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Design and Development of the Hypoglycaemia Symptom Rating Questionnaire (HypoSRQ).

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Access to HypoSRQ: please visit www.healthpsychologyresearch.com.

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Declaration of interests

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Abstract

Aims: To evaluate the Hypoglycaemia Symptom Rating Questionnaire (HypoSRQ[®]) and relationships between self-reported hypoglycaemia and hypoglycaemia measured using blinded continuous glucose monitoring (CGM).

Methods: Diabetes outpatients (n=113) recruited from Ashford and St. Peter's Hospital completed the HypoSRQ (recent weeks version) and provided clinical information. Thirty participants used blinded CGM for six days and completed the HypoSRQ (24-hour version) for seven days, at the end of each week (7-day version), and after four weeks (recent weeks version).

Results: The HypoSRQ had a single-factor structure and excellent internal consistency ($\alpha=0.90$). There was high correspondence in recalled symptoms, bother ratings and hypoglycaemic episodes across one week and four weeks ($r=0.84-0.98$, $p<0.001$). HypoSRQ-reported hypoglycaemia correlated significantly with CGM-measured hypoglycaemia (interstitial glucose $\leq 3.9\text{mmol/l}$) frequency ($r=0.72$, $p<0.001$) across six days. The magnitude of the correlation increased when the person's own threshold for detecting hypoglycaemia was used ($r=0.78$, $p<0.001$). The number of days (out of six) a person reported symptoms of hypoglycaemia was associated with the number of days CGM detected hypoglycaemia (interstitial glucose $\leq 3.9\text{mmol/l}$) ($r=0.83$, $p<0.001$) and remained significant after controlling for covariates.

Conclusions: Psychometric properties of the HypoSRQ make it attractive for use in people with insulin-treated diabetes. The HypoSRQ may be a less-invasive and more-economical alternative to CGM.

Key Words: diabetes mellitus; hypoglycaemic symptoms; questionnaire validation; continuous glucose monitoring

1. Introduction

There are few well-validated hypoglycaemia symptom questionnaires. The Edinburgh Hypoglycaemia Symptom Scale (1) records presence and intensity of hypoglycaemia symptoms but not how bothersome symptoms are. The Diabetes Symptoms Checklist-Revised (DSC-R) (2) contains a three-item factor termed 'hypoglycaemic symptoms' (*'Moodiness', 'Irritability just before a meal', 'Easily irritated or annoyed'*). Most hypoglycaemic symptoms are excluded and scale validity has been questioned due to lack of expected correlations with hypoglycaemia measures (3,4). Improved assessment of hypoglycaemia symptoms is important to identify those who are hypoglycaemia unaware, require treatment modification, education or other support, and will complement existing self-reported outcome measures (5-8).

Symptoms of hypoglycaemia have been investigated through observations of people with diabetes and during experimentally induced hypoglycaemia in individuals without diabetes (9). Autonomic symptoms, which are associated with counter-regulatory hormones and autonomic nervous system activation, include sweating, shaking, anxiety, palpitations and nausea (10). Neuroglycopenic symptoms,

attributed to glucose deprivation on higher mental functions, include dizziness, confusion, speech/coordination difficulties, and tiredness (10).

Previous studies have categorised hypoglycaemic symptoms using factor analysis (11,12), providing compelling evidence for the separation of hypoglycaemic symptoms into factors typically labelled autonomic, neuroglycopenic and malaise. However, hypoglycaemic symptom profiles are idiosyncratic, varying within and between individuals (13,14). For example, patients with Type 1 diabetes mellitus (DM) who were asked to record symptoms of each hypoglycaemic episode over 9-12 months varied substantially in between-episode consistency of symptom reports (14). Most research into hypoglycaemia has focused on people with Type 1 DM. However it is well-known that individuals with Type 2 DM treated with insulin therapy can also experience hypoglycaemia. Results from a systematic review of hypoglycaemia in people with Type 2 DM concluded that older patients and those with longer duration of diabetes, less insulin reserve, and/or comorbid health problems were at increased risk of hypoglycaemia (15). Educating people with Type 1 and insulin-treated Type 2 DM to identify hypoglycaemia symptoms is therefore important. It is likely people who understand their unique symptom profile will be better equipped to detect hypoglycaemia and respond appropriately.

Use of continuous glucose monitoring (CGM) provides a less economical alternative to self-reported hypoglycaemia detection in individuals with diabetes. Use of CGM by people with diabetes has been associated with improved glycated haemoglobin (HbA_{1c}) levels (16). Real-time CGM has also been associated with shorter

hypoglycaemic episodes in Type 1 DM (17). However, CGM accuracy is based on interstitial-fluid glucose which lags behind blood glucose by 7-15 minutes (18). Comparing different CGM devices, mean absolute hypoglycaemia ranged from 10.3-21.5% (18). CGM accuracy in identifying blood glucose <2.5mmol/l ranged from 84.4-97.0% (18). These findings suggest CGM has moderate-to-high levels of accuracy. To date, there have been no studies which have compared the accuracy of CGM-detected hypoglycaemic episodes with the person's own self-report of hypoglycaemia symptoms. In the present study, CGM was used to establish the criterion-related validity of the HypoSRQ, and served as the closest we have available to a gold standard assessment of hypoglycaemia.

The present study's objectives were to evaluate the psychometric properties of a newly developed measure of hypoglycaemia symptoms, the Hypoglycaemia Symptom Rating Questionnaire (HypoSRQ), and to provide preliminary evidence for the scale's validity by comparing, for the first time, the relationship between self-reported hypoglycaemia, measured by symptom reporting, and physiological detection of hypoglycaemia using blinded CGM.

2. Subjects, Materials and Methods

2.1. Participants

People with Type 1 or 2 DM, who were on intensive insulin therapy, defined as taking at least one basal insulin dose and two or more fast-acting insulin doses per day by injection or continuous subcutaneous insulin infusion (CSII) pump, were

recruited from diabetes outpatient clinics at Ashford and St. Peter's NHS Foundation Trust, Surrey, UK between January 2011 and May 2012. People were invited to take part in the study when they attended one of the diabetes outpatient clinics for a routine follow-up appointment. A total of 188 people were given the UK English HypoSRQ[®] (recent weeks version) to complete, along with other questionnaires reported elsewhere (19). Participants were free to complete the questionnaires at the diabetes clinic or at home and return in a pre-paid envelope. Written informed consent was obtained from each participant. A small number of people declined to take part after the nature of the study was explained to them. Of those who agreed to take part, 113 people (56 men, 57 women) returned a completed questionnaire; a 60.1% response rate. The questionnaire pack included an 'opt-in form' for people to complete to indicate their potential interest in using CGM. Blinded CGM was offered to individuals on a first-come-first-served basis. Participants who indicated that they would be interested in using CGM were contacted by telephone by the researcher to discuss this further and to arrange an appointment with the diabetes nurse to have the device fitted.

Thirty participants who were identified by diabetes specialist nurses as having experience and awareness of hypoglycaemia volunteered to use blinded CGM for six days. The recall period for symptoms in the HypoSRQ can be varied. Participants completed the 24-hour version of the HypoSRQ at the end of each of seven days, the 7-day version at the end of each of four weeks, and the recent weeks (i.e. about the past four weeks) version at endpoint.

Participants were aged 18 or older with fluent English. Excluded were individuals with a diagnosed learning disability, severe and enduring mental health problems, known history of or current alcohol/drug abuse, cognitive impairment, or severe head injury. People treated with just one basal insulin injection or with one basal and one fast-acting injection per day were excluded from the study. Those who were known to clinicians as having hypoglycaemia unawareness were also excluded. Wandsworth Local Research Ethics Committee approved the study.

2.2 Hypoglycaemia Symptom Rating Questionnaire (HypoSRQ)

The HypoSRQ was designed for use by people with Type 1 and Type 2 DM who are experiencing symptoms of hypoglycaemia. HypoSRQ items were generated following a literature review, consultation with a developer of blood-glucose-awareness training (BGAT) and review of the BGAT manual (20). The manual lists commonly experienced symptoms of hypoglycaemia, which were determined empirically. BGAT teaches use of symptoms and other cues in detecting high or low blood glucose (21). The HypoSRQ format was adapted from a measure of hypothyroidism (ThySRQ) (21). Further improvements were introduced following the study of optimal formats during the course of interviews with patients who had chronic kidney disease to inform the design of the Renal Symptom Rating Questionnaire (RenalSRQ; www.healthpsychologresearch.com) . It was established during development of the ThySRQ and the RenalSRQ that most existing symptom measures were not tapping into how “bothered” a patient is by a particular symptom (21). To overcome this problem the -SRQ measures provide a bother scale for rating

symptoms experienced, thus dealing with the fact that a symptom may occur frequently without bothering the person or may be infrequent but bothersome.

The UK English HypoSRQ includes seventeen symptom items associated with hypoglycaemia and one frequency of hypoglycaemia item. All items are self-administered and the questionnaire takes approximately five minutes to complete. Each item has two parts. Part (a) asks whether or not the symptom has been experienced during the time period (e.g. Have you had difficulty concentrating in recent weeks?), and part (b) asks how much the symptom has bothered the individual (e.g. If yes, how much has this bothered you?) with four response choices: 'not at all', 'a little', 'moderately' or 'a lot' (scoring 1, 2, 3, and 4 respectively). Any participants who reported that they did not have a symptom were given a bother rating of zero. See Figure 1 for an example item. There are three versions of the questionnaire: a past 24-hours version, a past 7-days version, and a recent weeks (i.e. about the past four weeks) version. The term "recent-weeks" has been found during interviews and questionnaire development work to be interpreted as meaning the past 3 to 6 weeks (21). Specifying "i.e. about the past four weeks" helped define what was intended by "recent weeks" while showing that we did not expect absolute precision.

The HypoSRQ has been linguistically validated into seven languages for North and South America and each language version pilot tested with a clinician and in cognitive debriefing interviews with five patients in each country. The UK English version of the HypoSRQ was tested in semi-structured cognitive debriefing

interviews with 5 people with diabetes in the UK (19, 22). The purpose of the interviews was to optimise the wording of symptoms.

2.3 Physiological and biochemical measures

Body mass index (BMI) was calculated from weight and height (kg/m^2). HbA1c measurement was carried out in the local laboratory based within Ashford & St Peter's NHS Foundation Trust and obtained from the computer system, with the participant's permission.

2.4 Continuous glucose monitoring

Five Medtronic iPro2 CGM devices were used with Enlite sensors (Medtronic Ltd.). The iPro2 is a Professional CGM device designed to provide a complete picture of a person's glucose levels using blinded data. CGM devices were fitted by a diabetes specialist nurse. Participants were instructed on the use of CGM, given a log sheet to record four capillary blood glucose readings daily (i.e. before breakfast, lunch, dinner and bedtime) for retrospective calibration of interstitial glucose readings, and information on who to contact if a problem arose. Participants were instructed to complete the 24-hour version of the HypoSRQ daily for seven days in the evening before bed. An appointment was made for participants to return to the diabetes clinic after six days to have the CGM sensor removed by the diabetes nurse.

CGM traces were examined to identify the frequency of low interstitial glucose (LIG). LIG was stratified into episodes of hypoglycaemia $\leq 3.9\text{mmol}/\text{l}$ and the person's self-reported blood glucose threshold for detecting hypoglycaemia. LIG $\leq 3.9\text{mmol}/\text{l}$ (70

mg/dl) is a commonly reported level of blood glucose used to indicate hypoglycaemia (23). A lower cut-off of $LIG \leq 2.7$ mmol/l (50 mg/dl) was also selected to capture those individuals who may not experience symptoms at 3.9 mmol/l (70 mg/dl) (24). In addition, the participant's own level to indicate hypoglycaemia was chosen to control for individual variation in the level at which people with diabetes pay attention to their low blood glucose levels and experience symptoms of hypoglycaemia. The pre-set minimal duration for valid hypoglycaemia was at least 10 minutes.

2.5 Statistical analyses

Data were analysed using SPSS, version 19 (Chicago, IL, USA). One hundred (88.5%) participants provided complete HypoSRQ data. Sample size was based on criteria for psychometric analyses (25). Means, standard deviations and frequency distributions were computed for each HypoSRQ item. Exploratory factor analysis (EFA) and internal consistency reliability analysis (Cronbach's alpha) were used to investigate the scale structure of the HypoSRQ and to guide removal of items. Normality of distributions was assessed by histograms and Z (skew) scores. HypoSRQ symptom frequency, bother ratings and the number of hypoglycaemic episodes reported were positively skewed. Square-root transformations resulted in these variables being normally distributed. Independent samples t-tests and chi-square tests were used to compare those who completed with HypoSRQ questionnaire only with those who completed blinded CGM for six days on all measured variables. Pearson's correlation coefficients examined consistency in recall of HypoSRQ symptom frequency, bother ratings and number of hypoglycaemic episodes over seven days and recent weeks (i.e. about the past four weeks), and the

relationships between HypoSRQ scores and blinded CGM-detected hypoglycaemia (over six days). Sensitivity and specificity of the HypoSRQ as a tool for detecting hypoglycaemia was compared against blinded CGM using the standard cut-off of $LIG \leq 3.9\text{mmol/l}$.

3. Results

Table 1 shows characteristics for the whole sample ($n=113$) and the subset of participants who completed blinded CGM for six days ($n=30$). There were no significant differences between participants who used blinded CGM for six days and those who completed questionnaires only in any of the variables measured.

Women reported a significantly greater number of hypoglycaemia symptoms ($t(100) = -3.91, p < 0.001$) and higher HypoSRQ bother ratings ($t(100) = -3.47, p < 0.001$) than men. Age was inversely correlated with the number of HypoSRQ symptoms that were reported ($r(98) = -0.33, p = 0.001$) and HypoSRQ symptom bother ratings ($r(98) = -0.31, p = 0.002$). Younger people also reported more episodes of hypoglycaemia than older people ($r(78) = 0.34, p < 0.01$). There was a small negative correlation between body mass index (kg/m^2) and HypoSRQ symptom frequency scores ($r(90) = -0.23, p = 0.03$) indicating that people who had a higher body mass index reported fewer symptoms of hypoglycaemia compared to people with a lower body mass index. Older age at leaving full-time education was significantly associated with higher HypoSRQ symptom frequency scores ($r(57) = 0.32, p = 0.02$) and HypoSRQ bother rating scores ($r(57) = 0.27, p = 0.04$). There were no significant differences in

HypoSRQ symptom frequency or symptom bother rating scores or the number of episodes of hypoglycaemia reported between people with Type 1 and Type 2 DM. Glycated haemoglobin (HbA_{1c}), duration of diabetes, and comorbidity were not significantly associated with HypoSRQ scores.

Table 2 shows the HypoSRQ symptom frequency and bother ratings for each item. Among the 71 participants who reported experiencing hypoglycaemia the mean number of episodes was 6.3 (SD=5.8) in recent weeks (i.e. about the past four weeks). The mean number of symptoms reported per participant was 6.6 (SD=4.4) with 26% reporting that they had experienced 10 or more symptoms in recent weeks.

The HypoSRQ provides space for participants to note symptoms that they experienced which had not been mentioned in the questionnaire. Fourteen participants responded in this section of the questionnaire. Examination of these responses found they were mostly expanding on existing questionnaire items, or were referring to symptoms which were more typically indicators of hyperglycaemia (i.e. numbness or tingling of mouth or face). Hunger, which was reported by 3 participants, was the one exception.

3.1 Factor structure

Prior to conducting the main exploratory factor analysis an unforced principal components analysis (PCA) was carried out. The unforced PCA included the 17 HypoSRQ (recent weeks version) symptom items and responses from 100

participants with complete data. Output from the PCA was used to check the data to ensure suitability for factor analysis. Inspection of the correlation matrix revealed no inter-item correlations exceeding $r=0.80$, thus indicating no problems with multicollinearity within the data. The Kaiser-Meyer-Olkin (KMO, measure of sampling adequacy) value was 0.831, which was well above the cut-off value of 0.60 (26) and Bartlett's Test of Sphericity (27) reached statistical significance. Initial data checks indicated that the properties of the correlation matrix justified a factor analysis being carried out. One item, 'Passed out/Lost consciousness', was problematic with all correlations <0.20 and was removed. After removal of this item the PCA revealed four components with eigenvalues greater than 1. However, visual inspection of Cattell's scree plot suggested a single component accounted for the majority of the variance. Horn's parallel analysis (28) also suggested a one component solution.

The structure of the HypoSRQ was explored using Principal Axis Factoring (PAF) with oblique rotation (to allow possible correlation between factors). Initially a forced three-factor solution was conducted on the 16 remaining HypoSRQ items to determine whether three factors could be distinguished representing groups of symptoms: neuroglycopenic, autonomic, and malaise as has previously been reported (1). The results revealed a 3-factor structure accounting for 38.96% of the variance. Examination of the pattern matrix revealed several items had loadings of <0.4 and there was no satisfactory evidence for clear subgroups of symptoms. Factor 1 and factor 2 were also moderately correlated ($r=0.618$) suggesting that they could be combined into a single factor.

The scree plot indicated there was one clear factor which accounted for the majority of the variance. Therefore, a forced one-factor PAF was conducted on the 16 HypoSRQ items (Table 3). Palpitations and blurred vision were found to have factor loadings <0.4 (0.356 and 0.374 respectively). The analyses were repeated after excluding these two items (Table 3). All of the remaining 14 items loaded well onto a single factor (all ≥ 0.4) and accounted for 31.83% of the variance.

3.2 Internal consistency reliability

Reliability analysis was initially conducted on all 17 HypoSRQ items. Cronbach's α was strong with an alpha of 0.898 (standardised alpha=0.889). Item-total correlations for all items (except passed out/lost consciousness) were well above the minimum satisfactory level of 0.2. Excluding passed out/lost consciousness, palpitations and blurred vision increased Cronbach's alpha to 0.905. These findings support the results of the PAF which suggested that passed out/lost consciousness, blurred vision and palpitations should be omitted from the scale score.

3.3 HypoSRQ scoring

A HypoSRQ symptom frequency score is obtained by summing the total number of 14 symptoms reported (range 0–14). A HypoSRQ bother rating score is obtained by summing bother ratings for each of the 14 items as follows: 0 'did not have the symptom', 1 'not at all', 2 'a little', 3 'moderately', 4 'a lot'. Total bother rating scores range from 0-56, with higher scores indicating that the person was more bothered by their hypoglycaemia symptoms. An additional item records the number of episodes

of hypoglycaemia a person has experienced during the time period being assessed and a separate bother rating ranging from 0-4.

3.4 Recall of hypoglycaemia over seven days and recent weeks

The number of participants for individual correlations varied due to missing data (n range=21-24). The 7-days version of the HypoSRQ correlated highly with the 24-hours version of the HypoSRQ summed across seven days: symptom frequency ($r=0.94$, $p<0.001$), bother ratings ($r=0.98$, $p<0.001$), and number of hypoglycaemic episodes ($r=0.97$, $p<0.001$). These results indicate that people were almost as good at recalling hypoglycaemia when asked at the end of seven days as they were when asked daily. The recent weeks version of the HypoSRQ was highly correlated with the 7-days version of the HypoSRQ summed across four weeks: symptom frequency ($r=0.91$, $p<0.001$), bother ratings ($r=0.94$, $p<0.001$) and number of hypoglycaemic episodes ($r=0.84$, $p<0.001$). Recall of hypoglycaemia across four weeks was almost as reliable as recall of hypoglycaemia over seven days.

3.5 Correlations between HypoSRQ and blinded CGM-measured hypoglycaemia

The relationships between HypoSRQ symptom frequency, bother ratings and number of hypoglycaemic episodes (summed across six days) and the frequency of blinded CGM-measured hypoglycaemia at $LIG \leq 3.9\text{mmol/l}$, $LIG \leq 2.9\text{mmol/l}$, and at the individual's own threshold for detecting hypoglycaemia (range 1.9-5.0mmol/l) were examined among the 30 participants who completed CGM for six days.

The number of hypoglycaemic episodes a person reported on the 24-hour version of the HypoSRQ (summed across 6 days) was significantly correlated with the frequency of blinded CGM-measured hypoglycaemic episodes at $LIG \leq 3.9\text{mmol/l}$ ($r=0.72$, $p<0.001$). There was a strong correlation between self-reported frequency of hypoglycaemia and blinded CGM-measured hypoglycaemic episodes when the person's own threshold for detecting hypoglycaemia was used ($r=0.78$, $p<0.001$). These correlations remained significant after adjustment for age, sex, insulin treatment duration, and type of diabetes ($r=0.55$, $p=0.004$, and $r=0.68$, $p=0.002$, respectively). The relationship between self-reported frequency of hypoglycaemia and blinded CGM-measured hypoglycaemia at the lower threshold of $LIG \leq 2.7\text{mmol/l}$ was non-significant ($r=0.36$, $p=0.11$). There was a strong significant association between the number of days (out of six) an individual reported having one or more symptoms of hypoglycaemia and the number of days (out of six) blinded CGM detected one or more hypoglycaemic episodes ($r=0.83$, $p<0.001$) using the 3.9mmol/l cut-off. The result was not changed when a partial correlation was used to adjust for age, sex, insulin treatment duration and type of diabetes ($r=0.83$, $p<0.001$). The number of symptoms a person reported and how bothered they were by their symptoms did not correlate significantly with blinded CGM-measured frequency of hypoglycaemic episodes over six days at $LIG \leq 3.9\text{mmol/l}$, $LIG \leq 2.7\text{mmol/l}$, or using the person's own threshold for detecting hypoglycaemia.

3.6 Sensitivity and specificity of the HypoSRQ

Of the 30 participants who completed blinded CGM for six days, 24 people experienced at least one blinded CGM-measured hypoglycaemic episode. There

were 86 hypoglycaemic episodes in total using the 3.9mmol/l cut off level. Of these, 53 episodes were identified by participants reporting one or more symptoms on the HypoSRQ ('true positives'); therefore the sensitivity of the HypoSRQ in detecting blinded CGM-measured hypoglycaemia using symptoms alone was 60.9% (95% CI 49.9-71.2) in this sample. Specificity refers to the proportion of occasions when blinded CGM showed no hypoglycaemia which was confirmed by no symptoms being reported. The HypoSRQ had lower levels of specificity (51.8%; 95% CI 38.0-65.3). There were 35 occasions when participants did not report any symptoms of hypoglycaemia and no hypoglycaemic episodes were detected using blinded CGM ('true negatives'). There were 33 occasions when participants reported one or more symptoms of hypoglycaemia in the absence of blinded CGM-detected hypoglycaemia (these would typically be known as 'false positives' if blinded CGM could be relied upon to be an accurate measure of hypoglycaemia). Similarly, there were 34 occasions when participants did not report any symptoms of hypoglycaemia but blinded CGM-measured hypoglycaemia was detected ('false negatives').

The sensitivity and specificity of the HypoSRQ was examined separately for people with Type 1 and Type 2 DM. For people with Type 1 DM (n=21), there were 60 blinded CGM detected hypoglycaemic episodes in total using the 3.9mmol/l cut off level over 6 days. Of these, 38 episodes were identified by participants reporting one or more symptoms on the HypoSRQ ('true positives'); therefore the sensitivity of the HypoSRQ was 67.9% (95% CI 53.9-79.3) among people with Type 1 DM. Specificity (i.e. the proportion of occasions [n=19] when blinded CGM showed no hypoglycaemia which was confirmed by no symptoms being reported on the HypoSRQ) was 46.3% (95% CI 30.9-62.3).

For people with Type 2 DM (n=9), there were 17 blinded CGM detected hypoglycaemic episodes in total using the 3.9mmol/l cut off level over 6 days. Of these, 12 episodes were identified by participants reporting one or more symptoms on the HypoSRQ. The sensitivity of the HypoSRQ to detect CGM-measured hypoglycaemia was 70.5 (95% CI 44.0-88.6) among people with Type 2 DM. Specificity (i.e. the proportion of occasions when blinded CGM showed no hypoglycaemia which was confirmed by no symptoms being reported on the HypoSRQ [n=22]) was 40.5% (95% CI 25.1-57.8).

4. Discussion

The HypoSRQ has a single-factor structure and excellent internal consistency. The HypoSRQ in the different versions, covering different time frames, reliably measures self-reported hypoglycaemia symptoms, bother ratings, and hypoglycaemic episodes over seven days and recent weeks (i.e. about the past four weeks) . The ability of people with diabetes to recall hypoglycaemic episodes and symptoms is not well documented. In one study recall of severe hypoglycaemia was well-preserved over one year among people with Type 1 DM (29). Similar results were found for people with Type 2 DM (30). In another study, recall of mild hypoglycaemia was unreliable after one week in people with Type 1 DM (31). These studies relied on subjective recall of the frequency of hypoglycaemia, which does not take account of symptom awareness. The HypoSRQ provides a more comprehensive assessment for use in future studies aiming to assess recall and awareness of hypoglycaemia symptoms.

Associations found between the number of hypoglycaemic episodes reported across six days and blinded CGM-measured hypoglycaemia frequency (using the 3.9mmol/l cut-off and the participants' self-reported threshold for detecting hypoglycaemia) provides preliminary support for the construct validity of the HypoSRQ. There was high correspondence between the number of days (out of six) hypoglycaemia symptoms were reported and the number of days on which blinded CGM indicated hypoglycaemia. The HypoSRQ, with its comprehensive list of 17 possible symptoms (including three items not included in the scale score), may help people recognise warning symptoms of personal relevance and take action to prevent a severe hypoglycaemic episode.

In previous research, people with one to three reliable warning symptoms correctly identified half of their hypoglycaemic episodes, while those with four or more symptoms correctly recognised over 70% of episodes (13). Using the HypoSRQ, 60.9% of blinded CGM-measured hypoglycaemic episodes were identified using one or more symptoms reported by participants. There were also 'false positives' (hypoglycaemia symptoms in the absence of blinded CGM-detected hypoglycaemia), and 'false negatives' (blinded CGM-detected hypoglycaemia in the absence of symptoms). It is likely some people detected hypoglycaemia CGM did not identify leading to 'false positives', which might actually be 'false negatives' for CGM if the HypoSRQ recorded hypoglycaemia CGM failed to detect. Concern has been expressed about the accuracy of CGM, particularly at lower interstitial glucose levels (32), due to the physiological delay between blood glucose and interstitial glucose,

which is greater when blood glucose is falling rapidly (33). This may partly explain why associations between the HypoSRQ and blinded CGM were not significant at $LIG \leq 2.7\text{mmol/l}$ in the present study. There have been significant improvements in the analytical performance, reliability, and usability of the CGM systems in recent years (34) leading to evidence of improved accuracy within the hypoglycaemic range (35). However, even the more recent CGM systems continue to have weaknesses in detecting hypoglycaemia. Although CGM is promising technology it is not yet a sufficiently gold standard measure that can be relied upon in the face of contradictory self-report.

Recognition of hypoglycaemia is not a simple reflection of biological events (13,36). For people to use symptoms to recognise hypoglycaemia they must be able to detect and interpret symptoms. Several modifiers interfere with these processes including antecedent hypoglycaemia, alcohol consumption, and activity. Psychological factors play a pivotal role in diabetes self-management decisions, appraisals of risk of severe hypoglycaemia, and response to low blood glucose (36). These factors add to the variability in frequency of symptoms reported and the extent to which a person is bothered by them. Understanding the mechanisms through which modifiers and psychological factors interfere with recognition of symptoms of hypoglycaemia warrants further investigation.

The present study had some limitations. Awareness of hypoglycaemia was not measured. Without this it is not possible to say for certain whether participants were unaware of 'true' hypoglycaemia or whether blinded CGM was detecting non-

significant dips in interstitial glucose. It was not possible to be certain participants completed the questionnaires as instructed during the blinded CGM monitoring period. Recording times automatically using electronic questionnaires would provide a more reliable way of matching self-reported hypoglycaemia with episodes of blinded CGM-measured hypoglycaemia.

Although hunger has been associated with hypoglycaemia in previous literature (37) it was not included in the original version of the HypoSRQ because it was expected this would occur frequently for most people before meals. In the present study only three participants mentioned this symptom in the free response section of the questionnaire suggesting it may not be so common among people with diabetes. Further work is needed to determine whether hunger is in fact a reliable symptom in the detection of hypoglycaemia. If so, there may be a case for inclusion of a hunger item in the HypoSRQ and this will be evaluated in future work with the HypoSRQ.

Associations between self-reported hypoglycaemia symptoms and blinded CGM-estimated hypoglycaemia suggest that the HypoSRQ may be a less-invasive and more-economical alternative to CGM, specifically with regard to identifying people who may be having difficulty with hypoglycaemia. Further work is needed to establish whether the HypoSRQ has value in identifying and monitoring hypoglycaemia among people with non-insulin dependent diabetes. The frequency of hypoglycaemia among patients with type 2 DM on oral agents alone is generally lower than among those treated with insulin. Non-insulin dependent Type 2 DM may confer greater protection against hypoglycaemia because the counter-regulatory responses commence at a

higher blood glucose level than in non-diabetic populations and people with type 1 DM (38).

The psychometric properties and the associations found between the HypoSRQ and blinded CGM-measured hypoglycaemia, make it an attractive measure for future research and clinical practice. Further research is needed to increase understanding of factors leading to changes in the frequency of different symptoms. The HypoSRQ will be useful in helping people to recognise and track changes in awareness of hypoglycaemia symptoms over time. Further validation and use of the HypoSRQ in different centres is recommended.

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References

- [1] McAulay V, Deary IJ, Frier BM. Symptoms of hypoglycaemia in people with diabetes. *Diabet Med* 2001;18:690-705.
- [2] Arbuckle RA, Humphrey L, Vardeva K, Arondekar B, Danten-Viala M, Scott JA, Snoek FJ. Psychometric evaluation of the Diabetes Symptom Checklist-Revised (DSC-R) - a measure of symptom distress. *Value Health* 2009;12:1168-1175.
- [3] Bradley C, Gilbride CJB. Improving treatment satisfaction and other patient-reported outcomes in people with type 2 diabetes: the role of once-daily insulin glargine. *Diabetes Obes Metab* 2008;10:50-65.
- [4] Vinik AI, Zhang Q. Adding insulin glargine versus rosiglitazone: health-related quality-of-life impact in type 2 diabetes. *Diabetes Care* 2007;30:795-800.
- [5] Bradley C, Todd C, Gorton T, Symonds E, Martin A, Plowright R. The development of an individualised questionnaire of perceived impact of diabetes on quality of life: the ADDQoL. *Qual Life Res* 1999;8:79-91.
- [6] Bradley C. The Diabetes Treatment Satisfaction Questionnaire. In Bradley, C. (Ed.) *Handbook of Psychology and Diabetes: A Guide to Psychological Measurement in Diabetes Research and Practice*. England: Harwood Academic Publishers; 1994.
- [7] Razi A, Bradley C, Barendse S, Ishii H. Development of the Well-being questionnaire short-form in Japanese: the W-BQ12. *Health and Quality of Life Outcomes* 2006;4:40.
- [8] Gonder-Frederick LA, Schmidt KM, Vajda KA, Greear ML, Singh H, Shepard JA, Cox DJ. Psychometric properties of the hypoglycemia fear survey-ii for adults with diabetes. *Diabetes Care* 2011;34:801-6.

- [9] Hepburn DA, Deary IJ, Frier BM, Patrick AW, Quinn JD, Fisher BM. Symptoms of acute insulin-induced hypoglycemia in humans with and without IDDM. Factor-analysis approach. *Diabetes Care* 1991;14:949-57.
- [10] Hepburn DA. Symptoms of hypoglycaemia. In *Hypoglycaemia and Diabetes: Clinical and Physiological Aspects*. Frier, B.M., & Fisher, M. eds. Edward Arnold: London; 1993: p. 93-103.
- [11] Hepburn DA, Deary IJ, Frier BM. Classification of the symptoms of hypoglycaemia in insulin-treated diabetic patients using factor analysis: relationship to hypoglycaemia unawareness. *Diabet Med* 1992;9:70-75.
- [12] Deary IJ, Hepburn DA, MacLeod KM, Frier BM. Partitioning the symptoms of hypoglycaemia using multi-sample confirmatory factor analysis. *Diabetologia* 1993;36:771-777.
- [13] Cox DJ, Gonder-Frederick L, Pohl S, Carter W, Clarke W, Bennette-Johnson S, Rosenbloom A, Bradley C, Moses JL. Symptoms and blood glucose levels in diabetes. *JAMA* 1985;253:1558.
- [14] Zammit NN, Streftaris G, Gibson GJ, Deary IJ, Frier BM. Modeling the consistency of hypoglycemic symptoms: high variability in diabetes. *Diabetes Technol Ther* 2011;13:571-578.
- [15] Amiel SA, Dixon T, Mann R, Jameson K. Hypoglycaemia in type 2 diabetes. *Diabetic Medicine* 2008;25:245-254.
- [16] Hoeks LB, Greven WL, de Valk HW. Real-time continuous glucose monitoring system for treatment of diabetes: a systematic review. *Diabet Med* 2011;28:386-394.
- [17] Battelino T, Phillip M, Bratina N, Nimri R, Oskarsson P, Bolinder J. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. *Diabetes Care* 2011;34:795-800.

- [18] Kovatchev B, Anderson S, Heinemann L, Clarke W. Comparison of the numerical and clinical accuracy of four continuous glucose monitors. *Diabetes Care* 2008;31:1160-1164.
- [19] Taylor MD. Evaluation of a new hypoglycaemia symptom measure: the Hypoglycaemia Symptom Rating Questionnaire (HypoSRQ). DClinPsy Thesis. Royal Holloway, University of London, UK; 2012.
- [20] Gonder-Frederick LA, Cox DJ, Clarke WL, Julian DM. Blood Glucose Awareness Training. In *Psychology in Diabetes Care*. Snoek FJ, Skinner TC, Eds. London, Wiley; 2000 p. 169–206.
- [21] McMillan C, Bradley C, Razvi S, Weaver J. Evaluation of new measures of the impact of hypothyroidism on quality of life and symptoms: the ThyDQoL and ThySRQ. *Value Health* 2008;2:285-294.
- [22] Taylor M.D., Han T.S., Ward, H., McBride, J., Yap I., Bradley C. (2013). Evaluation of the HYPOSRQ and its relationship with hypoglycaemic episodes measured using continuous glucose monitoring. *Diabetes Technology & Therapeutics* 15:A23-A24
- [23] American Diabetes Association Workgroup on Hypoglycaemia. Defining and reporting hypoglycaemia in diabetes. *Diabetes Care* 2005;28:1245-1249.
- [24] International Hypoglycaemia Group. Glucose concentrations of less than 3.0 mmol/l (54 mg/dl) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2017;40:155-157.
- [25] MacCallum RC, Widaman KF, Zhang S, Hong S. Sample size in factor analysis. *Psychol Methods* 1999;4:84-99.
- [26] Kaiser HF. An index of factorial simplicity. *Psychometrik* 1970;39:32-36.

- [27] Bartlett MS. A note on the multiplying factors for various chi square approximations. *Journal of the Royal Statistical Society* 1954;16 (Series B):296-298.
- [28] Horn JL. A rationale and test for the number of factors in factor analysis. *Psychometrika* 1965;30:179-185.
- [29] Pederson-Bjergaard U, Pramming S, Thorsteinsson B. Recall of severe hypoglycaemia and self-estimated state of awareness in type 1 diabetes. *Diabetes Metab Res Rev* 2003;19:232-240.
- [30] Akram K, Pedersen-Bjergaard U, Borch-Johnsen K, Thorsteinsson B. Frequency and risk factors of severe hypoglycemia in insulin-treated type 2 diabetes: a literature survey. *J Diabetes Complications* 2006;20:402-408.
- [31] Pramming S, Thorsteinsson B, Bendtson I, Binder C. Symptomatic hypoglycaemia in 411 type 1 diabetic patients. *Diabet Med* 1991;8:217-222.
- [32] McGowan K, Thomas W, Moran A. Spurious reporting of nocturnal hypoglycaemia by CGMS in patients with tightly controlled type 1 diabetes. *Diabetes Care* 2002;25:1499-1503.
- [33] Rebrin K, Steil GM. Can intersititial glucose assessment replace blood glucose measurements? *Diabetes Technol Ther* 2000;2:461-472.
- [34] Rodbard D. Continuous glucose monitoring: a review of recent studies demonstrating improved glycemic outcomes. *Diabetes Technology & Therapeutics*. 2017;19(Suppl 3): S-25–S-37.
- [35] Kovatchev BP. Hypoglycaemia reduction and accuracy of continuous glucose monitoring. *Diabetes Technology & Therapeutics*, 2015;17(8): 530–533.
- [36] Gonder-Frederick L, Cox D, Kovatchev B, Schlundt D, Clarke W. A biopsychobehavioural model of risk of severe hypoglycaemia. *Diabetes Care* 1997;20:661-669.

[37] Pennebaker JW, Cox DJ, Gonder-Frederick L, Wunsch MG, Evans WS, Pohl S. Physical symptoms related to blood glucose in insulin-dependent diabetics. *Psychosom Med* 1981;43:489-500.

[38] Levy CJ, Kinsley BT, Bajaj M, Simonson DC. Effects of glycemic control on glucose counterregulation during hypoglycaemia in NIDDM. *Diabetes Care* 1998;21, 1330-1338.

1 (a)	<p>Have you had palpitations (rapid or strong heart beat) in recent weeks?</p> <p>No <input type="checkbox"/> If <i>no</i>, go to next symptom</p> <p>Yes <input type="checkbox"/> If <i>yes</i>, complete part (b)</p>
(b)	<p>If yes, how much have these bothered you?</p> <p style="text-align: center;"> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> </p> <p style="text-align: center;"> not at all a little moderately a lot </p>

Have you ... (symptom) ... in recent weeks?

1. ... had palpitations ...
2. ...felt dizzy, light-headed or faint ...
3. ... passed out / lost consciousness ...
4. ... had difficulty concentrating ...
5. ... had difficulty thinking quickly and clearly ...
6. ... felt unusually tired, weak or lethargic ...
7. ... felt sick or vomited ...
8. ... had any headaches ...
9. ... felt unsteady or uncoordinated ...
10. ... had trembling ...
11. ... felt suddenly irritable or angry ...
12. ... felt unusually emotional ...
13. ... had excessive sweating ...
14. ... suddenly felt too hot or cold all over, or in part of your body ...
15. ... felt excessively sleepy ...
16. ... had blurred vision ...
17. ... had slurred speech or difficulty taking ...
18. ... experienced any hypos...

Figure 1: Example of a HypoSRQ item and an abbreviated form of the 18 items.

	Full sample (N=113)			CGM sample (N=30)			p-value
	N	Range	Mean (SD)	N	Range	Mean (SD)	
Age (yrs.)	113	18-86	48.0 (17.4)	30	20-85	48.1 (17.0)	0.67
Ratio of men to women	56:57			14:16			0.61
Age left full-time education (yrs.)	65	14-32	18.5 (3.4)	20	15-24	17.0 (2.2)	0.07
Currently in full-time education	9			1			0.34
Glycated Haemoglobin (HbA _{1c})	83	6.1-17.1	8.9 (2.0)	26	6.2-15.8	8.9 (2.2)	0.73
Body Mass Index (kg/m ²)	97	17.3-43.8	28.2 (5.8)	26	18.0-41.2	27.8 (5.5)	0.94
Type 1 diabetes (n = 77)							
Years since diagnosis	68	1-48	19.5 (12.9)	21	1-42	16.9 (13.6)	0.95
Years on insulin therapy	68	1-48	19.5 (12.9)	21	1-42	16.9 (13.6)	0.82
Number of injections per day	61	3-6	4.3 (0.9)	21	3-6	4.0 (0.8)	0.38
Insulin-treated	71			21			
Plus oral agents	0			0			
Insulin delivered by CSII pump*	12			3			
Number of hypoglycaemic episodes in recent weeks**	61	0-30	4.9 (6.1)	20	0-20	6.2 (5.7)	0.54
Type 2 diabetes (n = 36)							
Years since diagnosis	34	1-40	14.9 (9.3)	9	3-30	12.8 (9.2)	0.41
Years on insulin therapy	32	0.1-39	9.2 (8.6)	9	0.1-12	6.2 (4.3)	0.18
Number of injections per day	35	2-5	3.9 (1.0)	9	2-5	3.9 (0.9)	0.87
Insulin-treated	36			9			
Plus oral agents	21			6			
Insulin delivered by CSII pump*	1			0			
Number of hypoglycaemic episodes in recent weeks**	30	0-12	2.3 (3.1)	6	0-10	3.0 (4.0)	0.61

*CSII, Continuous Subcutaneous Insulin Infusion. Ns vary due to non-applicability and missing data. ** Recent weeks i.e. about the past four weeks.

In the full sample the following co-morbid conditions were reported (n=50): thyroid dysfunction, high blood pressure, high cholesterol, atrial fibrillation, Meniere's disease, epilepsy, depression, urticaria, arthritis, coeliac disease, polycystic ovaries, asthma, Addison's disease, sciatica, and diverticulitis. Several people had multiple co-morbid conditions. Diabetes complications were reported including diabetes-related eye disease (23), renal problems (8), heart problems (6), circulatory problems (5), foot problems (14), and neuropathy (8).

P-values were calculated using independent samples t-tests for continuous variables and chi-square tests for categorical variables.

Table 1: Characteristics of the study participants.

	Symptom* N/%**	Symptom bother rating				Mean (SD) [Range used]
		Not at all	A little	Moderately	A lot	
		(1)	(2)	(3)	(4)	
1. Palpitations	31	4	17	7	3	2.29 (0.82) [1-4]
2. Dizzy, light-headed and faint	43	1	24	14	4	2.49 (0.70) [1-4]
3. Passed out/lost consciousness	1	0	0	0	1	4.00 (0.00) [4]
4. Difficulty concentrating	45	3	20	16	6	2.56 (0.81) [1-4]
5. Difficulty thinking quickly and clearly	47	4	24	14	5	2.43 (0.80) [1-4]
6. Tired, weak or lethargic	63	3	15	26	19	2.97 (0.86) [1-4]
7. Felt sick or vomited	17	1	7	4	5	2.76 (0.97) [1-4]
8. Headaches	48	6	19	11	12	2.60 (1.01) [1-4]
9. Unsteady or uncoordinated	35	2	17	14	2	2.46 (0.70) [1-4]
10. Trembling	45	7	20	12	6	2.38 (0.91) [1-4]
11. Suddenly irritable or angry	51	0	21	18	12	2.82 (0.79) [2-4]
12. Unusually emotional	48	4	19	11	14	2.73 (0.98) [1-4]
13. Excessive sweating	48	2	16	18	12	2.83 (0.86) [1-4]
14. Suddenly too hot or cold	45	2	24	12	7	2.53 (0.82) [1-4]
15. Excessively sleepy	51	3	15	14	19	2.96 (0.96) [1-4]
16. Blurred vision	26	2	9	7	8	2.81 (0.98) [1-4]
17. Slurred speech or difficulty talking	14	0	9	4	1	2.43 (0.65) [2-4]
18. Recent hypoglycaemia	71	5	35	24	7	2.46 (0.77) [1-4]

* Symptom experienced in recent weeks (i.e. about the past four weeks)

** N=100 participants who provided complete HypoSRQ data

HypoSRQ, Hypoglycaemia Symptom Rating Questionnaire; SD, standard deviation

The HypoSRQ is available via www.healthpsychologyresearch.com.

The mean and range reported are bother ratings of those who said they had experienced the symptom. The possible range is 1-4 (Not at all – A lot).

Table 2: HypoSRQ symptom and bother rating frequencies, means (standard deviations) and ranges used for each of the 17 original symptom items and recent hypoglycaemia (N=100**).

HypoSRQ item	Pattern Matrix Coefficients									
	Unforced PCA (55.06%)				Forced 3-factor (37.57%)			Forced 1-factor		
	1	2	3	4	1	2	3	16-items (29.53%)	14-items (31.84%)	
1: Palpitations	.22	-.03	.17	.76	.30	.15	-.11	.36	<i>item omitted</i>	
2: Dizzy, light-headed or faint	.52	-.11	.02	.23	.42	.08	.07	.49	.49	
3: Passed out/lost consciousness	<i>item omitted</i>				<i>item omitted</i>			<i>item omitted</i>	<i>item omitted</i>	
4: Difficulty concentrating	.84	-.04	-.09	.06	.85	-.17	.09	.66	.66	
5: Difficulty thinking quickly and clearly	.74	-.20	-.07	-.12	.62	-.07	.27	.63	.65	
6: Tired, weak and lethargic	.23	.10	.58	.20	.26	.51	-.12	.62	.61	
7: Felt sick or vomited	.22	-.15	.41	-.41	.12	.32	.27	.52	.52	
8: Headaches	.64	.07	.05	.01	.48	.10	.03	.54	.54	
9: Unsteady or uncoordinated	.27	-.39	.28	-.02	.25	.21	.32	.57	.57	
10: Trembling	.13	-.22	.53	.14	.14	.45	.16	.60	.59	
11: Suddenly irritable or angry	.73	-.01	.07	.01	.65	.08	.06	.69	.70	
12: Unusually emotional	.59	.54	.27	-.08	.45	.26	-.29	.49	.49	
13: Excessive sweating	.12	-.64	.20	.11	.15	.17	.39	.46	.47	
14: Too hot or cold	-.02	-.12	.73	.07	-.01	.65	.09	.59	.58	
15: Excessively sleepy	-.13	-.09	.85	.07	-.13	.79	.07	.57	.57	
16: Blurred vision	.01	.22	.61	-.22	.07	.37	-.02	.37	<i>item omitted</i>	
17: Slurred speech or difficulty talking	.24	-.54	.05	-.39	.09	.10	.46	.38	.40	

* Figures in brackets are proportion of cumulative variance explained

HypoSRQ, Hypoglycaemia Symptom Rating Questionnaire. PCA; Principle Components Analysis; PAF, Principal Axis Factoring

Cell entries marked in bold refer to loadings ≥ 0.40 .

Table 3: Pattern matrix coefficients for exploratory PCA (unforced) and confirmatory PAF (forced three factor and one factor analyses) with oblique rotation of the HypoSRQ recent weeks (i.e. about the past four weeks) version.