Hypoglycemia Subtypes in Type 1 Diabetes: An Exploration of the Hypoglycemia Fear Survey-II

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OBJECTIVE

The Hypoglycemia Fear Survey-II (HFS-II) is a well-validated measure of fear of hypoglycemia in people with type 1 diabetes. The aim of this study was to explore the relationships between hypoglycemia worries, behaviors, and cognitive barriers to hypoglycemia avoidance and hypoglycemia awareness status, severe hypoglycemia, and HbA_{1c}.

RESEARCH DESIGN AND METHODS

Participants with type 1 diabetes ($n = 178$), with the study population enriched for people at risk for severe hypoglycemia (49%), completed questionnaires for assessing hypoglycemia fear (HFS-II), hyperglycemia avoidance (Hyperglycemia Avoidance Scale [HAS]), diabetes distress (Problem Areas In Diabetes [PAID]), and cognitive barriers to hypoglycemia avoidance (Attitudes to Awareness of Hypoglycemia [A2A]). Exploratory factor analysis was applied to the HFS-II. We sought to establish clusters based on HFS-II, A2A, Gold, HAS, and PAID using k-means clustering.

RESULTS

Four HFS-II factors were identified: Sought Safety, Restricted Activity, Ran High, and Worry. While Sought Safety, Restricted Activity, and Worry increased with progressively impaired awareness and recurrent severe hypoglycemia, Ran High did not. With cluster analysis we outlined four clusters: two clusters with preserved hypoglycemia awareness were differentiated by low fear/low cognitive barriers to hypoglycemia avoidance (cluster 1) versus high fear and distress and increased Ran High behaviors (cluster 2). Two clusters with impaired hypoglycemia awareness were differentiated by low fear/high cognitive barriers (cluster 3) as well as high fear/low cognitive barriers (cluster 4).

CONCLUSIONS

This is the first study to define clusters of hypoglycemia experience by worry, behaviors, and cognitive barriers to hypoglycemia avoidance. The resulting subtypes may be important in understanding and treating problematic hypoglycemia.

Hypoglycemia (low blood glucose) and fear of hypoglycemia can be a significant burden to people with type 1 diabetes. Modifiable behaviors related to fear of hypoglycemia may affect patients' diabetes self-management strategies (1) and, through them, influence risk both of hyperglycemia, with potential for worsening risk of vascular complications (2), and of severe hypoglycemia, episodes in which

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plasma glucose falls too low to sustain cognitive function sufficient to support self-treatment (3).

The Hypoglycemia Fear Survey (HFS) (4) and its second iteration, the Hypoglycemia Fear Survey-II (HFS-II) (5), have widely been used to measure fear of hypoglycemia. In studies with use of the HFS investigators have found that individuals at high risk of severe hypoglycemia commonly have higher fear of hypoglycemia, as one might expect (5), although a significant minority express low fear (6).

The HFS-II is comprised of Behavior (HFS-B) and Worry (HFS-W) subscales (5). The 15 HFS-B items relate to behaviors to avoid hypoglycemic episodes and their negative consequences, and the 18 HFS-W items include specific concerns about hypoglycemic episodes. Although initial studies suggested a unidimensional structure for the HFS-B, subsequent studies have suggested two (7–9) or three (10) separate behavioral constructs within this subscale. Consistent across studies, a "maintaining high glucose" factor has been established, which correlates with poorer glycemic control (7). The remaining HFS-B items have been grouped as "avoidance" behaviors; however, it is not clear whether this label reflects avoidance of activity (e.g., HFS-B8, "avoided visiting my friends") or avoidance of the negative consequences of hypoglycemia (e.g., HFS-B15, "asked people to check on me several times during the day or night," or HFS-B5, "made sure I had someone with me when I go out").

Treatment approaches to hypoglycemia must be tailored to the individual (11). Studies of fear of hypoglycemia have shown divergent subgroups, including individuals with high fear despite lower risk of severe hypoglycemia linked to higher trait anxiety and, by contrast, other individuals with low fear despite high risk of severe hypoglycemia (6). Identification of these subgroups has potential implications for therapeutic approaches to hypoglycemia management (12).

In contrast to the HFS-II, the Attitudes to Awareness of Hypoglycemia (A2A) questionnaire measures health beliefs or cognitions around hypoglycemia. The A2A originated in qualitative research among people experiencing impaired awareness of hypoglycemia, typically with recurrent severe hypoglycemia, where they described health beliefs that would be unhelpful to hypoglycemia avoidance: "thinking traps" that create barriers to hypoglycemia avoidance (13). A large-scale study demonstrated that A2A items segregate into three factors: Asymptomatic Hypoglycemia Normalized, Hypoglycemia Concerns Minimized, and Hyperglycemia Avoidance Prioritized (14). Those with impaired awareness of hypoglycemia ("impaired awareness") tended to prioritize hyperglycemia avoidance particularly. Relationships between behaviors and worry related to fear of hypoglycemia, and cognitive barriers to hypoglycemia avoidance have not been explored.

In this study, we investigated the factor structure of the HFS-II in a cohort of adults with type 1 diabetes enriched for problematic hypoglycemia by targeted recruitment. We hypothesized that there would be associations between cognitive barriers to hypoglycemia avoidance and behaviors around hypoglycemia fear and that these would associate with problematic hypoglycemia as classified by hypoglycemia awareness status and experience of recurrent severe hypoglycemia. In this article, we outline subtypes of hypoglycemia-related experience incorporating cognitive barriers to hypoglycemia avoidance and fear and link these to glycemic outcomes.

RESEARCH DESIGN AND METHODS

This was a cross-sectional questionnaire-based study conducted at four specialist diabetes centers: one in the U.S. and three in the U.K. The study cohort included adults with type 1 diabetes, with the study population enriched for problematic hypoglycemia through specific targeting of people of similar diabetes duration both with and without problematic hypoglycemia, defined as impaired awareness of hypoglycemia and reporting more than one severe hypoglycemia episode in the preceding 2 years. Inclusion criteria were previous receipt of structured education in flexible insulin therapy, or its equivalent, and use of an appropriate multiple daily injections or continuous infusion insulin regimen as well as age $\geq$18 years, diabetes duration $\geq$4 years, and ability to communicate in written and spoken English and give written informed consent. Pregnancy, severe mental disorder, and untreated comorbidities increasing hypoglycemia risk were exclusion criteria. Participants with impaired awareness and recurrent severe hypoglycemia then participated in a randomized controlled trial of an intervention targeting health beliefs as barriers to hypoglycemia avoidance (15); the current study includes their baseline data. All participants gave written informed consent. The study was approved by the London Dulwich and the Wales Research ethics committees (Integrated Research Application System [IRAS] nos. 216381, 271164) and the institutional review board of the Joslin Diabetes Center.

Participants were asked to recall and self-report their count of severe hypoglycemia events in the previous 12 months using the following definition: when cognitive function is so disturbed that third-party assistance is needed for treatment (3). Recurrent severe hypoglycemia was defined as two or more severe hypoglycemia episodes within 12 months (11). Demographic data and diabetes history were documented. HbA_{1c} was recorded prior to enrollment. Participants completed a book of validated questionnaires, including the following.

The 33-Item HFS-II

The HFS-II comprises the 18-item HFS-W and 15-item HFS-B (5). Items in HFS-W follow the stem "because my blood sugar could go low, I worried about . . . " Items in HFS-B follow the stem "To avoid low blood sugar and how it affects me, I . . . " Participants respond to all items on a 5-level Likert scale: "never," "rarely," "sometimes," "often," and "almost always."

The Single-Item Gold Score of Hypoglycemia Awareness

This which asks, "Do you know when your hypos are commencing?" and requires a response on a 7-level Likert scale from 1, "I am always aware," to 7, "I am never aware" (16). Impaired awareness of hypoglycemia was defined by a Gold score of at least 4.

The 19-Item A2A Questionnaire

With use of the A2A questionnaire investigators can assess unhelpful health beliefs that create cognitive barriers to hypoglycemia avoidance, e.g., "there are no serious consequences to leaving mild hypoglycemias untreated." Items 6–19 follow the stem, "How true do you consider the following statements for you personally?" with responses on a 4-level Likert scale:

"not true at all," "slightly true," "moderately true," and "very true" (14).

The 26-Item Hyperglycemia Avoidance Scale

The Hyperglycemia Avoidance Scale (HAS) includes 12 behavior items, 12 worry items, and two items relating to hyperglycemic measures, each scored on a 5-level Likert scale: "never," "rarely," "sometimes," "often," and "always" (17).

The 20-Item Problem Areas In Diabetes Questionnaire

The Problem Areas In Diabetes (PAID) scale is a measure of diabetes distress, with the questionnaire asking, "Which of the following diabetes issues are currently a problem for you?" Respondents rated those provided on a 5-level Likert scale: "not a problem," "minor problem," "moderate problem," "somewhat serious problem," and "serious problem" (18).

After March 2020, the questionnaires were offered online through Qualtrics (www.qualtrics.com) as well as on paper. Recruitment was converted to virtual for compliance with coronavirus disease 2019 restrictions.

Statistical Analysis

For investigation of the latent factor structure of the HFS-II in the study cohort, exploratory factor analysis (EFA) with maximum likelihood extraction and promax (oblique) factor rotation was used to permit the expected degree of correlation between latent HFS-II factors (19). The sample:item ratio was >10:1 for robustness. To determine the optimal number of factors, we considered the eigenvalue scree plot, the cumulative variance explained, the degree of item cross loading, and the factor loading table. Items were loaded onto a factor where the corresponding eigenvalue was >0.4. Cronbach α was calculated for each factor as a measure of internal consistency; >0.7 was considered adequate. Item statistics for each factor were calculated, including Cronbach α if item deleted and item-total correlations, and we considered dropping any item with poor item statistics.

The HFS-II factors were named in collaboration with our patient and public involvement group, considering the HFS-II question items on each factor. The eigenvalue-weighted mean was calculated as a summary score for each factor; similarly, an eigenvalue-weighted mean was calculated for each subscale in the A2A questionnaire data, with use of published EFA data (14).

The Wilcoxon rank sum test was used for two independent groups. Factor scores across more than two independent groups were compared using the Kruskal-Wallis test with Dunn post hoc test, with adjustment for multiple comparisons with the Benjamini-Hochberg procedure.

Multivariate logistic regression was used to model impaired awareness and recurrent severe hypoglycemia in relation to HFS-II factors and diabetes duration; regression estimates are presented as odds ratios with 95% CIs.

We used k-means to cluster study participants on A2A factors, Gold, HAS, HFS-II factors, and PAID (19). Individuals with complete data for these scores were included in the cluster analysis. Variables, which had skewed distributions, were centered and scaled before clustering, including a ranking step for HFS-II, A2A, and HAS, to improve balance between questionnaires. The Hartigan and Wong algorithm (20) with 10 random center starts and a maximum of 10 iterations was used. For each cluster we describe the position of its center across all questionnaire scales, the number of individuals, the median severe hypoglycemia, mean HbA_{1c}, and use of diabetes technologies. An individual was allocated to the cluster with the greatest similarity by Euclidian distance. Comparisons between clusters for HbA_{1c} and severe hypoglycemia were performed with the Kruskal-Wallis test with Dunn post hoc test, adjusted for multiple comparisons with the Benjamini-Hochberg procedure. χ^2 test was used to compare proportions of technology use between clusters.

All statistical computations were performed in R, version 4.0.3 (2020-10-10) (21).

RESULTS

The Study Cohort

A total of 178 individuals returned questionnaires, 19 online (recruitment diagram can be found in Supplementary Fig. 1). Their demographics are shown in Table 1, together with HbA_{1c}, hypoglycemia awareness (Gold score), and diabetes technology used. Fifty-three individuals (30%) were using continuous subcutaneous insulin infusion (CSII) plus either continuous glucose monitoring (CGM) or intermittently monitored retrospective CGM (isCGM), with 26 participants (15%) on CSII only, 52 (29%) using multiple daily insulin injections regimens plus either CGM or isCGM, and 47 (26%) using multiple daily injections and intermittent finger-prick glucose monitoring. Of respondents, 57% reported at least one episode of severe hypoglycemia in the previous 12 months and 49% reported recurrent severe hypoglycemia. The mean (SD) severe hypoglycemia count in 12 months was, for the total cohort, 10.8 (39.4); in those with hypoglycemia awareness, 0.06 (0.025); and in those with impaired awareness of hypoglycemia, 19.5 (52.6). Mean (SD) scores for the questionnaires are presented in Table 1.

Factor Analysis Revealed Four HFS-II Factors

EFA of the 33 HFS-II items yielded four factors, with a cumulative variance explained of 0.479 (Table 2). This four-factor solution was chosen after review of three-factor and five-factor solutions, with consideration of the cumulative variance explained, the degree of cross loading, and the item composition of each factor. Supporting item statistics are reported in Supplementary Table 1. With guidance from our Patient and Public Involvement group, we named the factors Restricted Activity, Ran High, Sought Safety, and Worry. Calculations of Cronbach α indicated high internal consistency of the factors.

Sought Safety items were linked to worries and actions taken to mitigate the harm of significant hypoglycemia, particularly through ensuring availability of help from others, with the highest factor loading for the HFS-W item "having a hypoglycemic episode while alone." Behaviors to ensure external help in case of need were included, such as "made sure there were other people around." Restricted Activity behaviors were associated with less involvement in normal activities because of hypoglycemia risk, with the highest factor loading for "avoided visiting my friends." In contrast, Ran High behaviors were linked to actions taken to reduce the risk of hypoglycemia by accepting greater hyperglycemia risk, with the highest factor loading for "kept my blood sugar higher than usual when doing important tasks."

Table 1—Participant characteristics

Age, years, mean (SD)	50.6 (14.2)
Diabetes duration, years, mean (SD)	32.5 (14.4)
Sex (% female)	56.7
Ethnicity (%)	
White	94.9
Black	1.1
Other	4.0
HbA_{1c}, %, mean (SD)	7.5 (1.1)
Use of technology, CGM/SAP/isCGM, *n*	49/20/73
Use of technology, CGM/SAP/isCGM, %	28/11/43
Insulin delivery, MDII/CSII, *n* (%)	99/79 (56/44)
Gold score, mean (SD)	3.8 (2.0)
Impaired awareness of hypoglycemia, *n* (%)	99 (56)
Recurrent severe hypoglycemia, *n* (%)	87 (49)
HFS-II score, mean (SD)	1.3 (0.8)
A2A score, mean (SD)	0.8 (0.4)
Asymptomatic Hypoglycemia Normalized	0.4 (0.5)
Hypoglycemia Concerns Minimized	0.6 (0.5)
Hyperglycemia Avoidance Prioritized	1.4 (0.6)
HAS score, mean (SD)	1.8 (0.5)
PAID score, mean (SD)	23 (15)

MDII, multiple daily insulin injections; SAP, sensor augmented pump therapy, with automated suspension of insulin infusion features.

The Worry factor comprised mostly items included in the original HFS-W items, with the highest factor loading for "embarrassing myself or my friends in a social situation."

Associations Between the HFS-II Factors and Problematic Hypoglycemia

As shown in Fig. 1*A* (and Supplementary Table 3), Worry ($P < 0.001$), Sought Safety ($P < 0.001$), and Restricted Activity ($P < 0.001$) HFS-II factor scores increased with increasingly impaired awareness (increasing Gold score). In contrast, Ran High scores did not increase with progressively impaired awareness ($P = 0.109$).

Those with recurrent severe hypoglycemia showed increased Worry ($P < 0.001$), Sought Safety ($P < 0.001$), and Restricted Activity ($P < 0.001$) but not Ran High ($P = 0.440$) score (Fig. 1*B*).

Multivariate Model of Impaired Awareness of Hypoglycemia and Recurrent Severe Hypoglycemia

In a multivariate logistic regression model of impaired awareness and recurrent severe hypoglycemia (Supplementary Fig. 2), Sought Safety had the largest association with both outcomes (odds ratio 7.39 [95% CI 2.93, 18.6] and 5.29 [2.43, 11.5], respectively; both $P < 0.001$). In contrast, Ran High was associated with a lower likelihood of both impaired awareness and recurrent severe hypoglycemia (0.39 [0.22, 0.71] and 0.42 [0.24, 0.73], both $P < 0.001$). Restricted Activity was associated with impaired awareness (3.12 times increased likelihood of impaired awareness [95% CI 1.24, 7.85], $P = 0.02$) but was not associated with recurrent severe hypoglycemia (odds ratio 1.36 [95% CI 0.68, 2.74], $P = 0.38$). Worry did not demonstrate an association with either outcome. Diabetes duration (per decade) was associated with impaired awareness (1.49 [1.08, 2.04], $P = 0.02$) and recurrent severe hypoglycemia (1.36 [1.02, 1.82], $P = 0.04$).

Cluster Analysis With Hypoglycemia-Related Variables

A four-cluster solution gave the optimal balance between model fit and interpretability (Fig. 2 and Supplementary Tables 3 and 4).

Cluster 1, $n = 52$, was characterized by the lowest Gold score, low scores across HFS-derived variables, and the lower HAS. The mean (SD) severe hypoglycemia count was 1.9 (7.5), and mean HbA_{1c} was 7.7% (0.9%).

Cluster 2, $n = 26$, was characterized by low Gold score and, relative to the other clusters, high PAID, Worry, Ran High, and HAS scores and relatively high A2A. The mean (SD) severe hypoglycemia count was 1.3 (2.4), and mean HbA_{1c} was 8.0% (1.1%).

Cluster 3, $n = 21$, was characterized by high Gold score, high scores for A2A variables, in particular for Hyperglycemia Avoidance Prioritized, with markedly low Ran High and relatively low Restricted Activity and Sought Safety factor scores. The mean (SD) severe hypoglycemia count was 14.3 (25.0) (the highest among clusters), and mean HbA_{1c} was 6.8% (1.1%) (the lowest).

Cluster 4, $n = 37$, was characterized by the highest Gold score and high HFS factors, in particular Sought Safety; A2A scores were relatively low. The mean (SD) severe hypoglycemia count was 11.4 (21.4), and mean HbA_{1c} was 7.2% (1.1%).

Statistical comparisons between clusters (Supplementary Table 3) revealed significant differences between the clusters for severe hypoglycemia count ($P < 0.001$) and HbA_{1c} ($P = 0.001$), with low rate of severe hypoglycemia and lower HbA_{1c} in those with less evidence of cognitive barriers to hypoglycemia avoidance and lower hypoglycemia fear scores. Within the impaired awareness clusters, which had high severe hypoglycemia rates, there was lower HbA_{1c} with greater endorsement of the cognitive barriers to hypoglycemia avoidance and less fear of hypoglycemia. Use of CGM ($P = 0.023$), though not of CSII ($P = 0.11$) or isCGM ($P = 0.065$), was higher in clusters expressing higher fear of hypoglycemia.

CONCLUSIONS

In this examination of fear of hypoglycemia in adults with type 1 diabetes, we have demonstrated a four-factor structure of the HFS-II: three factors were dominated by behaviors related to hypoglycemia (Sought Safety, Restricted Activity, and Ran High), and the other was related to worry (Worry). Worry, Sought

Table 2—EFA of the HFS-II

	Four-factor solution*			
	Worry	Sought Safety	Restricted Activity	Ran High
To avoid low blood glucose and how it affects me, I …				
1) ate large snacks.				
2) tried to keep my blood glucose >8.3 mmol/L (150 mg/dL).				0.602
3) reduced my insulin when my blood glucose was low.				
4) measured my blood glucose six or more times a day.				
5) made sure I had someone with me when I go out.		0.584		
6) kept my travel local.			0.499	
7) limited my driving (car, van, or bicycle).			0.501	
8) avoided visiting my friends.			1.000	
9) stayed at home more than I liked.			0.759	
10) limited my exercise/physical activity.				
11) made sure there were other people around.		0.653		
12) avoided sex.			0.558	
13) kept my blood glucose higher than usual in social situations.				0.876
14) kept my blood glucose higher than usual when doing important tasks.				0.905
15) asked people to check on me several times during the day or night.		0.619		
Because my blood glucose could go low, I worried about ...				
16) not recognizing/realizing I was having low blood glucose.				
17) not having food, fruit, or juice available.	0.634			
18) passing out in public.	0.559			
19) embarrassing myself or my friends in a social situation.	0.826			
20) having a hypoglycemic episode while alone.		0.903		
21) appearing stupid or drunk.	0.742			
22) losing control.	0.642			
23) no one being around to help me during a hypoglycemic episode.		0.857		
24) having a hypoglycemic episode while driving.	0.523			
25) making a mistake or having an accident.	0.701			
26) getting a bad evaluation or being criticized.	0.773			
27) difficulty thinking clearly when responsible for others.	0.744			
28) feeling light-headed or dizzy.	0.482			
29) accidentally injuring myself or others.	0.580			
30) permanent injury or damage to my health or body.		0.488		
31) low blood glucose interfering with important things I was doing.	0.667			
32) becoming hypoglycemic during sleep.				
33) getting emotionally upset and difficult to deal with.	0.703			
Metrics				
% variance explained	0.192	0.118	0.094	0.075
Cronbach α	0.937	0.896	0.857	0.771

*Factor loadings <0.4 not presented.

Safety, and Restricted Activity were positively related to both impaired awareness of hypoglycemia and recurrent severe hypoglycemia. The other factor, Ran High score, did not increase with progressive impairment of awareness. In a clustering analysis with inclusion of the HFS-II factors, cognitive barriers (A2A factors), hypoglycemia awareness status (Gold score), hyperglycemia avoidance (HAS), and problems related to diabetes (PAID), we found four clusters. Two clusters had preserved awareness of hypoglycemia, and two had impaired awareness. The latter pair comprised one cluster in which fear of hypoglycemia was low and cognitive barriers to hypoglycemia avoidance (A2A scores) dominant (cluster 3) and one cluster in which, conversely, fear of hypoglycemia was high and cognitive barriers to hypoglycemia avoidance low (cluster 4). In the former two clusters (with preserved awareness), one, with the best awareness of hypoglycemia (cluster 1), had low fear and low cognitive barriers, while the other, cluster 2, had high scores for fear, cognitive barriers, hyperglycemia avoidance (HAS), and diabetes distress (PAID). Linking to average severe hypoglycemia and HbA_{1c} outcomes revealed clear demarcation between high and low severe hypoglycemia and higher and lower HbA_{1c}. There were higher rates of severe hypoglycemia and of lower HbA_{1c} among those with impaired awareness of hypoglycemia (clusters 3 and 4) versus preserved awareness (clusters 1 and 2), but also, within the impaired awareness groups (clusters 3 and 4), there was a relationship between scores for cognitive barriers to hypoglycemia avoidance and fear of hypoglycemia and HbA_{1c}.

Previous Factor Structures of the HFS

In previous factor analysis of the HFS-II, the HFS-W has been shown to be unidimensional, although both a Chinese (9) and a Swedish (22) study described two HFS-W factors. Our Sought Safety factor shows similarity to the "Aloneness" factor in the Swedish study, although in this

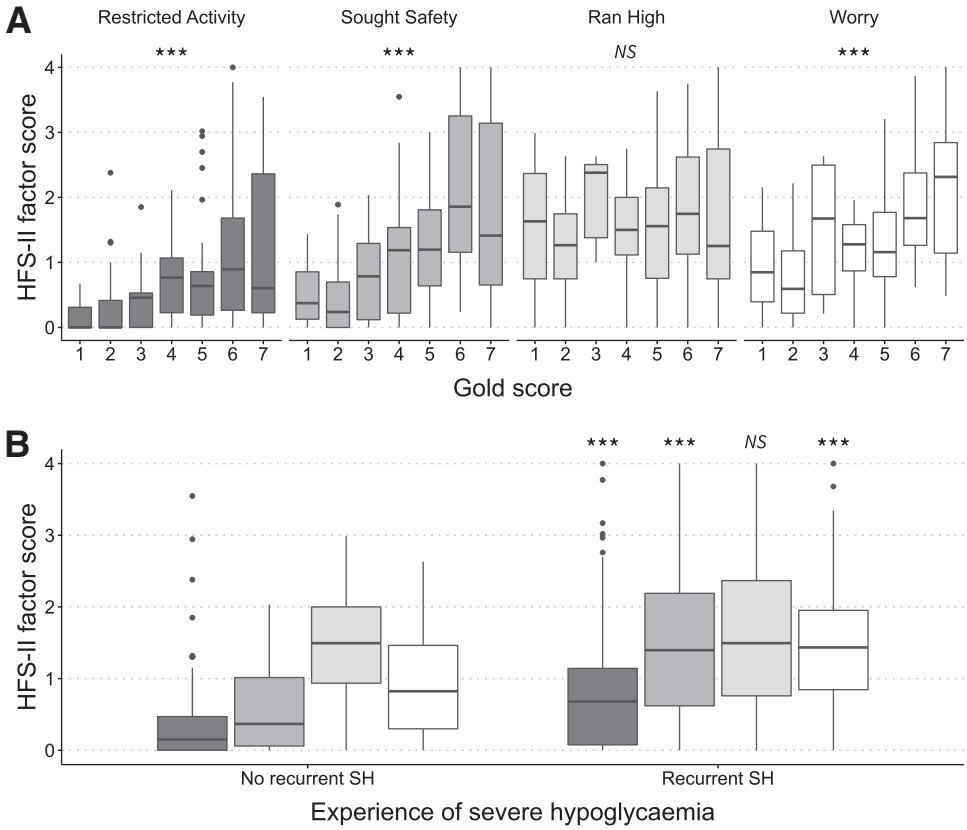

Figure 1—Associations between HFS-II–derived factor scores and Gold score (*A*) and recurrent severe hypoglycemia (SH) (*B*). Dark-gray bars, Restricted Activity; mid-gray bars, Sought Safety; light-gray bars, Ran High; open bars, Worry. Statistical analysis can be found in Supplementary Table 1. ***$P < 0.001$; *NS* = not significant, $P > 0.05$.

study, with a different version of the HFS, Sought Safety shifts toward actions taken to avoid being alone, with the inclusion of three behavior items. In the Chinese study, an HFS-W "Embarrassing" factor was described, in addition to a "Worry" factor: the authors speculated this might be related to Chinese culture and language. Our data are most similar to those from a study of the Norwegian HFS-II, which also found a four-factor structure for the HFS, with three HFS-B factors (10). The authors referred to the factors as "blood glucose–regulating behavior" (items 2, 3, 13, and 14), "avoidance behavior" (items 6, 7, 8, 9, 10, and 12), and "seeking support from others" (items 5, 11, and 15).

Across studies, the "running blood glucose high" factor is consistent. On the other hand, our Sought Safety and Felt Restricted factors have previously been grouped as an "Avoidance" factor. In distinguishing Sought Safety and Restricted Activity behaviors, we suggest a distinction between safety-seeking actions to mitigate harm from hypoglycemia and limitations to activity as a negative consequence of hypoglycemia.

Statistical Relationships Between Factors and Outcomes

In the presence of impaired awareness, Sought Safety, Restricted Activity, and Worry scores all increased. Impaired awareness is a major risk factor for severe hypoglycemia (16), experiences of which might be expected to result in behaviors to ensure help will be at hand and limit experiences where hypoglycemia may occur or be embarrassing, and high scores were found for these factors associated with recurrent severe hypoglycemia. The increase in worry with greater degree of impaired awareness and recurrent severe hypoglycemia may thus be considered appropriate. In contrast, Ran High score did not increase with progressively impaired awareness—those with hypoglycemia awareness had a Ran High score not different from the score of those with impaired awareness—and Ran High score was not increased in those with recurrent severe hypoglycemia. Individuals may be balancing fear of hypoglycemia against glucose targets, leading to reluctance to increase Ran High behaviors despite increased experience of hypoglycemia.

Nevertheless, in the logistic regression analysis, Ran High behaviors were associated with a lower likelihood of impaired awareness and recurrent severe hypoglycemia. Thus, it is possible that Ran High behaviors can be linked to a recognition of the negative impact of hypoglycemia, leading to actions to help reduce risk of severe hypoglycemia. In contrast, Sought Safety was linked to increased impaired awareness. In summary, with increased risk of severe hypoglycemia, people reported increased actions to mitigate the impact of severe hypoglycemia (Sought Safety) and the chance of it happening by avoidance of precipitants (Felt Restricted) but not other actions to prevent severe hypoglycemia (Ran High). In some individuals, this may reflect an acceptance of severe hypoglycemia, hampering the prevention of further episodes.

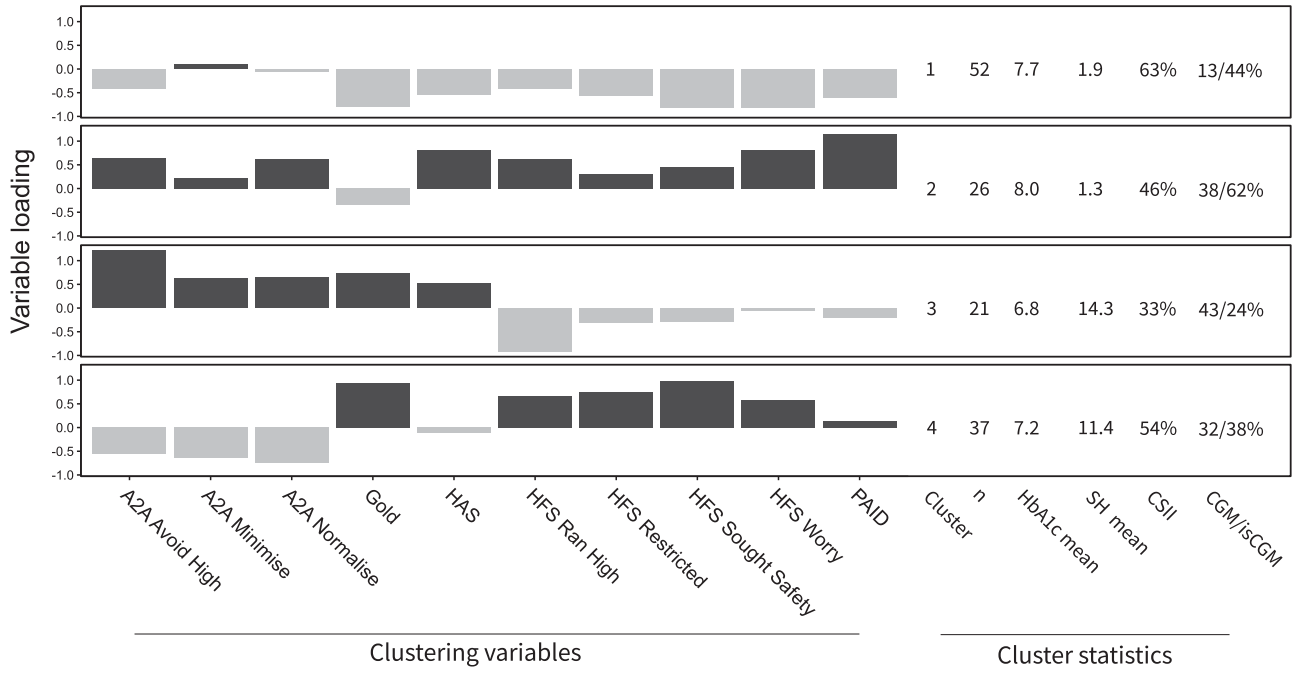

Figure 2—Cluster analysis of the cohort, with four hypoglycemia subtypes shown. For each cluster, the cluster center with respect to each variable is presented. Black bars indicate values above the mean, and gray bars values below the mean. The full statistical analysis can be found in Supplementary Table 3. SH, severe hypoglycemia.

Cluster Analysis

The clusters allow us to make clinically plausible speculations about the role of cognitive barriers as well as behaviors and worries around hypoglycemia in clinical risk and outcomes. Within each pair of clusters defined by hypoglycemia awareness status, there are two patterns of cognitions and fears that associate with different clinical outcomes and may suggest a requirement for different therapeutic approaches. Among those with impaired awareness, just over one-third (cluster 3) more strongly expressed health beliefs that form cognitive barriers to prioritizing hypoglycemia avoidance and had contrastingly low fear and low diabetes distress, both of which may be considered inappropriate to their risk: this group had the highest severe hypoglycemia rate. They also had the lowest HbA_{1c}. They were characterized by high Hyperglycemia Avoidance Prioritized in the A2A, low tolerance for Ran High, and, of the two impaired awareness clusters, the higher HAS score. This group's fear of hyperglycemia, associated with high tolerance of hypoglycemia, drives their increased risk of severe hypoglycemia, which they may accept as an inevitable exchange for lower HbA_{1c}. People in this cluster may struggle to engage with conventional therapies to reduce their hypoglycemia risk unless their cognitive barriers are addressed (23). The proportion of our cohort in this cluster is remarkably similar to the proportion of people at high risk for severe hypoglycemia expressing low fear in a Swedish clinic-based study (6).

When impaired awareness is accompanied by low cognitive barriers, as in cluster 4, fear of hypoglycemia is increased. We speculate that fewer cognitive barriers mean this group is amenable to conventional interventions such as education and diabetes technologies (CGM, insulin infusion devices, and hybrid closed loop systems): their worry and fear may help them engage with such strategies.

In people with preserved awareness of hypoglycemia, low cognitive barriers, and low fear, as in cluster 1, may be permissive of a relatively low HbA_{1c}. The low worry about hypoglycemia may be a realistic response to (relatively) low experience (24,25). However, some people endorse the statements about thoughts that form cognitive barriers to hypoglycemia avoidance even where hypoglycemia awareness is maintained, as in cluster 2. In this cluster, high cognitive barriers to hypoglycemia avoidance associated with high worry about hypoglycemia and hyperglycemia avoidance behaviors may reflect generalized as well as diabetes-specific anxieties: this cluster had the highest level of diabetes distress measured with PAID. Further work needs to be done to determine quality of life in this cluster, as it is likely to be poorer than for people in cluster 1. People falling within this cluster may benefit from therapies to address their fears and anxieties.

One of the strengths of this analysis is that three separate statistical strategies provide a clinically logical and mutually agreeable set of findings. The results of the factor analysis are demonstrated to be relevant to hard clinical outcomes and contribute to a cluster analysis that has parallels with the four groups identified by Anderbro et al. (6) in a clinic-based study of the HFS but adds the cognitive elements that have not previously been studied. Thus, our cluster 1, 38% of our population, may correspond to the "low risk, low fear" group of Anderbro (43% of the clinic population studied), cluster 2 to the "low risk, high fear" (19% here vs. 32% in the study by Anderbro et al.), cluster 3 to "low fear, high risk" (15% vs. 8%), and cluster 4 to "high fear, high risk" (27% vs. 17%), with the differences in distribution among clusters versus groups explained by the selective recruitment of a population enriched for experiencing problematic hypoglycemia

in our study. The addition of the cognitions reported by each cluster adds to our understanding of how these clinical phenotypes come about.

Limitations

While this study had a favorable sample size for reliable factor analysis, EFA is not inferential. Our participants were all attending specialist diabetes centers with tertiary practices, and by design the proportion of people with problematic hypoglycemia was higher than would be expected in an unselected cohort of people with type 1 diabetes. This has resulted in a population with long mean diabetes duration. The factor structure described in this study should be repeated in other cohorts to support its validity and to explore further the hypotheses generated here. A longitudinal study of hypoglycemia-related behaviors and the occurrence of severe hypoglycemia would be valuable to explore the temporal relationship between behaviors and the experience of severe hypoglycemia and to study how behavioral patterns vary over time and in response to interventions.

In conclusion, we have shown a four-factor structure to the HFS-II that increases our understanding of its link with severe hypoglycemia risk and even HbA_{1c}. These HFS-II factors are linked to both impaired awareness of hypoglycemia and severe hypoglycemia. In particular, the lack of increase in Ran High score despite impaired awareness may be important in understanding why problematic hypoglycemia can persist and be resistant to treatment. The strong association between Sought Safety and severe hypoglycemia reveals that such behaviors are important to individuals with problematic hypoglycemia. The link between Restricted Activity and impaired awareness demonstrates the profound negative impact of impaired awareness and severe hypoglycemia on quality of life and emphasizes the priority of understanding and treating impaired awareness and recurrent severe hypoglycemia. Interactions between these factors and cognitions around hypoglycemia in people provide a plausible basis for determining the therapeutic needs of people with type 1 diabetes, in tackling problematic hypoglycemia and diabetes distress. The evaluation of hypoglycemia-related behaviors and cognitions may be integrated into personalized interventions for both these issues.

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Duality of Interest. S.A.A. has served on advisory boards for Novo Nordisk and Medtronic in the past year and is a co-investigator in the European Union Innovative Medicines Initiative (IMI) HypoRESOLVE (Hypoglycaemia – Redefining SOLutions for better liVEs) program. P.C. has received personal fees from Abbott, Dexcom, Insulet, Medtronic, Novo Nordisk, Lilly, and Sanofi. S.R.H. has served on advisory boards for and consulted with Eli Lilly, Novo Nordisk, and Zealand Pharma and served on speaker panels for Novo Nordisk. S.R.H. is a co-investigator in the EU IMI HypoRESOLVE program. E.T. is a consultant to Medtronic. A.B. has received honoraria from AstraZeneca and Sanofi for speaking at educational events and sponsorship from Lilly and Janssen to attend conferences. L.A.G.-F. in partnership with the University of Virginia heads HFS-Global LLC, which licenses use of the HFS questionnaires for fees for for-profit organizations, and these funds are used in part to support ongoing research and education in hypoglycemia. No other potential conflicts of interest relevant to this article were reported.
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Author Contributions. R.H.M., P.J., P.C., and S.A.A. designed the study. R.H.M., S.R.H., E.T., D.K., and A.B. collected data. R.H.M. and P.J., with N.d.Z. and L.A.G.-F., conducted the data analyses. All of the authors contributed to data interpretation, and all authors reviewed and contributed to this manuscript. R.H.M. and S.A.A. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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