Speight, J, Barendse, SM, Singh, H, Little, SA, Inkster, B, Frier, BM, Heller, SR, Rutter, MK and Shaw, JA 2016, Characterizing problematic hypoglycaemia: iterative design and preliminary psychometric validation of the Hypoglycaemia Awareness Questionnaire (HypoA-Q)*, Diabetic medicine*, vol. 33, no. 3, pp. 376-385.

Received Date : 01-Jan-2015

Revised Date : 10-Apr-2015

Accepted Date : 01-Jun-2015

Article type : Research Article

Short title:Validation of the HypoA-Q

Research: Complications

Characterizing problematic hypoglycaemia: iterative design and preliminary psychometric validation of the Hypoglycaemia Awareness Questionnaire (HypoA-Q)

J. Speight[1,2,3], S. M. Barendse[1], H. Singh[4], S. A. Little[5], B. Inkster[6], B. M. Frier[6], S. R. Heller[7], M. K. Rutter[8, 9] and J. A. M. Shaw[5]

[1]AHP Research, Hornchurch, UK, [2]The Australian Centre for Behavioural Research in Diabetes, Diabetes Australia, Victoria, Melbourne, Australia, [3]Centre for Mental Health and Wellbeing Research, School of Psychology, Deakin University, Burwood, Australia, [4]Department of Psychiatry and Neurobehavioral Sciences, Division of Behavioral Health and Technology, University of Virginia School of Medicine, Charlottesville, USA, [5]Institute of Cellular Medicine, Newcastle University, Newcastle, UK, [6]Department of Diabetes, Royal Infirmary, Edinburgh, UK, [7]Academic Unit of Diabetes, Endocrinology & Metabolism, University of Sheffield, UK, [8]Endocrinology and Diabetes Research Group, Institute of Human Development, Faculty of Medical and Human Sciences, University of Manchester, UK and [9]Manchester

Diabetes Centre, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

Correspondence to: Jane Speight. E-mail: jane.speight@deakin.edu.au

What's new?

- Approximately 20–25% of adults with Type 1 diabetes have impaired awareness of hypoglycaemia (IAH), which is associated with a six-fold higher risk of severe hypoglycaemia. Existing measures of impaired awareness of hypoglycaemia have acknowledged limitations.
- Comprehensive, collaborative and iterative qualitative work (including adults with Type 1 diabetes and clinicians) has generated a new questionnaire designed to characterize IAH and problematical hypoglycaemia when awake and asleep, as well as to assess changes over time.
- Preliminary psychometric validation has shown that the Hypoglycaemia Awareness Questionnaire has: good face and content validity; convergent, divergent and known-groups validity; satisfactory scale structure and internal consistency reliability; and early indication of predictive validity.

Abstract

Aims: To design and conduct preliminary validation of a measure of hypoglycaemia awareness and problematic hypoglycaemia, the Hypoglycaemia Awareness Questionnaire.

Methods: Exploratory and cognitive debriefing interviews were conducted with 17 adults (nine of whom were women) with Type 1 diabetes (mean ± SD age 48±10 years). Questionnaire items were modified in consultation with diabetologists/psychologists. Psychometric validation was undertaken using data from 120 adults (53 women) with Type 1 diabetes (mean ± SD age 44±16 years; 50% with clinically diagnosed

impaired awareness of hypoglycaemia), who completed the following questionnaires: the Hypoglycaemia Awareness Questionnaire, the Gold score, the Clarke questionnaire and the Problem Areas in Diabetes questionnaire.

Results: Iterative design resulted in 33 items eliciting answers on awareness of hypoglycaemia when awake/asleep and hypoglycaemia frequency, severity and impact (healthcare utilization). Psychometric analysis identified three subscales reflecting 'impaired awareness', 'symptom level' and 'symptom frequency'. Convergent validity was indicated by strong correlations between the impaired awareness subscale and existing measures of awareness: (Gold: r_s=0.75, *P*<0.01; Clarke: r_s=0.76, *P*<0.01). Divergent validity was indicated by weaker correlations with diabetes-related distress (Problem Areas in Diabetes: r_s=0.25, *P*<0.01) and HbA_{1c} (r_s=-0.05, non-significant). The impaired awareness subscale and other items discriminated between those with impaired and intact awareness (Gold score). The impaired awareness subscale and other items contributed significantly to models explaining the occurrence of severe hypoglycaemia and hypoglycaemia when asleep.

Conclusions: This preliminary validation shows the Hypoglycaemia Awareness Questionnaire has robust face and content validity; satisfactory structure; internal reliability; convergent, divergent and known groups validity. The impaired awareness subscale and other items contribute significantly to models explaining recall of severe and nocturnal hypoglycaemia. Prospective validation, including determination of a threshold to identify impaired awareness, is now warranted.

Introduction

Approximately 20–25% of adults with Type 1 diabetes have impaired awareness of hypoglycaemia (IAH) [1]; after 25 years almost 50% are affected [2] and the risk of severe hypoglycaemia (SH) is sixfold higher [1,3]. IAH may compromise activities such as driving, and glycaemic targets may need to be modified to avoid SH [4,5]. While significant impairment can debar affected individuals from driving, neither a

definition of IAH nor how it should be assessed are described in the European Union licensing regulations [6]. An accurate, reliable and validated method to characterize problematic hypoglycaemia (frequency, severity, impact and impaired awareness), is needed to inform compilation of medical reports for driving licensing authorities.

Current methods for identifying IAH involve use of the self-report measures the Gold score [3] and the Clarke questionnaire [7], separately or in combination [8]. The Gold score is brief (a single question with a seven-point response scale) with good face validity but it enables identification only and does not facilitate detailed characterization of IAH. The Clarke questionnaire [7] comprises eight questions documenting exposure to hypoglycaemia and a subjective estimation of the glycaemic threshold for symptom generation. It provides a detailed assessment but has limitations: the SH definition is not that of the American Diabetes Association Hypoglycaemia Workgroup [9]; consensus for the glycaemic thresholds used is lacking; the recall periods are inconsistent between questions and with the time periods used in most clinical trials; and most notably, nocturnal hypoglycaemic events are not captured. Although the Gold score and Clarke questionnaire have good concordance in detecting IAH, they share a limited ability to characterize or evaluate the severity of IAH and lack some sensitivity to change [8].

Our aim was to design and conduct preliminary psychometric validation of a novel, optimized measure for detailed characterization of problematic hypoglycaemia, including frequency, severity, impact and onset awareness: the Hypoglycaemia Awareness Questionnaire (HypoA-Q).

Patients and methods

Study 1: design and debriefing of the Hypoglycaemia Awareness Questionnaire

The design of the HypoA-Q was rigorous and iterative, involving multiple interviews with adults with Type 1 diabetes who were experiencing problematic hypoglycaemia. After every two to three interviews, diabetologists and psychologists discussed findings, and questionnaire items were refined. Interviews continued until an optimized design was achieved (10th draft) with no further concerns being raised. Full study details are provided in Appendix S1.

Study 2: psychometric validation of the Hypoglycaemia Awareness Questionnaire

Procedure

Adults with Type 1 diabetes were invited to participate during clinic attendance at the Royal Infirmary and Western General Hospital, Edinburgh. After providing formal consent, they completed the questionnaire booklet (see below). Ethics approval was granted by the West of Scotland Research Ethics Committee.

Participants

Eligible participants were adults (aged 18–75 years), with established Type 1 diabetes (≥12 months), able to read/write in English and who were willing to complete the questionnaires and have clinical data extracted from medical records. Half of those approached had been listed on an IAH register after clinical assessment by one of the authors (B.M.F.), without application of a scoring system.

Study measures

In addition to the newly developed HypoA-Q (described in the Results section), the questionnaire booklet included:

- Gold score [3]: a score of ≥4 designates IAH.
- The Guy's and St Thomas' Minimally Modified Clarke Hypoglycaemia Survey, derived from the Clarke questionnaire [7]: a score of ≥4 designates IAH.
- Problem Areas in Diabetes (PAID) scale [10]: the total score, derived from this 20-item measure, ranges from 0 to 100, with higher scores indicating greater diabetes distress [11].

Statistical analysis

The scoring on the HypoA-Q was determined using a combination of statistics to yield a profile measure, i.e. several item and subscale scores. Exploratory factor analysis was conducted on 17 items (5a–d; 6a–c; 7–13; 17–19) considered suitable for profiling IAH (including symptoms whether awake or asleep). Notably, questions about previous experience of SH were excluded from the impaired awareness subscale explorations, on the basis that SH is a consequence of IAH and should not be part of its definition. Factor loadings ≥0.3 and ≥0.6 were considered meaningful and high, respectively [12]. To support internal consistency reliability, Cronbach's α of ≥0.70 was considered satisfactory [13]. Sixteen items were considered conceptually distinct, relating to reporting of hypoglycaemic events (frequency and severity) and related healthcare utilization (items 1, 2a–d), while awake (items 3, 4a–d), and while asleep (items 15, 16a–e). These were scored separately and analysed individually providing descriptive statistics of frequency, severity and impact of hypoglycaemia. Two open-ended questions (items 14 and 20) invited qualitative responses.

Statistical analyses were conducted using IBM SPSS for Windows version 21 (Chicago, IL, USA). Descriptive statistics are shown as number (percentage) and mean ± SD unless otherwise indicated. All statistical tests were conducted using non-parametric statistics because distributions of several variables were skewed. Missing data were considered 'missing completely at random'.

Frequency analyses were conducted to examine HypoA-Q completion rates and response ranges. High overall completion rates (>95%) were taken as evidence of the questionnaire's acceptability.

Convergent validity is an expected strong relationship (i.e. $r_s \geq 0.7$) between two similar measures. It was assessed by correlating the HypoA-Q 'impaired awareness' subscale with Gold score and Clarke questionaire scores. Divergent validity is an expected weak relationship (i.e. $r_s < 0.3$) between two dissimilar measures. It was assessed by correlating the HypoA-Q impaired awareness subscale with diabetes distress (PAID total score), diabetes duration and HbA_{1c}.

Known-groups validity is the ability of a measure to discriminate between populations when a difference is expected. This was assessed by examining differences in HypoA-Q subscale scores according to participants' known hypoglycaemia awareness status (measured with Gold score: <4 vs. ≥4, indicating IAH), using the Mann–Whitney test (or a chi-squared test for categorical data).

While predictive validity can only be assessed truly in a prospective study, logistic regression was undertaken to examine variables associated with experiencing at least one event (vs. zero events) of SH (item 2a; model 1) or hypoglycaemia when asleep (item 15; model 2) in the preceding 6 months. Variables with near-significant correlations ($P<0.20$) were block-entered into the regression models [14]. Models were generated to include the Gold score (where $P<0.20$) and either Clarke score (model A) or HypoA-Q (model B), to provide an indication of the extent to which the HypoA-Q may add value over existing measures of IAH. It should be noted that questions 3 and 4 on the Clarke questionnaire ask about SH in the preceding 6 months and year, respectively, and are included in the Clarke composite score, artificially inflating any relationship with self-reported SH.

Results

Study 1: design and debriefing of the Hypoglycaemia Awareness Questionnaire

The 17 participants [nine women (53%)] were aged 48±10 years, with a mean ± SD Type 1 diabetes duration of 28±12 years and HbA_{1c} concentration of 62±11 mmol/mol (7.8±1.0%). All had experienced IAH previously but did not necessarily have IAH at time of assessment. Eight (47%) used multiple daily injections and nine (53%) used continuous subcutaneous insulin infusion (insulin pump therapy).

The themes and issues raised by patients, that informed the content of our draft items, are summarized using verbatim quotes in Table 1. Further results are provided in Appendix S1. The questionnaire (Appendix S2) includes 33 items, plus two free-text items, assessing:

- recall of hypoglycaemia, including mild (self-treated) and severe events (requiring assistance for recovery);
- healthcare utilization related to SH (i.e. paramedic attendance, treatment in casualty department or hospital admission);
- blood glucose thresholds at which symptoms commence and the nature of symptoms generated at those thresholds;
- perceived awareness of symptoms;
- perceived diminished awareness;
- frequency of capillary blood glucose monitoring when 'feeling low'.

Separate questions enquire about hypoglycaemia while awake and asleep.

Study 2: psychometric validation of the Hypoglycaemia Awareness Questionnaire

Participant characteristics

Of the 141 clinic attendees approached, 120 (85%) participated, of whom 53 (44%) were women. Their mean ± SD age was 44±16 years, Type 1 diabetes duration was 22±13 years and HbA_{1c} concentration 66±14 mmol/mol (8.2±1.3%). Of the 21 non-participants, 10 agreed but did not return the questionnaire, nine gave no reason for non-participation, one had a conflicting appointment and one was unable to complete the questionnaire because of SH. Of the 21, nine (43%) were women. Their mean ± SD age was 52±11 years and Type 1 diabetes duration 27±15 years. Eleven (52%) had a clinical diagnosis of IAH.

Acceptability

Completion rates were ≥95% for 20 of the 33 items, ≥90% for another 11 and ≥80% for the remaining two. One third of participants wrote comments in the free-text boxes (items 14 and 20). Comments included details of idiosyncratic symptomatology, typical circumstances surrounding hypoglycaemia onset and information to clarify responses to other items. No issues warranted the design of additional items.

Scale structure and internal consistency reliability

Factor loadings and internal consistency reliability are shown in Table 2. Three subscales were identified, with total scores for each derived by summating item scores (with higher scores indicating greater impairment of awareness):

- impaired awareness (items 7, 8, 10, 11 and 12);
- symptom level (items 6a, b and c), reflecting blood glucose thresholds at which autonomic, neuroglycopenic and non-specific (malaise) symptoms of hypoglycaemia [15] are experienced;

- symptom frequency (items 5a, b, c and d), detailing symptoms associated with differing levels of blood glucose (<2.5; 2.5–2.9; 3.0–3.4; 3.5–3.9 mmol/l).

Items 9, 13 and 17–19 did not load on these factors and were treated as separate items for scoring purposes. The hypoglycaemia while asleep items (17–19) describe a qualitatively different experience and the latter two include a 'not applicable' response option.

Frequency of hypoglycaemia events and healthcare utilization

In the preceding week, 73% of participants (86/118) reported having one or more hypoglycaemic event (mild or severe, when awake or asleep), with 18% (21/118) reporting three or more events, while 20% (23/115) experienced at least one SH event in the preceding 6months. A total of 62 SH events were reported by this group (mean ± SD 2.7 ± 3.1 events per person with SH), of which 12 events (19%) required paramedic attendance and one resulted in transfer and admission to hospital.

During the preceding 6 months, 94% of participants (111/118) had experienced at least one hypoglycaemic event (mild or severe) while awake; 72% (85/118) reported three or more events, and 33% (39/118) reported experiencing hypoglycaemia at least once a week. A total of 21% (23/109) had experienced SH while awake.

During the preceding 6 months, hypoglycaemia while asleep (predominantly nocturnal hypoglycaemia) was reported by 64% of participants (75/117). A total of 41% (48/117) had experienced episodes less than once a month, while 10% (12/117) reported hypoglycaemia while asleep at least weekly and 28% (32/116) had experienced at least one SH event while asleep. Of those, 21 had experienced events where they had been given glucose orally, 12 had required glucagon by injection, two had experienced a

'major problem' (defined as, e.g. a fit, tongue biting, fall, collapse or incontinence). A total of 27 participants had experienced episodes where they did not wake and only realised afterwards that they had experienced a hypoglycaemic event.

Convergent and divergent validity

Satisfactory convergent validity was demonstrated by highly significant inter-scale correlations between the HypoA-Q impaired awareness subscale and both the Gold score (r_s=0.70, *P*<0.01) and the Clarke questionnaire (r_s=0.76, *P*<0.01); the Gold and Clarke measures were also strongly correlated (r_s=0.70, *P*<0.01). Divergent validity was demonstrated, with impaired awareness being only weakly correlated, as expected, with diabetes distress (PAID: r_s=0.25, *P*<0.01) and diabetes duration (r_s=0.22, *P*<0.05), and unrelated to HbA_{1c} (r_s=-0.04, ns). Lack of correlation between the symptom level/symptom frequency subscales and the other measures of IAH (data not reported) suggest that they add a qualitatively distinct assessment of IAH.

Known-groups validity

The impaired awareness subscale discriminated, as expected, between those with and without known IAH, according to the Gold score (10.80±3.42 vs 5.09±3.20; *P*<0.001), although symptom level and symptom frequency did not differentiate. Findings were similar when the Clarke questionnaire was used to identify IAH (data not shown). As expected, HypoA-Q items that focused on the frequency of SH events (items 2a, 4b, 4c) also showed expected differences between those with and without IAH (Table 3). As expected, items that focused on experience of mild hypoglycaemia did not discriminate between those with and without known IAH.

Predictive validity

The HypoA-Q subscales and individual items contributed significantly to a model explaining the presence of SH events in the preceding 6 months (Table 4). In model 1A, significant associations with SH included sex, Gold score and Clarke questionnaire score, explaining 44% of the variance in SH. When the Clarke questionnaire was removed and HypoA-Q included (model 1B), the contribution of the Gold score became insignificant; the impaired awareness subscale, being 'more aware [in the past 6 months] of my hypos coming on than I used to be' (item 13) and 'others aware first' of hypoglycaemia while asleep (item 18), contributed significantly to a model explaining 61% of the variance in SH.

For associations with hypoglycaemia while asleep, none of the variables included in model 2A contributed significantly and the overall model explained 10% of the variance. Neither Gold score nor Clarke questionnaire score were associated with hypoglycaemia while asleep. When the Clarke questionnaire was excluded and HypoA-Q included (model 2B), being 'more aware [in the past 6 months] of my hypos coming on than I used to be' (item 13) and reporting 'symptoms wake me' (item 17) contributed significantly to the model, explaining 37% of the variance in hypoglycaemia when asleep.

Discussion

The HypoA-Q fulfils the need for a contemporary, comprehensive assessment of IAH, to improve characterization of IAH when awake and asleep. HypoA-Q items also enable systematic characterization of frequency and severity of recent hypoglycaemia, including SH-related healthcare utilization.

A comprehensive, iterative design study generated a detailed profile measure and has shown that the questionnaire has good breadth of content, face and content validity. The preliminary psychometric validation study showed satisfactory scale structure and internal consistency reliability. Convergent

validity was strong: correlations with the Gold score and Clarke questionnaire score were $r_s \geq 0.7$, suggesting that the five-item impaired awareness subscale was a very satisfactory measure of IAH; while divergent validity was demonstrated with low correlations between impaired awareness and HbA_{1c} and PAID scores. Known-groups validity was also demonstrated. The impaired awareness subscale and several SH items distinguished, as expected, between those with impaired and intact awareness (according to the Gold score; Table 3). Indeed, the former scored almost two standard deviations higher than the latter on the impaired awareness subscale, equivalent to a very large effect size [20]. While it is too soon to determine a clinically important cut-off point for impaired awareness, which would require longitudinal data and multiple datasets, this sensitivity to between-group differences is certainly promising.

The lack of relationships between the symptom level and symptom frequency subscales and other variables raises uncertainty about their discriminatory properties and responsiveness; however, it was clear in the questionnaire design phase that such subscales added a qualitatively distinct method of assessing IAH, which may be useful in routine clinical practice and merits further exploration.

Logistical regression analyses showed that including the HypoA-Q variables in models of severe hypoglycaemia and hypoglycaemia while asleep provided greater explanatory power than including the Gold score or Clarke questionnaire alone. The impaired awareness subscale score and item 13 (being 'more aware [in the past 6 months] of my hypos coming on than I used to be') were associated significantly with severe hypoglycaemia (Table 4; model 1B), suggesting that they may have predictive validity. Item 9 'check blood glucose if I feel low' is likely to be important in the context of those whose awareness may not be adequate for driving, although many other behavioural factors determine driving risk. While these findings suggest that HypoA-Q is likely to have predictive validity and to be responsive,

this needs to be tested fully in a prospective study. The HypoA-Q has been used in the HypoCOMPaSS trial [17], with recently documented evidence of its responsiveness to intervention to improve awareness of hypoglycaemia [18].

The HypoA-Q includes items about awareness and hypoglycaemia while asleep, which is not addressed by the Gold score or Clarke questionnaire. While the latter were not associated with hypoglycaemia while asleep (Table 4; model 2A), item 13 (being 'more aware [in the past 6 months] of my hypos coming on than I used to be') and item 9 ('symptoms wake me') were both associated with hypoglycaemia while asleep (Table 4; model 2B). While this information can be gleaned in a clinical interview, the use of systematic and comprehensive questioning should be encouraged in clinical and research settings, and the HypoA-Q is designed to facilitate this.

Although it takes <7 min to complete, the HypoA-Q was never intended to match the simplicity or brevity of the single-item Gold score [3]. Feedback from design study participants indicated they considered a single-page questionnaire neither feasible nor desirable. Paradoxically, they found the longer questionnaire more acceptable and easier to complete than the initial shorter draft.

A key strength of Study 1 is the rigour with which the questionnaire was designed and debriefed. Questionnaire design took account of existing knowledge of problematic hypoglycaemia, IAH syndrome and its pathogenesis. It benefited from broad, in-depth consultation, which continued until all issues were resolved. Patients with Type 1 diabetes were selected purposefully for their experience of hypoglycaemia and IAH, rather than to represent all adults with the condition, but it is important to acknowledge that such experience means this was a relatively homogeneous group. A strength of Study 2 (psychometric validation) is that data were collected in a routine clinical setting, offering opportunity to assess HypoA-Q suitability in a broad cross-section of adults with Type 1 diabetes (half with clinically

diagnosed IAH), comparing against validated measures of IAH. Despite high response rates, the sample size fell slightly short of the ideal (four to five respondents per item) but was more than adequate, according to Kline's criteria of a respondent to item ratio of 2:1 and a minimum of 100 participants [13]. Some might regard self-reported hypoglycaemic events rather than objective blinded continuous glucose monitoring as a potential limitation of the study; however, the latter does not enable data collection over a long period of time in a large number of people or provide a clear assessment of event severity without a parallel diary, and is of limited use for diagnosing IAH [16]. Both studies are limited by the relative homogeneity of the samples (middle-aged white people with long-standing Type 1 diabetes). Use of this questionnaire in other populations (e.g. other cultural backgrounds, insulin-treated Type 2 diabetes) is now required to confirm and expand upon these findings, and prospective studies are warranted to demonstrate test–retest reliability, responsiveness and predictive validity.

Overall, the HypoA-Q is likely to enable a more definitive diagnosis of IAH, and comprehensive characterization of those with problematic hypoglycaemia who are at high risk of SH and nocturnal hypoglycaemic events. This will enable improved classification of the spectrum of hypoglycaemia awareness in clinical practice, including evaluation of medical fitness, e.g. for activities such as driving. The promising psychometric properties of the HypoA-Q suggest its potential value in clinical trials in which IAH is a primary or secondary endpoint.

Funding sources

We thank Diabetes UK for funding the design of the HypoA-Q (Study 1) as part of the HypoCOMPaSS trial (ref: 07/0003556). No funding was sought for the psychometric validation (Study 2).

Competing interests

J.S. is a director of AHP Research Ltd, which owns the copyright of the HypoA-Q. All other authors have no competing interests to declare.

Access to the HypoA-Q

The HypoA-Q is available free of charge to clinicians, academic researchers and students for use in clinical practice or non-commercially funded research. Please contact Prof Jane Speight (jane.speight@ahpresearch.com or jane.speight@deakin.edu.au) to enquire about whether the version published here has been superseded and to request the latest version and scoring guidance. For commercially funded studies (whether initiated or sponsored by industry), a licence fee will apply and potential users should contact Prof. Speight for details.

Acknowledgements

We thank the people with diabetes who participated in this study. In addition to the authors, the following diabetologists contributed to the consultation that informed the design of the HypoA-Q (Study 1): Prof. Stephanie Amiel (Kings College Hospital, London), Dr Jackie Elliott (University of Sheffield), Prof. Mark Evans (University of Cambridge), Dr Daniel Flanagan (Derriford Hospital, Plymouth), Prof. David Kerr (Royal Bournemouth Hospital). We also acknowledge the assistance of Dr Ganesan Arunagirinathan with data collection (Study 2) at the Western General Hospital, Edinburgh, David Wilson, AHP Research, who conducted the data entry for study 2, and Dr Lucy Busija, previously at Deakin University, for her advice on statistical analyses.

References

1. Geddes J, Schopman JE, Zammitt NN, et al. Prevalence of impaired awareness of hypoglycaemia in adults with type 1 diabetes. *Diabetic Med* 2008; **25**: 501–504
2. Pramming S, Thorsteinsson B, Bendtson I, Binder C. Symptomatic hypoglycaemia in 411 type 1 diabetic patients. *Diabetic Med* 1991;**8**: 217–222
3. Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycemia in patients with type 1 diabetes with impaired awareness of hypoglycemia. *Diabetes Care* 1994; **17**: 697–703
4. Cryer PE. The pathophysiology of hypoglycaemia in diabetes. *Diabetes Nutr Metab* 2002; **15**: 330–333
5. Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER *et al*. Evaluation and management of adult hypoglycemic disorders: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2009; **94**: 709–728
6. Inkster B, Frier BM. Diabetes and driving. *Diabetes Obes Metab* 2013; **15**: 775–783
7. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM: A prospective study of hypoglycemic frequency and associated symptoms. *Diabetes Care* 1995;**18**: 517–522
8. Geddes J, Wright RJ, Zammitt NN, Deary IJ, Frier BM. An evaluation of methods of assessing impaired awareness of hypoglycemia in type 1 diabetes. *Diabetes Care* 2007; **30**: 1868–1870
9. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L *et al.* Hypoglycemia and diabetes: A report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 2013; **36**:1384–1395
10. Polonsky WH, Anderson BJ, Lohrer PA, Welch G, Jacobson AM, Aponte JE *et al.* Assessment of diabetes-related distress. *Diabetes Care* 1995; **18**: 754–760
11. Snoek FJ, Kersch NYA, Eldrup E, Harman-Boehm I, Hermanns N, Kokoszka A et al. Monitoring of Individual Needs in Diabetes (MIND): Baseline data from the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) MIND study. *Diabetes Care* 2011; **34**: 601–603
12. Kline P. *An Easy Guide to Factor Analysis*. London: Routledge, 1994.

13. Kline P. *Handbook of Psychological Testing*. London: Routledge, 1997.

14. Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. *Am J Epidemiol* 1989;**129**:125–137

15. Deary IJ, Hepburn DA, MacLeod KM, Frier BM. Partitioning the symptoms of hypoglycaemia using multi-sample confirmatory factor analysis. *Diabetologia* 1993; **36**: 771–777.

16. Choudhary P, Geddes J, Freeman JV, Emery CJ, Heller SR, Frier BM. Frequency of biochemical hypoglycaemia in adults with type 1 diabetes with and without impaired awareness of hypoglycaemia: no identifiable differences using continuous glucose monitoring. *Diabetic Med* 2010; **27**: 666–672.

17. Little S, Chadwick T, Choudhary P, Brennand C, Stickland J, Barendse S et al. Comparison of Optimised MDI versus Pumps with or without Sensors in Severe Hypoglycaemia (the Hypo COMPaSS trial). *BMC Endocr Disord* 2012;**12:** 33.

18. Little SA, Leelarathna L, Walkinshaw E, Tan HK, Chapple O, Lubina-Solomon A et al. Recovery of hypoglycemia awareness in long-standing type 1 diabetes: A multicenter 2 × 2 factorial randomized controlled trial comparing insulin pump with multiple daily injections and continuous with conventional glucose self-monitoring (HypoCOMPaSS). *Diabetes Care* 2014; **37**: 2114–2122.

19. Willis GB. *Cognitive Interviewing: a tool for improving questionnaire design*. Thousand Oaks, California: Sage Publications, 2005.

20. Cohen J. A power primer. Psychol Bull 1992; **112**:155.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Design and debriefing of the Hypoglycaemia Awareness Questionnaire.

Appendix S2. The Hypoglycaemia Awareness Questionnaire.

Table 1 Themes identified during exploratory interviews indicating the need for new questionnaire content

Themes	Participant comments
Differentiating between hypoglycaemia when awake and when asleep	'It's not necessarily during the day because mine only affect me at night-time' (F12) 'I always have symptoms when it's low? Well, 'yes' during the day, and 'no' during the night' (M9)
Awareness as 'just knowing'	'I can tell if I'm low without the blood sugar test. I just can't tell you how low it is' (F6) 'Sometimes I'll get a hypo where I have no warning and all of a sudden I'm jerking and sometimes I'll have a hypo where I get to the very early stages and I just know I'm going hypo' (F5)
Idiosyncrasy of symptoms (the need to refer to symptoms in general)	'I think sometimes it's very hard to explain symptoms isn't it? You know how you feel when you have hypos. It's symptoms that you only know yourself really' (F6)
Regaining awareness	'I'm starting to regain some of the symptoms, which, I just couldn't pick up anything before, but now the sweating and that is starting to come back' (F12) 'I'm more aware than I was. If you take [me] as I am now, with everything I'm

Themes	Participant comments
	taking, with everything I've got working for me monitoring-wise, then I'm actually better than I used to be' (M9) 'If you'd gone back before some of the monitoring, hypo awareness was a lot less than it is now. I would have quite low blood sugar before I'd have any symptoms at all' (M11)
Checking blood glucose when low	'I think calling it on autopilot is pretty good because the first thing I think is, 'I'll check my blood sugar'. That's the first thing I tend to think. Go check it, just make sure. Go check it, stop what you're doing, because, inevitably, it just gets worse. So, I don't tend to leave it. I'll check it as soon as I can and correct it' (M9)
Differentiating between mild and severe events	'It depends on how severe a hypo. It's ... how do you describe, or how do you word a question for a mild, severe [hypo]?' (M9)
Predefined blood glucose levels that might be personally relevant to experience of hypoglycaemia	'I suppose I've got kind of, for me I've got like three levels of hypo and one is kind of, you know… 3.5 upwards, which, to me, really isn't hypo. I don't really get any symptoms at all but I would usually eat something or drink something at that point because I don't want to go any lower than that. And then there's the kind of middle one, which I suppose is anything, well maybe even from kind of 2.8 up to 3.4, which is my, you know, mild hypo and then there's, there would be the kind of below 2.8, especially when it gets down to close to 2, where I would then get the very severe symptoms' (F7)

Table 2 Hypoglycaemia Awareness Questionnaire scale structure and internal consistency reliability

HypoA-Q item		HypoA-Q subscales factor loadings* (principal components)†		
		Impaired awareness	**Symptom level**	**Symptom frequency**
5a	Symptoms experienced at blood glucose readings '3.5-3.9 mmol/l'	-	-	0.80
5b	Symptoms experienced at blood glucose readings '3.0-3.4 mmol/l'	-	-	0.92
5c	Symptoms experienced at blood glucose readings '2.5-2.9 mmol/l'	-	-	0.92
5d	Symptoms experienced at blood glucose readings 'Less than 2.5 mmol/l'	-	-	0.84
6a	'Trembling, shakiness, pounding heart, warmth, sweating, hunger'	-	0.91	-
6b	'Weakness, lack of coordination, confusion, dizziness, inability to concentrate, difficulty speaking, blurred vision, drowsiness, tiredness, irritability, odd behaviour'	-	0.88	-
6c	'Nausea, tingling, headache'	-	0.88	-
7	'I have symptoms when my blood glucose is low'	0.66	-	-
8	'I 'just know' when I'm going hypo by the way I feel'	0.69	-	-
10	'Other people recognise I am hypo before I do'	0.64	-	-
11	'I am less aware of my hypos coming on than I used to be'	0.82	-	-
12	'I have lost symptoms I used to have when my blood glucose is low'	0.84	-	-
Cronbach's α‡		**0.79**	**0.86**	**0.89**

HypoA-Q, Hypoglycaemia Awareness Questionnaire.

*Factor loadings <0.3 suppressed.

†Principal component analysis transforms a number of (possibly) correlated variables into a (smaller) number of uncorrelated variables called principal components. These components show the internal structure of the data in a way that best explains the variance in the data. The factor loadings represent the correlation between the original variables and the factors. Suppressing factor loadings <0.3 cleans up the rotated factor matrix and makes it easier to interpret.

‡Cronbach's α assesses internal consistency by describing the degree of correlation between various items of the same scale. Cronbach's α has values ranging from 0 to 1. Values between 0.7 and 0.9 indicate good internal consistency and, in general, values >0.95 indicate some redundancy among items.

Table 3 (a) Known-groups validity: Hypoglycaemia Awareness Questionnaire event frequency, severity and hypoglycaemia awareness scores (continuous variables) by known awareness status (Gold score <4 or ≥4)

HypoA-Q item / subscale	Gold score				
	Awareness impaired (≥4) n=35		Awareness partial or intact (<4) n=81		
	Mean (SD)	Median (range)	Mean (SD)	Median (range)	Significance
1 **Hypoglycaemia in past week (mild or severe, when awake or asleep)**	2.06 (3.58)	1.00 (0–20)	1.59 (1.91)	1.00 (0–11)	1457.5
2 **Hypoglycaemia in past 6 months:**					
2a Needed help to recover	0.82 (1.53)	0 (0–7)	0.44 (1.86)	0 (0–15)	1594.5**
2b Used emergency services	0.09 (0.29)	0 (0–1)	0.12 (0.60)	0 (0–5)	1320.0
2c Taken to Accident & Emergency (casualty department)	0.00 (0.00)	0 (0)	0.03 (0.16)	0 (0–1)	1237.5
2d Admitted to hospital	0.00 (0.00)	0 (0)	0.01 (0.11)	0 (0 –1)	1254.0
Impaired awareness subscale (scored 0–20)	10.80 (3.42)	10 (2–18)	5.09 (3.20)	5 (0–14)	2530.5***
Symptom level subscale (scored 0–12)	8.03 (2.96)	8 (1–12)	7.30 (3.16)	8 (0–12)	1573.0
Symptom frequency subscale (scored 0–16)	8.41 (5.00)	8 (0–16)	8.00 (4.52)	8 (0–16)	1327.0
9 **'Check blood glucose if feel low'**	3.36 (0.93)	4 (1–4)	3.38 (0.94)	4 (0–4)	1330.0
13 **'More aware in past 6 months'**	1.54 (1.04)	2 (0–4)	1.38 (1.05)	1 (0–4)	1504.5
17 **When asleep, 'symptoms wake me'**	2.52 (1.54)	3 (0–4)	1.82 (1.29)	2 (0–4)	941.5*
18 **When asleep, 'others aware first'**	1.25 (1.35)	1 (0–4)	0.68 (1.12)	0 (0–4)	1247.0*

HypoA-Q, Hypoglycaemia Awareness Questionnaire.
Data are the average number of events or the average score per person. * P<0.05, ** P<0.01, *** P<0.001 (Mann–Whitney test)
Known-groups validity is determined by the degree to which the questionnaire (i.e. HypoA-Q) demonstrates significant expected differences between two groups groups, i.e. people with impaired or intact hypoglycaemia awareness (assessed by the Gold score).

Table 3b: Known-groups validity: Hypoglycaemia Awareness Questionnaire event frequency, severity and hypoglycaemia awareness scores (categorical variables) by known awareness status (Gold score <4 or ≥4)

HypoA-Q item / subscale		Gold score												Significance
		Hypoglycaemia awareness impaired (≥4) n=35						Hypoglycaemia awareness partial or intact (<4) n=81						
		Never	Once or twice	Three or four times	About once or twice a month	About once a week	More than once a week	Never	Once or twice	Three or four times	About once or twice a month	About once a week	More than once a week	
Hypoglycaemia in past 6 months, when awake:														
3	**Any hypo when awake**	0 (7.6)	10 (28.6)	5 (14.3)	9 (25.7)	6 (17.1)	5 (14.3)	6 (7.6)	16 (24.1)	19 (24.1)	11 (13.9)	16 (20.3)	11 (13.9)	6.54
4a	**Had symptoms and able to treat self**	2 (6.1)	8 (24.2)	6 (18.2)	7 (21.2)	7 (21.2)	3 (9.1)	6 (7.5)	21 (26.3)	15 (18.8)	12 (15.0)	16 (20.0)	10 (12.5)	0.90
4b	**Had symptoms and unable to treat self**	18 (56.3)	12 (37.5)	1 (3.1)	1 (3.1)	0 (0)	0 (0)	65 (87.8)	8 (10.8)	1 (1.4)	0 (0)	0 (0)	0 (0)	13.97**
4c	**Needed someone else to give sugar by mouth**	25.4 (64.5)	10 (32.3)	0 (0)	0(0)	0 (0)	0 (0)	67 (89.3)	6 (8.0)	2 (2.7)	0 (0)	0 (0)	0 (0)	13.44**
4d	**Needed someone else to give a glucagon injection**	27 (87.1)	4 (3.7)	0 (0)	0 (0)	0 (0)	0 (0)	71 (93.4)	5 (6.6)	0 (0)	0 (0)	0 (0)	0 (0)	1.14
Hypoglycaemia in past 6 months, when asleep:														
15	**Any hypo**	15 (44.1)	11 (32.4)	5 (14.7)	2 (5.9)	1 (2.9)	0 (0)	26 (32.9)	34 (43.0)	10 (12.7)	8 (10.1)	1 (1.3)	0 (0)	2.44
16a	**Unable to treat self when woke**	19 (57.6)	11 (33.3)	1 (3.0)	1 (3.0)	1 (3.0)	0 (0)	61 (77.2)	12 (15.2)	3 (3.8)	2 (2.5)	1 (1.3)	0 (0)	5.45
16b	**Someone else gave sugar by mouth**	25 (78.1)	6 (18.8)	1 (3.1)	0 (0)	0 (0)	0 (0)	63 (81.8)	11 (14.3)	2 (2.6)	1 (1.3)	0 (0)	0 (0)	0.77
16c	**Someone else gave a glucagon injection**	29 (90.6)	3 (9.4)	0 (0)	0 (0)	0 (0)	0 (0)	68 (88.3)	6 (7.8)	2 (2.6)	1 (1.3)	0 (0)	0 (0)	1.33
16d	**Which led to a major problem, e.g. fit, tongue biting, fall, collapse, incontinence**	30 (96.8)	1 (3.2)	0 (0)	0 (0)	0 (0)	0 (0)	74 (98.7)	1 (1.3)	0 (0)	0 (0)	0 (0)	0 (0)	0.42
16e	**Did not waken and only later realised hypoglycaemia had occurred**	24 (75.0)	6 (18.8)	1 (3.1)	1 (3.1)	0 (0)	0 (0)	60 (77.9)	13 (16.9)	2 (2.6)	1 (1.3)	1 (1.3)	0 (0)	0.92

HypoA-Q, Hypoglycaemia Awareness Questionnaire.

Data are the number (percentage) in each frequency category. * $P<0.05$, ** $P<0.01$, *** $P<0.001$ (chi-squared test).

Known-groups validity is determined by the degree to which the questionnaire (i.e. HypoA-Q) demonstrates significant expected differences between two groups, i.e. people with impaired or intact hypoglycaemia awareness (assessed by the Gold score).

Table 4 Associations with severe hypoglycaemia (Model 1) and hypoglycaemia when asleep (Model 2)

Predictor variables	**Exp(B)**	**95% CI**	***P***	**Predictor variables**	**Exp(B)**	**95% CI**	***P***
Model 1A: SH* (model includes Gold score and Clarke questionnaire)				**Model 1B: SH* (model includes Gold questionnaire and HypoA-Q)**			
Sex	.20	0.05, 0.81	<0.05	Sex	0.06	0.01, 0.39	<0.01
Age (years)	1.02	0.96, 1.08	ns	Age (years)	1.03	0.96, 1.11	ns
Diabetes duration (years)	0.98	0.93, 1.04	ns	Diabetes duration (years)	0.96	0.88, 1.06	ns
Gold score	0.48	0.24, 0.92	<0.05	Gold score	.28	0.09, .80	ns
Diabetes distress (PAID)	1.05	0.99, 1.07	ns	Diabetes distress (PAID)	1.04	0.99, 1.10	ns
Clarke questionnaire score	3.08	1.69, 5.60	<0.001	'Impaired awareness' (HypoA-Q subscale)	2.11	1.29, 3.46	<0.01
Constant	0.12		ns	'Symptom Frequency' (HypoA-Q subscale)	0.97	.85, 1.12	ns
				'More aware in past 6 months' (HypoA-Q item 13)	3.39	1.23, 9.36	<0.05
				'Symptoms wake me' (HypoA-Q item 17)	0.77	0.38, 1.58	ns
				'Others aware first' (HypoA-Q item 18)	2.29	1.08, 4.85	<0.05
				Constant	0.00		
R^2 = .44. Model $X^2(6)$ = 32.70, *P*<0.001				R^2 = .61. Model $X^2(10)$ = 47.53, *P*<0.001			
Model 2A: Hypoglycaemia when asleep† (model includes Gold score and Clarke questionnaire)				**Model 2B: Hypoglycaemia when asleep† (model includes Gold score and HypoA-Q)**			
Age	0.98	0.95, 1.01	ns	Age	0.98	0.95, 1.01	ns
Diabetes distress (PAID)	1.02	1.00, 1.05	ns	Diabetes distress (PAID)	1.02	0.99, 1.06	ns
Clarke questionnaire score	0.98	0.77, 1.24	ns	'Impaired awareness' (HypoA-Q subscale)	1.14	1.00, 1.30	sn
Constant	3.37		ns	'More aware in past 6 months' (HypoA-Q item 13)	0.58	0.35, 0.97	<0.05
				'Symptoms wake me' (HypoA-Q item 17)	2.08	1.47, 2.93	<0.001
				Constant	0.61		ns
R^2 = 0.10. Model $X^2(3)$ = 8.71, *P*<0.05				R^2 = 0.37. Model $X^2(5)$ = 34.74, *P*<0.001			

HypoA-Q: Hypoglycaemia Awareness Questionnaire; PAID: Problem Areas In Diabetes scale; SH, severe hypoglycaemia; ns, non-significant.
R^2 (Nagelkerke) is the percent of variance explained by the model.
*At least one severe hypoglycaemic event in the past 6 months, assessed using HypoA-Q item 2a; †At least one hypoglycaemic event when asleep, assessed using HypoA-Q item 15.