<sup>26,35</sup> Having had a severe hypoglycemic event was associated with greater worry and performing compensatory behaviors more frequently, thereby decreasing perceived health status. Activities such as traveling, which inherently contain more uncertainty, were affected more than study/work for all frequencies of severity. There were not enough patients with type 1 diabetes to present those results separately for different subgroups.

## Limitations

It should be noted that due to the intentional selection bias to obtain a sample of patients with sufficient experience with



**Figure 3** Effect of hypoglycemia on 35 aspects of daily life for 247 patients from a diabetes panel, according to severity of hypoglycemia. The figure shows the mean score on the aspects of daily life where “Never” = 1 and “Always” = 5, for two exclusive groups as well as the combined sample. The blue bar represents the mean for the group of patients having experienced only non-severe hypoglycemic events or “hypos”. The blue and yellow bars combined represent the mean of the entire sample, and the cumulative total of the bars (blue, yellow, and red) represents the mean of the sample of patients having experienced severe hypoglycemia. Differences between non-severe and severe groups were statistically significant ( $P < 0.05$ ) for all questions except “Closely follow a special diet in order to avoid a hypo?”

hypoglycemic events, the number of hypoglycemic events reported for these respondents does not reflect the prevalence in the general population of people with diabetes. It does, however, ensure a truly validated description of the consequences of hypoglycemia.

One limitation of this study is a potential selection bias in relation to the patients in the survey panel. To be included in the survey panel, people needed to be comfortable with computers and online surveys, which may have excluded less literate individuals, for example. Therefore, we do not know what proportion of patients this sample represents, compared with the general population. This criterion, in addition to the required experience with hypoglycemia, may have resulted in a sample that was not truly representative of all patients with diabetes. There were also about twice as many participants with type 2 diabetes. It was unknown which oral antihyperglycemic agents or insulin regimens respondents were using, or what their level of glycemic control may have been. It would be interesting to know whether these differences could bias patients’ reporting of their experiences of hypoglycemia. We did not obtain information on other aspects of hypoglycemia, such as emotional trauma or physical injury arising from an event, which can affect subsequent behavior and emotional status.

## Conclusion

This study highlights the importance, from the quality-of-life perspective, of adopting treatment and educational strategies aimed at reducing the risk of hypoglycemia for people with diabetes, especially nocturnal or severe events. Furthermore, the novel use of validated descriptions of health states arising from different frequencies of occurrence of non-severe, severe, and nocturnal hypoglycemia from the patient’s perspective as used in this study may be useful in further qualitative and quantitative research.

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## Author contributions

SBH contributed to the study design, identification of data outcomes and analysis, and writing the manuscript, and takes responsibility for the integrity of the work as a whole. KK contributed to the analysis of the data, preparation of the tables, and writing/reviewing the manuscript. MLO contrib-

uted to the work by analyzing data, discussing the results, and reviewing and revising the manuscript. CBGJ contributed to the study design and conduct, data collection and analysis, and writing the manuscript. MB contributed to the study design and conduct, data collection and analysis, and writing the manuscript. BC contributed to the study design, and writing/reviewing the manuscript. JG contributed to the study design, data analysis and interpretation, and writing the manuscript. ME contributed to study design, evaluation of the results, and the preparation of the final manuscript.

## Disclosure

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## References

1. Brod M, Christensen T, Thomsen TL, Bushnell DM. The impact of non-severe hypoglycemic events on diabetes management and work productivity. *Value Health*. 2011;14(5):665–671.
2. Kahn SE, Haffner SM, Heise MA, et al; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med*. 2006;355(23):2427–2443.
3. Miller CD, Phillips LS, Ziemer DC, Gallina DL, Cook CB, El-Kebbi IM. Hypoglycemia in patients with type 2 diabetes mellitus. *Arch Intern Med*. 2001;161(13):1653–1659.
4. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia*. 2007;50(6):1140–1147.
5. Vexiau P, Mavros P, Krishnarajah G, Lyu R, Yin D. Hypoglycaemia in patients with type 2 diabetes treated with a combination of metformin and sulphonylurea therapy in France. *Diabetes Obes Metab*. 2008;10 Suppl 1:16–24.
6. Viberti G, Kahn SE, Greene DA, et al. A diabetes outcome progression trial (ADOPT): an international multicenter study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes. *Diabetes Care*. 2002;25(10):1737–1743.
7. Zoungas S, Patel A, Chalmers J, et al; ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med*. 2010;363(15):1410–1418.
8. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care*. 2013;36(5):1384–1395.
9. Donnelly LA, Morris AD, Frier BM, et al. Frequency and predictors of hypoglycaemia in Type 1 and insulin-treated Type 2 diabetes: a population-based study. *Diabet Med*. 2005;22(6):749–755.
10. Alvarez Guisasola F, Tofé Povedano S, Krishnarajah G, Lyu R, Mavros P, Yin D. Hypoglycaemic symptoms, treatment satisfaction, adherence and their associations with glycaemic goal in patients with type 2 diabetes mellitus: findings from the Real-Life Effectiveness and Care Patterns of Diabetes Management (RECAP-DM) Study. *Diabetes Obes Metab*. 2008;10 Suppl 1:25–32.
11. Henderson JN, Allen KV, Deary IJ, Frier BM. Hypoglycaemia in insulin-treated Type 2 diabetes: frequency, symptoms and impaired awareness. *Diabet Med*. 2003;20(12):1016–1021.
12. Lammert M, Hammer M, Frier BM. Management of severe hypoglycemia: cultural similarities, differences and resource consumption in three European countries. *J Med Econ*. 2009;12(4):269–280.
13. Barendse S, Singh H, Frier BM, Speight J. The impact of hypoglycaemia on quality of life and related patient-reported outcomes in Type 2 diabetes: a narrative review. *Diabet Med*. 2012;29(3):293–302.
14. Frier BM. How hypoglycemia can affect the life of a person with diabetes. *Diabetes Metab Res Rev*. 2008;24(2):87–92.
15. Graveling AJ, Frier BM. Hypoglycaemia: an overview. *Prim Care Diabetes*. 2009;3(3):131–139.
16. Leiter LA, Yale J-F, Chiasson J-L, Harris S, Kleinstiver P, Luc Sauriol L. Assessment of the impact of fear of hypoglycemic episodes on glycemic and hypoglycemia management. *Can J Diab*. 2005;29(3):186–192.
17. Marrett E, Stargardt T, Mavros P, Alexander CM. Patient-reported outcomes in a survey of patients treated with oral antihyperglycaemic medications: associations with hypoglycaemia and weight gain. *Diabetes Obes Metab*. 2009;11(12):1138–1144.
18. Nafees B, Lloyd A, Kennedy-Martin T, Hynd S. How diabetes and insulin therapy affects the lives of people with type 1 diabetes. *Eur Diabetes Nurs*. 2006;3(1):92–97.
19. Peyrot M, Barnett AH, Meneghini LF, Schumm-Draeger PM. Insulin adherence behaviours and barriers in the multinational Global Attitudes of Patients and Physicians in Insulin Therapy study. *Diabet Med*. 2012;29(5):682–689.
20. Wild D, von Maltzahn R, Brohan E, Christensen T, Clauson P, Gonder-Frederick L. A critical review of the literature on fear of hypoglycemia in diabetes: Implications for diabetes management and patient education. *Patient Educ Couns*. 2007;68(1):10–15.
21. Williams SA, Pollack MF, Dibonaventura M. Effects of hypoglycemia on health-related quality of life, treatment satisfaction and healthcare resource utilization in patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract*. 2011;91(3):363–370.
22. Cryer PE. Hypoglycaemia: the limiting factor in the glycaemic management of Type I and Type II diabetes. *Diabetologia*. 2002;45(7):937–948.



23. Unger J. Uncovering undetected hypoglycemic events. *Diabetes Metab Syndr Obes*. 2012;5:57–74.
24. Kilpatrick ES, Das AK, Orskov C, Berntorp K. Good glycaemic control: an international perspective on bridging the gap between theory and practice in type 2 diabetes. *Curr Med Res Opin*. 2008;24(9):2651–2661.
25. Alvarez-Guisasola F, Yin DD, Nocea G, Qiu Y, Mavros P. Association of hypoglycemic symptoms with patients' rating of their health-related quality of life state: a cross sectional study. *Health Qual Life Outcomes*. 2010;8:86.
26. Davis RE, Morrissey M, Peters JR, Wittrup-Jensen K, Kennedy-Martin T, Currie CJ. Impact of hypoglycaemia on quality of life and productivity in type 1 and type 2 diabetes. *Curr Med Res Opin*. 2005;21(9):1477–1483.
27. Matza LS, Boye KS, Yurgin N, et al. Utilities and disutilities for type 2 diabetes treatment-related attributes. *Qual Life Res*. 2007;16(7):1251–1265.
28. Evans M, Khunti K, Mamdani M, et al. Health-related quality of life associated with daytime and nocturnal hypoglycaemic events: a time trade-off survey in five countries. *Health Qual Life Outcomes*. 2013;11(1):90. [Epub ahead of print.]
29. Szende A, Brazier J, Schaefer C, Deuson R, Isitt JJ, Vyas P. Measurement of utility values in the UK for health states related to immune thrombocytopenic purpura. *Curr Med Res Opin*. 2010;26(8):1893–1903.
30. Lieu TA, Ray GT, Ortega-Sanchez IR, Kleinman K, Rusinak D, Prosser LA. Willingness to pay for a QALY based on community member and patient preferences for temporary health states associated with herpes zoster. *Pharmacoeconomics*. 2009;27(12):1005–1016.
31. Chang WT, Collins ED, Kerrigan CL. An Internet-based utility assessment of breast hypertrophy. *Plast Reconstr Surg*. 2001;108(2):370–377.
32. Brooks R. EuroQol: the current state of play. *Health Policy*. 1996;37(1):53–72.
33. Dolan P. Modeling valuations for EuroQol health states. *Med Care*. 1997;35(11):1095–1108.
34. The EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199–208.
35. Currie CJ, Morgan CL, Poole CD, et al. Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes. *Curr Med Res Opin*. 2006;22(8):1523–1534.

## Supplementary tables

**Table SI** Scheme for describing actions and worries associated with hypoglycemic events

Occurrence of hypoglycemia <sup>a</sup>	Patient actions and worries collected			
	Daytime infrequent actions and worries	Daytime frequent actions and worries	Night-time infrequent actions and worries	Night-time frequent actions and worries
1. Daytime 1× quarterly	X			
2. Daytime 1× monthly	X			
3. Daytime 1× weekly		X		
4. Daytime 3× weekly		X		
5. Night-time 1× quarterly			X	
6. Night-time 1× monthly			X	
7. Night-time 1× weekly				X
8. Night-time 3× weekly				X
9. Daytime severe yearly		X		
10. Daytime severe quarterly		X		
11. Night-time severe yearly				X
12. Night-time severe quarterly				X

**Notes:** <sup>a</sup>Description of actions and worries depends on the time of day. There are two descriptions for each time of day: one with infrequent and one with frequent actions and worries.

**Table S2** Detailed descriptions of health states, including acute symptoms and effect on patients' lives, associated with various combinations of frequency and severity of hypoglycemia

### 1. Description of baseline diabetes health state

You have diabetes

- This means that your body cannot keep your blood sugar at a constant level.
- To control this, you often follow a special diet, are careful about eating regularly and take steps to have something sugary nearby.
- You take medication on a daily basis and sometimes need to plan your life around food and medicine.
- You need to check your blood sugar from time to time.
- You need to consider your diabetes when you are planning to exercise, travel, go out with friends, and drive.
- Your diabetes does not affect your work/study, and you don't have any problems looking after yourself.
- You occasionally worry about the effects of your diabetes on your day-to-day life.
- [Patients with diabetes are shown the following] Your diabetes is well-controlled and you do not experience hypos (hypoglycemic events)

### 2. Description of non-severe daytime hypo health states, occurring 1× quarterly or 1× monthly

A minor daytime hypo happens suddenly because of low blood sugar. You might feel shaky, dizzy, sweaty or irritable. You might also feel confused or sick, get a headache, or feel your heart pounding (have palpitations). These symptoms usually do not last long and will go away when you eat or drink something that contains sugar. After a minor daytime hypo, you might feel tired and not even remember what happened.

Due to the fact that you are experiencing minor daytime hypos [once quarterly or once monthly]:

- You often plan your life around food and medication.
- You occasionally divert from your normal routine (medication and/or food intake) in order to avoid a hypo. This may cause negative effects on your health in the long run.
- You occasionally consider the risk of having a hypo when working, driving, exercising, traveling and going out with friends. Occasionally, you even limit these activities for fear of having a hypo.
- You rarely ask others to check in on you during the day and worry about having to ask others to do so.
- You occasionally worry about the effects of your diabetes on your day-to-day life.

### 3. Description of non-severe daytime hypo health states, occurring 1× weekly or 3× weekly

A minor daytime hypo happens suddenly because of low blood sugar. You might feel shaky, dizzy, sweaty or irritable. You might also feel confused or sick, get a headache, or feel your heart pounding (have palpitations). These symptoms usually do not last long and will go away when you eat or drink something that contains sugar. After a minor daytime hypo, you might feel tired and not even remember what happened.

Due to the fact that you are experiencing minor daytime hypos [once weekly or three times weekly]:

- You almost always plan your life around food and medication.
- You fairly often divert from your normal routine (medication and/or food intake) in order to avoid a hypo. This may cause negative effects on your health in the long run.
- You often consider the risk of having a hypo when driving, working, exercising, traveling and going out with friends. Sometimes, you even limit these activities for fear of having a hypo.
- You sometimes ask others to check in on you during the day and worry about having to ask others to do so.
- You often worry about the effects of your diabetes on your day-to-day life.

### 4. Description of non-severe nocturnal hypo health states, occurring 1× quarterly or 1× monthly

A night-time (nocturnal) hypo happens without warning during the night because of low blood sugar. You might wake up, feel shaky, hungry, irritable, extremely sweaty, confused, sick and feel your heart pounding (have palpitations). This can be treated by eating or drinking something that contains sugar. You may have difficulty in getting back to sleep. You might have nightmares and when you wake up in the morning you might have a headache or be unusually tired for the whole of the following day.

Due to the fact that you are experiencing night-time hypos [once quarterly or once monthly]:

- You often plan your life around food and medication.
- You occasionally divert from your normal routine (medication and/or food intake) in order to avoid a hypo. This may cause negative effects on your health in the long run.
- You occasionally consider the risk of having a hypo when working, driving, exercising, traveling and going out with friends. Occasionally, you even limit these activities for fear of having a hypo.
- You occasionally ask others to check in on you during the night and worry about having to ask others to do so.
- You sometimes worry about the effects of your diabetes on your day-to-day life.

### 5. Description of non-severe nocturnal hypo health states, occurring 1× weekly or 3× weekly

A night-time (nocturnal) hypo happens without warning during the night because of low blood sugar. You might wake up, feel shaky, hungry, irritable, extremely sweaty, confused, sick and feel your heart pounding (have palpitations). This can be treated by eating or drinking something that contains sugar. You may have difficulty in getting back to sleep. You might have nightmares and when you wake up in the morning you might have a headache or be unusually tired for the whole of the following day.

Due to the fact that you are experiencing night-time hypos [once weekly or three times weekly]:

- You almost always plan your life around food and medication.
- You fairly often divert from your normal routine (medication and/or food intake) in order to avoid a hypo. This may cause negative effects on your health in the long run.

(Continued)

**Table S2 (Continued)**

- You often consider the risk of having a hypo when driving, working, exercising, traveling and going out with friends. Sometimes, you even limit these activities for fear of having a hypo.
- You fairly often ask others to check in on you during the night and worry about having to ask others to do so.
- You almost always worry about the effects of your diabetes on your day-to-day life.

**6. Description of severe daytime hypo health states, occurring 1x annually or 1x quarterly**

A major hypo happens suddenly because of very low blood sugar. You will not be able to treat it yourself; you will need help from another person, possibly medical assistance. A major hypo may occur after a brief period of feeling shaky, dizzy, sweaty, irritable or confused. You may experience seizures, convulsions, further confusion, fainting or fall into a coma. In very rare cases it can be life-threatening.

Due to the fact that you are experiencing a major daytime hypo [once annually or once quarterly]:

- You almost always plan your life around food and medication.
- You fairly often divert from your normal routine (medication and/or food intake) in order to avoid a hypo. This may cause negative effects on your health in the long run.
- You often consider the risk of having a hypo when driving, working, exercising, traveling and going out with friends. Sometimes, you even limit these activities for fear of having a hypo.
- You sometimes ask others to check in on you during the day and worry about having to ask others to do so.
- You often worry about the effects of your diabetes on your day-to-day life.

**7. Description of severe nocturnal hypo health states, occurring 1x annually or 1x quarterly**

A major hypo happens suddenly because of very low blood sugar. You will not be able to treat it yourself; you will need help from another person, possibly medical assistance. A major hypo may occur after a brief period of feeling shaky, dizzy, sweaty, irritable or confused. You may experience seizures, convulsions, further confusion, fainting or fall into a coma. In very rare cases it can be life-threatening.

Due to the fact that you are experiencing a major night-time hypo [once annually or once quarterly]:

- You almost always plan your life around food and medication.
- You fairly often divert from your normal routine (medication and/or food intake) in order to avoid a hypo. This may cause negative effects on your health in the long run.
- You often consider the risk of having a hypo when driving, working, exercising, traveling and going out with friends. Sometimes, you even limit these activities for fear of having a hypo.
- You fairly often ask others to check in on you during the night and worry about having to ask others to do so.
- You almost always worry about the effects of your diabetes on your day-to-day life.

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