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ORIGINAL RESEARCH ARTICLE

# Development and Psychometric Evaluation of the Hypoglycemia Perspectives Questionnaire in Patients with Type 2 Diabetes Mellitus

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**Abstract**

*Aims* The aim of this study was to evaluate the factor structure and psychometric characteristics of the Hypoglycemia Perspectives Questionnaire (HPQ) assessing experience and perceptions of hypoglycemia in patients with type 2 diabetes mellitus (T2DM).

*Methods* HPQ was administered to adults with T2DM in a clinical sample from Cyprus (HYPO-Cyprus, $n = 500$) and a community sample in the United States (US, $n = 1257$) from the 2011 US National Health and Wellness Survey. Demographic and clinical data were collected. Analysis of HPQ data from two convenience samples examined item performance, factor structure, and HPQ measurement properties (reliability, convergent validity, known-groups validity).

*Results* Analyses supported three HPQ domains: symptom concern (six items), compensatory behavior (five items), and worry (five items). Internal consistency was high for all three domains (all $\geq$0.75), supporting reliability. Convergent validity was supported by moderate Spearman correlations between HPQ domain scores and the Audit of Diabetes-Dependent Quality of Life (ADDQoL-19) total score. Patients with recent hypoglycemia events had significantly higher HPQ scores, supporting known-group validity.

*Conclusions* HPQ may be a valid and reliable measure capturing the experience and impact of hypoglycemia and useful in clinical trials and community-based settings.

**Abbreviations**

| | |
|---|---|
| ADDQoL-19 | Audit of Diabetes Dependent Quality of Life |
| ANCOVA | Analysis of covariance |
| AWI | Averaged weighted impact |
| BMI | Body mass index |
| CFI | Comparative fit index |
| CFA | Confirmatory factor analysis |
| DTSQ | Diabetes Treatment Satisfaction Questionnaire |
| EFA | Exploratory factor analysis |
| EQ-5D | EuroQol-5 Dimensions |
| EQ-VAS | EuroQol Visual Analog Scale |
| FDA | Food and Drug Administration |
| HbA1c | Glycosylated hemoglobin |
| HFS-II | Hypoglycemia Fear Survey II |
| HPQ | Hypoglycemia Perspectives Questionnaire |
| HRQoL | Health-related quality of life |
| HYPO-Cyprus | Epidemiological study to evaluate the prevalence of HYPOglycemia and its impact on quality of life in type 2 diabetes mellitus |
| KOL | Key opinion leader |
| LS | Least-square |
| NRS | Numeric rating scale |
| PRO | Patient-reported outcome |
| RMSEA | Root mean square error of approximation |
| SD | Standard deviation |
| SE | Standard error |
| SRMR | Standardized root mean residual |
| T2DM | Type 2 diabetes mellitus |
| US | United States |

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**Key Points for Decision Makers**

Hypoglycemia can impact health-related quality of life and treatment satisfaction.

The Hypoglycemia Perspectives Questionnaire (HPQ) captures the experience and impact of hypoglycemia from the patient perspective and includes the symptom concern, compensatory behavior, and worry domains.

HPQ may be a valid and reliable measure useful in clinical and community settings.

Identifying patients with high levels of symptom concern and worry may help to target interventions for patients with impaired awareness at higher risk for future hypoglycemia events.

## 1 Introduction

Diabetes is a rapidly growing epidemic affecting 347 million people worldwide [1]. The World Health Organization projects that by 2030, diabetes will be the seventh leading cause of death [2]. Hypoglycemia occurs when blood sugar (glucose) is too low and can occur as a side effect of both oral and insulin anti-diabetic treatments [3, 4]. Fear of hypoglycemia has been documented as one factor limiting patients from initiating insulin [5, 6] and is associated with higher risk of discontinuation of anti-diabetic treatments and increased healthcare costs [7].

Detrimental effects of hypoglycemia include lower health-related quality of life (HRQoL), diminished treatment satisfaction, more fear, and decreased work productivity in patients with type 2 diabetes mellitus (T2DM) who experienced hypoglycemia compared with those who had not [8]. T2DM patients reporting hypoglycemia also had significantly worse physical and mental health and greater burden of depression than those without hypoglycemia in the past 12 months [9].

Given the impact and fear associated with hypoglycemia, it would be useful to obtain information from the patient perspective on hypoglycemia frequency, symptoms, and impact to better understand their experience and improve treatment adherence. Existing instruments assessing HRQoL impact of diabetes are not specific to hypoglycemia [10–12], and measures that are specific to hypoglycemia may only relate to one aspect of hypoglycemia, such as fear and coping, symptoms, or awareness [13–17]; no comprehensive measure is currently available that addresses the multifaceted impact of hypoglycemia. The Hypoglycemia Perspectives Questionnaire (HPQ) was developed as a new patient-reported outcome (PRO) instrument to assess attitudes of patients with diabetes regarding hypoglycemia. HPQ content was developed for use in clinical practice and research following the principles of the Food and Drug Administration's (FDA) PRO Guidance document [18] with input from key opinion leaders (KOLs), literature review, and patient interviews. The primary objective of this research was to evaluate the factor structure and psychometric characteristics of the HPQ in two different samples of diabetes patients.

## 2 Materials and Methods

### 2.1 Study Design Overview

This was a secondary analysis of HPQ data from convenience samples collected in two different populations of T2DM patients: (1) clinic patients enrolled in a phase IV cross-sectional epidemiology study conducted in Cyprus [19], and (2) a community sample of internet panel participants from a nationwide sample of adults (aged 18 or older) in the United States (US; [20]). Previously-collected data from these two studies were used to conduct a secondary analysis evaluating HPQ item functioning and psychometric properties in different countries/cultures and patient settings, and examine whether the measure generalizes to a broader population. In accordance with ethical practice and compliance with human-subject research requirements, Institutional Review Board approval was obtained prior to initiation of patient recruitment or administration of measures. All participants provided written informed consent to participate in this research study.

### 2.2 Study Population

#### *2.2.1 HYPO-Cyprus Sample*

A phase IV cross-sectional epidemiological study conducted from October 2011 to April 2012 evaluated the prevalence of hypoglycemia and its impact on HRQoL in T2DM patients in Cyprus. The single-visit study (HYPO-Cyprus) included patients aged 18 and older ($n = 500$) who were currently receiving any type of anti-diabetic treatment. Participants completed four patient-reported questionnaires, and the physician completed a demographic/clinical case report form.

#### 2.2.2 Kantar–United States Sample

An Internet-based health survey conducted by Kantar Health evaluated the prevalence of hypoglycemia and its impact on HRQoL in a community sample of T2DM patients in the US. A subset of participants in the 2011 National Health and Wellness Survey ($n = 75{,}000$), an annual Internet-based health survey of a representative population of US adults (>18 years), who reported having T2DM were invited to participate in the study. A total of 1257 participants completed demographic/clinical questions and patient-reported questionnaires.

### 2.3 Study Measures

#### 2.3.1 Demographic and Clinical Characteristics

Demographic and clinical data collected by the HYPO-Cyprus physician based on medical records included gender, age, height, weight, duration of T2DM (in years), glycosylated hemoglobin (HbA1c %) (HYPO-Cyprus only), and current anti-diabetic treatments. For the US study, these items were patient self-reported at the beginning of the survey, prior to administration of PRO instruments.

### 2.4 Patient-Reported Outcomes

#### 2.4.1 Hypoglycemia Perspectives Questionnaire (Preliminary Versions in HYPO-Cyprus and US)

The preliminary version of the HPQ was developed as a comprehensive assessment of the experience of hypoglycemic symptoms and has demonstrated content validity among T2DM patients [21, 22]. Key concepts for hypoglycemia were identified based on evidence collected from patient insight interviews, peer-reviewed literature, discussion with four treatment-area KOLs, existing PRO instruments used in diabetes, and Novartis documentation (e.g., clinical trials data, marketing interviews). Draft items were generated and reviewed by KOLs and revised accordingly. Preliminary versions of the HPQ were administered in observational studies; later quantitative analyses were conducted to evaluate HPQ content and domains, and assess the psychometric properties of the revised instrument.

The HPQ addresses the severity of symptom concerns, importance of compensatory behaviors, personal control of hypoglycemia, hypoglycemia-related worries, and functional impact of hypoglycemia. Response choices are presented using an 11-point numeric rating scale (NRS) from 0 to 10, with higher scores indicating greater severity/impact. Item response scales are anchored at 0 and 10, with labels 'Not concerned' and 'Extremely concerned' for symptom concern items, 'Not important at all' and 'Extremely important' for importance of compensatory behaviors, and 'Not worried at all' and 'Extremely worried' for worry items. An extended version of the preliminary questionnaire includes additional items intended to be descriptive only that characterize the frequency of low blood sugar events in the past 7 days and severe events in the past year, emotional response to hypoglycemia events, and overall level of symptom awareness. The HPQ can be completed by most patients within 15 min or less.

Preliminary versions of the HPQ were administered in Greek for the HYPO-Cyprus study and in English for the US study. The Greek language version based on the original English questionnaire underwent a full translation and linguistic validation in keeping with the principles set forth by the International Society for Pharmacoeconomics and Outcomes Research [23].

There were some minor differences in the HPQ versions administered in the HYPO-Cyprus and US studies. Modifications included re-arrangement of the presentation order of a few items, slight wording changes to clarify meaning, omission of two items ('embarrassed after event', 'embarrassing yourself in public') in the US study that were found to be not relevant based on communication from patients in cognitive debriefing interviews, and addition of one new item ('mood changes') in the US study.

#### 2.4.2 Audit of Diabetes-Dependent Quality of Life Questionnaire (ADDQoL-19)

The ADDQoL-19 questionnaire measures patients' perceptions of the impact of diabetes on their HRQoL [10–12]. There are 19 domain scores, which range from −9 (maximum negative impact of diabetes) to +3 (maximum positive impact of diabetes). An average weighted impact (AWI) score assesses overall impact of diabetes on HRQoL, and ranges from −9 to +3. The ADDQoL-19 in English was used in the US study and a Greek version in the HYPO-Cyprus study.

#### 2.4.3 Treatment Satisfaction Questionnaire

The treatment satisfaction questionnaire completed in the HYPO-Cyprus study included two questions assessing patient satisfaction with their diabetes medications. Patients rated their level of satisfaction with their current diabetes medication(s) on a scale of 0 ('not satisfied at all') to 10 ('completely satisfied') and how strong their desire was to change from their current diabetes medication(s) to another type of medication on a scale of 0 ('no desire to change') to 10 ('extremely strong desire to change').

#### 2.4.4 Diabetes Treatment Satisfaction Questionnaire (DTSQ)

The US study assessed treatment satisfaction using the DTSQ in English [24]. DTSQ is an eight-item questionnaire designed to assess total diabetes treatment satisfaction, treatment satisfaction in specific areas, and perceived frequencies of hyperglycemia and hypoglycemia. Each item is scored on a scale of 0–6. A treatment satisfaction score ranging from 0 to 36 is generated, where higher scores indicate greater satisfaction.

#### 2.4.5 EuroQol-5 Dimensions (EQ-5D)

EQ-5D is a standardized measure developed by the EuroQol Group as a simple, generic measure of health status for clinical and economic appraisal [25]. The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The visual analog scale (EQ-VAS) records the respondent's self-rated health on a vertical scale with endpoints labeled 'Best imaginable health state' and 'Worst imaginable health state'. EQ-5D in Greek was completed in HYPO-Cyprus only.

### 2.5 Statistical Analyses

All analyses were conducted separately on each sample. SAS 9.2 [26] software was used for all analyses except for confirmatory factor analyses (CFA) where MPLUS software [27] was used. For descriptive characteristics, mean and standard deviation (SD) were calculated for continuous variables, and frequency and percent for categorical variables. No missing data were imputed. Pairwise deletion was employed if a patient was missing data for a particular PRO measure, thus retaining as much patient-level data as possible. All analyses were conducted according to recommendations outlined in the FDA PRO Guidance document [18].

#### 2.5.1 Item Characteristics

Descriptive statistics were used to examine the distributional characteristics of individual HPQ items from the pool of 41 diabetes impact/behavior items administered in the two studies. Percentages of patients endorsing the lowest (0) and highest (10) possible scores in each HPQ item were calculated to examine floor and ceiling effects. An item was flagged as a candidate for deletion if it showed a floor (% of cases at lowest score >50 %) or ceiling effect (% of cases at highest possible score >50 %). Inter-item Spearman correlations were calculated to assess the extent to which the HPQ items correlated with each other and with the hypothesized domains as a whole. Items with inter-item correlations >0.80 or <0.20 were flagged for further evaluation [28].

#### 2.5.2 Preliminary Factor Analysis

Split-half random samples were generated for both the HYPO-Cyprus and US samples. An exploratory factor analysis (EFA) was conducted on the first split-half of each sample. Eigenvalues and associated scree plots and factor loadings were examined to empirically determine the number of factors. Factor solutions with eigenvalues near or greater than 1.0 were examined. Oblique (Promax) rotated solutions were examined, as correlated factors were expected. Items with factor loadings <0.40 or items loading on two or more factors (>0.40) were reviewed for possible deletion [27].

#### 2.5.3 Item Deletion

Item reduction is an iterative analytical process in which potential candidates for item deletion are identified and evaluated. HPQ items flagged based on results from descriptive item analysis (via floor and ceiling effects and inter-item correlations) and dimensionality analyses (exploratory and confirmatory factor analyses) were candidates for item reduction. These results were considered together with previous qualitative research findings with patients (i.e., concept elicitation, cognitive interviews), input from experts on the clinical relevance/importance of items, and potential differences in results in the HYPO-Cyprus and US samples in making final decisions regarding item deletion and retention, and the final domain structure. Items flagged based on item results may have been retained if qualitative data and clinical feedback supported the content as important and necessary. Additional CFAs were run as needed to explore the model fit with various items deleted in the first split-half samples. Upon finalizing the domains, CFA models were conducted using the second split-half sample in each study to confirm factor structure. The final HPQ structure and item pool were confirmed prior to proceeding with the psychometric evaluation described in Sect. 2.6.

#### 2.5.4 Final Confirmatory Factor Analysis

Final CFAs were run on the full HYPO-Cyprus and US samples in order to report final model fit statistics and provide additional evidence supporting the measurement properties of the final HPQ. Model fit was assessed with comparative fit index (CFI), root mean square error of approximation (RMSEA), and standardized root mean residual (SRMR). In general, the model was considered to

have good fit if CFI was ≥0.90 [29], RMSEA was <0.08 [30], and SRMR was <0.05. A scoring algorithm was then developed for the final HPQ instrument.

### 2.6 Psychometric Properties of the Hypoglycemia Perspectives Questionnaire (HPQ)

The final HPQ scores were used to evaluate internal consistency reliability, convergent validity, and known-group validity. Internal consistency reliability was evaluated using Cronbach's alpha [31] with a target alpha >0.70 to demonstrate acceptable reliability [32]. Convergent validity was assessed using Spearman's correlations to evaluate relationships between HPQ scores and the ADDQoL. Correlations between HPQ domain scores and DTSQ domain scores were calculated for the US study and correlations between HPQ scores and Treatment Satisfaction Questionnaire, EQ-5D, and HbA1c levels were evaluated in the HYPO-Cyprus study. Correlation coefficients can generally be interpreted as small (0.10), moderate (0.30), or large (0.50) [33].

Known-group validity was evaluated by comparing mean HPQ domain scores by the number of hypoglycemic events and level of symptom awareness using analysis of covariance (ANCOVA), with age, gender, duration of disease, and antidiabetes treatment as covariates.

## 3 Results

### 3.1 Sample Characteristics

Demographic and clinical characteristics for the HYPO-Cyprus and US samples are presented in Table 1. The HYPO-Cyprus ($n = 500$) and US ($n = 1257$) samples had a similar mean age (HYPO-Cyprus 61.0 ± 10 years, US 59.9 ± 11 years) (Table 1). Over half of the HYPO-Cyprus sample (67.4 %) and the US sample (54.2 %) were male. Less than half (45.6 %) of HYPO-Cyprus participants were obese (body mass index [BMI] ≥30) and approximately two-thirds (67.8 %) of the US sample were obese. Duration of T2DM was 10.7 ± 7.8 years in HYPO-Cyprus participants and 9.6 ± 7.6 years in US participants. Prescription oral diabetes medication use was reported by 90.3 % in the HYPO-Cyprus sample and 83.6 % in the US sample, and insulin use by 32.9 and 25.3 %, respectively. Approximately 49 % of the HYPO-Cyprus sample had controlled (<7 %) HbA1c and 51 % had uncontrolled (≥7 % HbA1c) diabetes, but all were in a relatively tight range with 83 % of patients at HbA1c ≤8 % (range 4.4–13.0).

All ADDQoL scores were negative in both samples (−0.5 to −3.6), indicating an overall negative impact of diabetes. Generally, participants were satisfied with their current diabetes treatment. Treatment satisfaction was high in both studies with a mean of 9.1 (±1.7 out of 10) on the HYPO-Cyprus treatment satisfaction questionnaire and 27.5 (±6.6 out of 36) on the DTSQ in the US, indicating that participants were satisfied with their current diabetes treatments.

**Table 1** Demographic and clinical characteristics

| | HYPO-Cyprus ($n = 500$) | US ($n = 1257$) |
|---|---|---|
| Age (years), mean (SD) | 61.0 (10.0) | 59.9 (11.0) |
| Male gender, *n* (%) | 337 (67.4 %) | 682 (54.2 %) |
| BMI, mean (SD) | 30.2 (5.3) | 33.9 (7.6) |
| BMI group, *n* (%) | | |
| Underweight (below 18.5) | 1 (0.2 %) | 2 (0.2 %) |
| Normal (18.5–24.9) | 62 (12.4 %) | 96 (8.0 %) |
| Overweight (25.0–29.9) | 209 (41.8 %) | 288 (24.0 %) |
| Obese (30.0 and above) | 228 (45.6 %) | 813 (67.8 %) |
| Duration of type 2 diabetes mellitus (years), mean (SD) | 10.7 (7.8) | 9.6 (7.6) |
| Prescription oral diabetes medication, *n* (%) | 448 (90.3 %) | 1051 (83.6 %) |
| Insulin use, *n* (%) | 163 (32.9 %) | 318 (25.3 %) |
| Most recent HbA1c, mean (SD) | 7.2 (1.1) | |
| HbA1c level, *n* (%) | | |
| <7 % (controlled diabetes) | 246 (49.2 %) | |
| ≥7 % (uncontrolled diabetes) | 253 (50.6 %) | |

*BMI* body mass index, *HbA1c* glycosylated hemoglobin, *SD* standard deviation, *US* United States

### 3.2 HPQ Item-Level Evaluation

#### *3.2.1 Item Descriptive Statistics*

Based on the preliminary version of the HPQ administered in the HYPO-Cyprus and US samples, distributional characteristics of individual HPQ items were examined. Based on descriptive items in the extended version of the HPQ, the frequency of hypoglycemia events in the past 7 days was 27.7 % with ≥1 event in the US sample and 16.6 % with ≥1 event in HYPO-Cyprus. Frequency of hospitalizations was 2.6 % in the US sample and 1.4 % in HYPO-Cyprus. Emergency room visits were 3.4 % in the US sample and 2.6 % in HYPO-Cyprus.

Overall, HYPO-Cyprus patients reported moderate concern about symptoms (mean range 3.0–4.3), with greatest emphasis on 'blurred vision' and 'passing out'. US patients were mildly–moderately concerned about symptoms (mean range 2.9–3.5), with greatest concern placed on 'dizziness' and 'shaking'. Several floor effects were noted

for items assessing the importance of specific compensatory behaviors; 'keeping blood sugar high', 'reducing insulin', and 'limiting physical activity' were reported by <75 % of the HYPO-Cyprus sample (floor effects 70–75 %), and approximately half of the US sample (floor effects 47–58 %). US participants reported feeling low control over preventing low blood sugar (7.3 ± 2.3). The HYPO-Cyprus patient sample (2.5 ± 3.3) reported feeling relatively high control. In general, US sample patients reported a low level of worry about low blood sugar (mean scores 2.2–3.4) and moderate levels of worry were endorsed in the HYPO-Cyprus sample (mean scores 4.0–5.1). Substantial floor effects were present for all seven functional impact items in both samples, indicating minimal impact of low blood sugar symptoms on functional activities. These items were considered for deletion from the HPQ item pool. In HYPO-Cyprus, 71.2–80.7 % reported experiencing no limitations at all in their functional abilities to perform any of the activities. In the US sample, floor effects for functional impact items ranged from 58.4 to 64.3 %.

### 3.2.2 Inter-Item Correlations

Overall, Spearman correlations reflected a pattern of statistically significant small to moderate-sized correlations (>0.20) among HPQ items. Larger correlations were generally observed between items in the same hypothesized domains (usually ≥0.30) and smaller correlations between items in different domains (usually ≤0.20). Appendix A provides additional results on item–item correlations in the HYPO-Cyprus and US samples (see electronic supplementary material [ESM]).

### 3.2.3 Preliminary Factor Analysis

Exploratory factor analyses were conducted on the first split-half of the two samples separately (HYPO-Cyprus Sample 1 = 251, Sample 2 = 249; US Sample 1 = 629, Sample 2 = 628). Results based on preliminary EFA models in each sample with no pre-specified number of factors suggested that three, four, or five factor solutions should be examined further. A series of three to five factor EFA models were performed in each sample to help identify the factor structure of the HPQ. Functional impact items exhibited very large floor effects, particularly in the HYPO-Cyprus study, and these items were omitted from EFA models using the HYPO-Cyprus sample.

A three-factor solution in HYPO-Cyprus was found to have the best fit. Eigenvalues for fourth and fifth factors were consistently below 1.0 and scree plots suggested that additional factors were not necessary based on the HPQ items included in HYPO-Cyprus EFA models. Factor 1 (eigenvalue 7.7) included symptom concern-related items, factor 2 (eigenvalue 1.9) included worry-related items, and factor 3 (eigenvalue 1.6) comprised compensatory behavior items based on the HYPO-Cyprus split-half sample.

It was determined that a four-factor model, which included items loading on symptom concern, compensatory behavior, functional impact, and worry domains, offered the most parsimonious fit based on the US study split-half sample. Factor 1 (eigenvalue 21.2) included symptom concern-related items, factor 2 (eigenvalue 3.1) included compensatory behavior items, factor 3 (eigenvalue 2.2) comprised functional impact items, and factor 4 (eigenvalue 1.2) comprised worry-related items based on the US split-half sample.

Factor loadings in the Promax-rotated models for symptom concern items ranged from 0.42 to 0.88 in HYPO-Cyprus and 0.63 to 0.87 in the US study, for worry items from 0.52 to 0.87 in HYPO-Cyprus and 0.57 to 0.77 in the US study, for compensatory behavior items from 0.42 to 0.71 in HYPO-Cyprus and 0.53 to 0.80 in the US study, and 0.81 to 0.93 for functional impact items (US study only). Inter-factor correlations between factors ranged from 0.33 to 0.55 in the HYPO-Cyprus and 0.50 to 0.66 in the US sample, suggesting that the factors were related to an overall construct of hypoglycemia impact.

### 3.2.4 Item Deletion and Domain Structure

Results from the EFA models were considered in parallel with item-to-item correlations, ceiling and floor effects, as well as previous qualitative evidence from patient interviews and clinical experts, and decisions were made regarding item deletion and retention. Several CFA models were run in the first split-half samples testing model fit with various items omitted from the model based on these considerations.

Ultimately, 25 out of the 41 diabetes impact/behavior items were deleted from the preliminary version of the HPQ. A total of 12 items were removed due to large floor effects, five items due to high overlap/redundancy with other items, four items based on double-loading onto two factors in EFA, three items had inadequate/low factor loadings in EFA, and one item based on patient feedback that the item was not relevant. In addition, among descriptive items in the preliminary version of the extended HPQ, one item was omitted due to redundancy with other items and one item based on patient feedback. Additional details on item deletion and domain structure are provided in Appendix B (see ESM).

### 3.2.5 Final Confirmatory Factor Analysis

CFA models were evaluated for the remaining 16 diabetes impact/behavior items covering the three domains of

**Table 2** Final model fit statistics for HPQ domains: symptom concern, compensatory behavior, and worry domains

| | Factor loading | |
|---|---|---|
| | HYPO-Cyprus ($n = 496$) | US ($n = 1257$) |
| Symptom concern domain | | |
| H5a. Sweating as result of low blood sugar | 0.62 | 0.79 |
| H5b. Dizziness as result of low blood sugar | 0.80 | 0.90 |
| H5c. Shaking as result of low blood sugar | 0.80 | 0.91 |
| H5e. Headache as result of low blood sugar | 0.69 | 0.85 |
| H5g. Difficulty concentrating as result of low blood sugar | 0.81 | 0.89 |
| H5h. Blurred vision as result of low blood sugar | 0.81 | 0.85 |
| Model fit statistics | | |
| CFI | 0.927 | 0.941 |
| RMSEA (90 % CI) | 0.162 (0.137–0.187) | 0.195 (0.180–0.211) |
| SRMR | 0.040 | 0.028 |
| Compensatory behavior domain | | |
| H6b. Bringing food, juice or soda as an emergency snack when you leave home | 0.63 | 0.82 |
| H6c. Eating a bedtime snack to avoid low blood sugar | 0.62 | 0.79 |
| H6e. Checking your sugar more than once per day to make sure you are within your ideal range | 0.54 | 0.69 |
| H6f. Eating or drinking something at the first sign of low blood sugar | 0.64 | 0.86 |
| H6g. Planning ahead so that your blood sugar will not get low while you are away from home | 0.65 | 0.90 |
| Model fit statistics | | |
| CFI | 0.983 | 0.978 |
| RMSEA (90 % CI) | 0.059 (0.022–0.98) | 0.119 (0.099–0.141) |
| SRMR | 0.022 | 0.021 |
| Worry domain | | |
| H8b. Being unaware of low blood sugar | 0.68 | 0.776 |
| H8d. Getting into an accident while driving due to low blood sugar | 0.80 | 0.87 |
| H8e. Being alone and having an episode of low blood sugar | 0.88 | 0.91 |
| H8f. Passing out in public due to low blood sugar | 0.84 | 0.93 |
| H8g. Having an episode of low blood sugar while caring for others | 0.80 | 0.90 |
| Model fit statistics | | |
| CFI | 1.000 | 0.984 |
| RMSEA (90 % CI) | 0.013 (0.000–0.069) | 0.123 (0.103–0.145) |
| SRMR | 0.009 | 0.016 |

*CFI* comparative fit index, *CI* confidence interval, *RMSEA* root mean square error of approximation, *SRMR* standardized root mean residual, *US* United States

symptom concern (six items), compensatory behavior (five items), and worry (five items). Functional impact, corresponding to the fourth factor identified in previous EFA models, was not included in the confirmatory analysis as the seven functional impact items were deleted during the item deletion/retention stage due to high floor effects. CFA models were run for each of the three domains in the second split-half samples (HYPO-Cyprus Sample 2 = 249; US Sample 2 = 628) to confirm the three factors identified in the EFA solutions and then again in the full HYPO-Cyprus and US samples (Table 2). Model fit statistics indicated that unidimensional models fit the symptom concern, compensatory behavior, and worry domains well in both samples (loadings within each factor model >0.50, CFIs >0.90, RMSEAs <0.19, SRMRs <0.05), providing evidence of construct validity for the HPQ. RMSEA was above the ideal threshold of <0.08 in the symptom concern models; however, RMSEA can be inflated for simple models, which is very common for PRO instruments [34]. Evaluation of RMSEA relative to cutoff values may falsely indicate poor fit for a properly specified model that has low degrees of freedom and small sample size; in cases where

**Table 3** Descriptive statistics of HPQ domain scores

| HPQ domain | HYPO-Cyprus $N = 500$ | | | US $N = 1257$ | | |
|---|---|---|---|---|---|---|
| | Mean (SD) | Floor (%) | Ceiling (%) | Mean (SD) | Floor (%) | Ceiling (%) |
| Symptom concern | 4.5 (3.30) | 76 (15.2 %) | 29 (5.8 %) | 3.6 (3.1) | 281 (22.4 %) | 34 (2.7 %) |
| Compensatory behavior | 5.4 (2.93) | 29 (5.8 %) | 36 (7.2 %) | 4.3 (3.2) | 222 (17.7 %) | 45 (3.6 %) |
| Worry | 4.3 (3.63) | 126 (25.2 %) | 40 (8.0 %) | 2.7 (3.0) | 379 (30.2 %) | 31 (2.5 %) |

Score range = 0–10

*HPQ* Hypoglycemia Perspectives Questionnaire, *SD* standard deviation

other fit statistics (i.e., CFI, SRMR, factor loadings) suggest an acceptable fit, a large RMSEA value can be overlooked [35].

#### *3.2.6 Final HPQ and Domain Scoring System*

The final HPQ consists of 16 diabetes impact/behavior items covering the domains of symptom concern (six items), compensatory behavior (five items), and worry (five items). HPQ domain scores were computed as an average summed score of items for each of the three domains (Table 3). Domain scores ranged from 0 to 10, where higher scores represented greater symptom concern, importance of compensatory behaviors, and increased worry. No domain score was calculated if more than half of the domain items were missing. No total score is generated for the HPQ. An extended version was also created and includes ten optional event frequency and emotional response items which are intended for descriptive purposes only and therefore not scored. Descriptive items comprise one item on overall level of symptom awareness, six event frequency items about the number of low blood sugar events experienced in the past 7 days and number of times in the past year that a severe low blood sugar event has occurred (e.g., hospital admission, emergency room visit, required assistance, passed out), and three emotional response items about tiredness, worry, and frustration after a recent low blood sugar event.

### 3.3 Psychometric Evaluation

#### *3.3.1 Internal Consistency Reliability*

The three HPQ domains had high internal consistency (Table 2), with reliability values exceeding 0.70 in HYPO-Cyprus (alpha = 0.75–0.90) and the US (alpha = 0.91–0.95). The symptom concern (HYPO-Cyprus: alpha = 0.89; US: alpha = 0.95) and worry domains (HYPO-Cyprus: alpha = 0.90; US: alpha = 0.94) had higher reliability in both samples. Alpha with an item deleted for each HPQ domain in both samples also reflected that removing any of the items within a domain would not improve reliability and generally resulted in a lower alpha value. Appendix C (see ESM) provides additional results on alpha with item deleted in the HYPO-Cyprus and US samples.

#### *3.3.2 Convergent Validity*

All correlations were in the expected directions. HPQ domains had small to moderate correlations with the ADDQoL: symptom concern (HYPO-Cyprus: $r = -0.17$; US: $r = -0.39$), compensatory behavior (HYPO-Cyprus: $r = -0.27$; US: $r = -0.40$), and worry (HYPO-Cyprus: $r = -0.31$; US: $r = -0.39$) were related to negative overall impact of diabetes based on ADDQoL-19 AWI score (all $p < 0.0001$). Spearman correlations between HPQ domains and individual ADDQoL-19 domains ranged from $-0.10$ to $-0.30$ ($p < 0.05$) in HYPO-Cyprus and $-0.21$ to $-0.35$ ($p < 0.0001$) in the US sample. Satisfaction with current medication in HYPO-Cyprus ($r = -0.13$ to $-0.22$) and DTSQ treatment satisfaction scores in the US sample ($r = -0.06$ to $-0.23$) had small negative correlations with the HPQ domains ($p < 0.05$), suggesting that greater hypoglycemia impact may be related to lower treatment satisfaction.

Overall health status and HbA1c were also available in the HYPO-Cyprus sample. Greater symptom concern ($r = -0.10$, $p < 0.05$) and worry ($r = -0.15$, $p < 0.001$) were associated with worse patient-rated current health on the EQ-VAS. EQ-5D index scores also indicated that more compensatory behaviors ($r = -0.13$, $p < 0.01$) corresponded to lower (worse) health utilities. HPQ scores were unrelated to most recent HbA1c level with correlation coefficients ranging from 0.01 (symptom concern) to 0.12 (compensatory behaviors).

#### *3.3.3 Known-Group Validity*

HPQ domain scores between hypoglycemia frequency groups were compared, with age, gender, duration of disease, and anti-diabetes treatment as covariates (Fig. 1). In

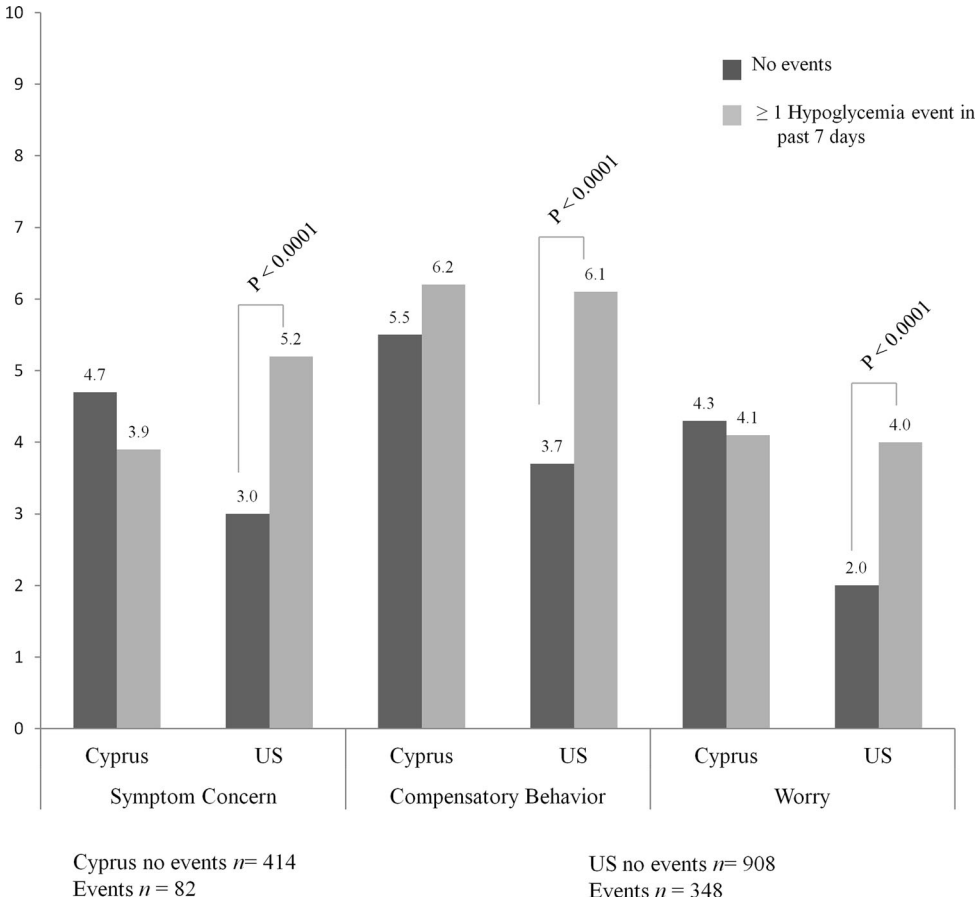


**Fig. 1** HPQ domain scores by hypoglycemic event frequency. *HPQ* Hypoglycemia Perspectives Questionnaire, *US* United States

the HYPO-Cyprus sample, patients with at least one event ($n = 82$) had less symptom concern and less worry, but more compensatory behaviors than those with no events ($n = 414$). However, none of these group differences were statistically significant (all $p > 0.05$). US patients with at least one hypoglycemia event in the past 7 days ($n = 348$) had significantly more symptom concern ($p < 0.0001$), engaged in more compensatory behaviors ($p < 0.0001$), and had greater worry ($p < 0.0001$) relative to patients with no hypoglycemia events ($n = 908$), respectively.

HPQ domain scores were also examined by patient-reported level of symptom awareness (Fig. 2). Symptom awareness groups were identified based on median split, with low awareness defined as ≤8 and high awareness as >8. After controlling for age, gender, duration of disease, and anti-diabetes treatment, patients in the HYPO-Cyprus sample with low symptom awareness had more symptom concern ($p = 0.052$) and significantly more worry ($p < 0.0001$) and less compensatory behaviors ($p < 0.001$) than patients with high symptom awareness. In the US sample and among participants who had a hypoglycemic event in the past week, results reflected similar symptom concern, but more worry and less compensatory behaviors among patients with low relative to high symptom awareness (all $p > 0.05$). Although some differences were not statistically significant, both studies exhibited the expected pattern of more symptom concern, more worry, and less compensatory behavior for low compared with high symptom awareness.

## 4 Discussion

The HPQ is a PRO instrument that evaluates patients with diabetes' symptoms, experiences, and perceptions of hypoglycemia. The final version of the HPQ includes 16 items that comprise the symptom concern (six items), compensatory behavior (five items), and worry (five items) domains. An extended 26-item version is also available that includes ten additional descriptive items that characterize hypoglycemia frequency, awareness, and emotional response to these events, which can be useful in providing clinical context for the impact/behavior domain scores.

HPQ addresses multiple aspects of the impact of hypoglycemia that are not captured by existing instruments. For example, the Hypoglycemia Fear Survey II (HFS-II) [13] assesses behaviors and worries related to the fear of hypoglycemia, but it does not have an extensive list of

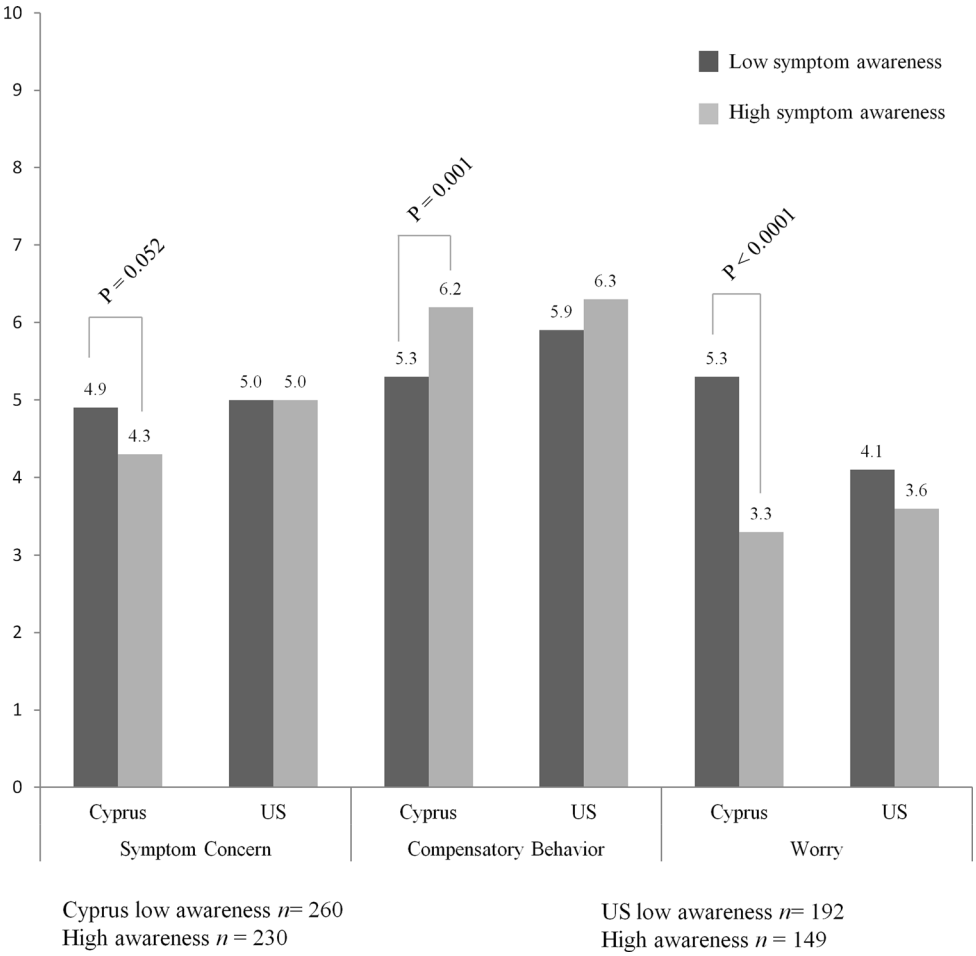


**Fig. 2** HPQ domain scores by symptom awareness. *HPQ* Hypoglycemia Perspectives Questionnaire, *US* United States

symptom concerns. The Diabetes Symptom Checklist [14] and Edinburgh Hypoglycaemia Scale [15] assess hypoglycemia symptoms, but lack coverage of behaviors, beliefs, and worries. The ADDQol-19 [10–12] assesses the impact of diabetes on patients' HRQoL, but is not specific to hypoglycemia and does not assess worries or compensatory behaviors. The Gold scale primarily addresses hypoglycemia unawareness [16].

As a comprehensive, validated measure of the frequency, symptoms, worries, and compensatory behaviors related to hypoglycemia, the HPQ has relevance for assessing impact across the spectrum of diabetes patients with mild, moderate, and severe hypoglycemia. The HPQ may be particularly useful for identifying diabetes patients with high levels of symptoms and concern who may benefit from early intervention [36]. There is some evidence that education efforts to increase awareness of the symptoms of, and factors leading to, hypoglycemia, can help decrease the frequency, fear, and uncertainty associated with hypoglycemia [37–39]. A subset of patients with diabetes experience an impaired awareness of hypoglycemia: the inability to recognize the signs and symptoms of the onset of hypoglycemia. Patients with impaired awareness of hypoglycemia have significantly more episodes of hypoglycemia, and previous research suggests they worry more about hypoglycemia than patients with normal awareness [16]. Despite increased worry about hypoglycemia, patients with impaired awareness seldom modify their behavior in order to avoid hypoglycemia events [16]. Results from this study are consistent with this research, as patients with low awareness had significantly higher (more severe) mean HPQ worry and symptom concern domain scores, but lower (less severe) mean compensatory behavior scores relative to patients with more awareness. The hypoglycemia awareness item, which is a descriptive item included in the extended version of the HPQ, and the HPQ symptom concern and worry domains, may be particularly useful in identifying this population that may benefit most from educational intervention. The HYPO-Cyprus and US studies did not include any similar hypoglycemia unawareness items that could be used to examine convergent validity in relation to the HPQ's awareness item. Additional research comparing HPQ's symptom awareness item in relation to other items or measures that capture hypoglycemia unawareness, such as the Hypoglycemia Awareness Questionnaire (HypoA-Q) [17] or Gold scale [16], will aid in establishing the validity of the item and its

usefulness as a potential tool to screen patients with symptom unawareness.

The availability of cross-cultural convenience samples provided a unique opportunity to examine differences in symptom concern and hypoglycemia experience among people from Cyprus and the US. Patients in the HYPO-Cyprus study placed greater emphasis on symptoms of 'passing out' and 'blurred vision', while participants in the US study placed greater emphasis on 'dizziness' and 'shaking.' One recent study examining cultural differences in hypoglycemia symptom perception among people living in different regions of India found differences in both the patient-reported impact and symptom experience of hypoglycemia [40]. Punjabi-speaking patients placed great emphases on hollowness, cold sweats, and headache, whereas these symptoms were not commonly reported among Hindi-speaking patients. Differences in hypoglycemia symptom reporting have also been observed among Russian-speaking Slavic immigrant American and English-speaking nonimmigrant Caucasian American women [41]. Although evidence evaluating cross-cultural and linguistic differences in the experience of hypoglycemia is currently limited and primarily examined in culturally distinct populations that may not be directly comparable to European and US populations, these results suggest that there may be variation in perception of hypoglycemia symptoms across cultures. Significant differences between different hypoglycemia event frequency groups were detected in the US sample, but not HYPO-Cyprus, while significant differences were observed between low versus high symptom awareness in HYPO-Cyprus, but not in the US sample. This variation in the results may possibly be related to cultural differences between the samples or perhaps the smaller number of hypoglycemia events observed in the Cyprus sample, which appeared to have more well-controlled diabetes. In addition, although group differences in symptom awareness in the US sample did not attain statistical significance, the pattern of results was largely consistent in Cyprus and the US. Either way, inconsistencies such as these that occur in distinct populations highlight the need for critical examination of the possible impact of culture. However, it is important to note that factors other than culture should also be considered. For example, physiological differences such as longer disease duration can contribute to patients relying more on neuroglycopenic symptoms (i.e., dizziness, difficulty concentrating, vision changes) that can be more severe and apparent, than neurogenic (autonomic) symptoms of hypoglycemia (i.e., sweating, shaking). Awareness of hypoglycemia is also thought to be largely perceived through neurogenic rather than neuroglycopenic symptoms. In addition to clinical factors, culture is an important consideration for clinicians treating cross-cultural groups of patients with hypoglycemia, as well as in clinical trial research design and instrument development.

A key strength of this secondary data analysis was that the measurement properties were evaluated in convenience samples from two widely different patient populations, which occurred in two different regions and types of samples. This diversity in the instrument validation process increases the ability of the measure to generalize to a broader population. There were also certain limitations to this psychometric analysis. Minor differences in the HPQ versions administered in the HYPO-Cyprus and US studies (i.e., slight wording changes, re-ordering of items) and different ancillary measures collected may confound differences in HPQ scores between the two samples, and also made a direct comparison of the items, domain structures, and psychometric properties difficult. Also, the sample size in the HYPO-Cyprus was less than half the size of the US sample, with considerably fewer hypoglycemic events. The HPQ to date has not been administered extensively or to large numbers of respondents. Therefore, this study utilized the only data that were available, based on a small sample of Cyprus patients and a larger sample of US panel participants. It is important to note that instrument validation is an ongoing process; an important part of establishing the measurement properties of the HPQ will be examining the measure in multiple, larger samples of the American population, as well as in a variety of different cultures and languages. If the HPQ is administered more widely in the future, its psychometric properties in different countries, cultures, and/or languages should be evaluated.

## 5 Conclusion

The HPQ may be a valid and reliable measure that captures the experience and impact of hypoglycemia on individuals' lives. The measure may be useful in both clinical trial settings and community-based assessments of the impact of hypoglycemia. Future psychometric evaluation of the HPQ using longitudinal data should include assessment of test–retest reliability and the responsiveness of the HPQ to detect change over time.

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**Compliance with Ethical Standards**

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