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

Short running title

Fear of hypoglycemia in type 1 diabetes

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Abstract

Objectives: 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 HbA1c.

Research design and methods: Participants with type 1 diabetes (n = 178), enriched for people at risk of severe hypoglycemia (49%), completed questionnaires assessing hypoglycemia fear (HFS-II), hyperglycemia avoidance (HAS), diabetes distress (PAID), and cognitive barriers to hypoglycemia avoidance (A2A). Exploratory factor analysis was applied to the HFS-II. Clusters based on HFS-II, A2A, Gold, HAS, and PAID were outlined using k-means clustering.

Results: Four HFS-II factors were identified: Sought Safety, Restricted Activity, Ran High, and Worry. Whilst Sought Safety, Restricted Activity, and Worry increased with progressively impaired awareness and recurrent severe hypoglycemia, Ran High did not. Cluster analysis outlined four clusters: two clusters with preserved hypoglycemia awareness were differentiated by low fear / low cognitive barriers (cluster 1), and 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), and high fear / low cognitive barriers (cluster 4).

Conclusion: 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.

Abbreviations: A2A: Attitudes to Awareness Questionnaire; CGM: continuous glucose monitoring; CSII: continuous subcutaneous insulin infusion; EFA: exploratory factor analysis; HAS: Hyperglycemia Avoidance Scale; HFS(-II): Hypoglycemia Fear Survey(-II); HFS-B: HFS behavior subscale; HFS-W: HFS worry subscale; isCGM: intermittently scanned continuous glucose monitoring; MDII: multiple daily insulin injection; PAID: Problem Areas in Diabetes questionnaire.

Introduction

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 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 HFS-II (5), have been widely used to measure fear of hypoglycemia. Studies using the HFS have found that individuals at a high risk of severe hypoglycemia tend to have higher fear of hypoglycemia, as one might expect (5), with a significant minority expressing low fear of hypoglycemia (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 describe 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, with 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 (A2A) questionnaire measures unhelpful health beliefs that might lead to *cognitive barriers* to hypoglycemia avoidance. The A2A originated in qualitative research in people experiencing recurrent severe hypoglycemia and revealed unhelpful health beliefs, or “thinking traps”, that might 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. Relationships between behaviors, worry, and cognitive barriers 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 and

behaviors around hypoglycemia and that these would associate with problematic hypoglycemia as described by hypoglycemia awareness status and experience of recurrent severe hypoglycemia. This paper outlines subtypes of hypoglycemia-related experience incorporating cognitive barriers and fear, and links 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 United States and three in the United Kingdom. The study cohort included adults with type 1 diabetes, enriched for problematic hypoglycemia by specifically targeting both people with and without problematic hypoglycemia, defined as impaired awareness of hypoglycemia and reporting more than one severe hypoglycemia episode in the preceding two years. Inclusion criteria included previous receipt of structured education in flexible insulin therapy, or its equivalent, and use of an appropriate multiple-daily injection or continuous infusion insulin regimen as well as age 18 or older, diabetes duration four years or more, ability to communicate in written and spoken English and give written informed consent. Pregnancy, severe mental disorder, and untreated co-morbidities 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; the present 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

(IRAS numbers 216381 and 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 definition: when cognitive function is so disturbed that third-party assistance is needed for treatment (3). Recurrent severe hypoglycemia (rSH) was defined as two or more severe hypoglycemia episodes within 12 months (12). Demographic data and diabetes history were documented. HbA1c was recorded prior to enrollment. Participants completed a book of validated questionnaires, including:

(*1) The 33-item Hypoglycemia Fear Survey-II (HFS-II)* comprising an 18-item worry subscale and a 15-item behavior subscale (5). Items in the worry subscale follow the stem “because my blood sugar could go low, I worried about”. Items in the behavior subscale follow the stem “to avoid low blood sugar and how it affects me, I”. Participants respond to all items on a five-level Likert scale: “never”, “rarely”, “sometimes”, “often”, “almost always”.

(2) *The single-item Gold score of hypoglycemia awareness*, which asks “do you know when your hypos are commencing?”, requiring a response on a seven-level Likert scale from one, “I am always aware”, to seven, “I am never aware” (16). Impaired awareness of hypoglycemia was defined by a Gold score of at least four.

(3) *The 19-item Attitudes to Awareness (A2A) questionnaire* assesses unhelpful health beliefs that might lead to cognitive barriers to hypoglycemia avoidance, e.g “there are no serious consequences to leaving mild hypoglycemias untreated”. Items six to 19

follow the stem “how true do you consider the following statements for you personally?”, with responses on a four-level Likert scale: “not true at all”, “slightly true”, “moderately true”, “very true”(14).

(4) *The 26-item Hyperglycemia Avoidance Scale (HAS)* includes 12 behavior items, 12 worry items and two relating to hyperglycemic measures, each scored on a five-level Likert scale, “never”, “rarely”, “sometimes”, “often”, “always” (16).

(5) *The 20-item Problem Areas In Diabetes questionnaire (PAID)* measures diabetes distress, asking “which of the following diabetes issues are currently a problem for you?”, responding on a five-level Likert scale: “not a problem”, “minor problem”, “moderate problem”, “somewhat serious problem”, “serious problem”.

After March 2020, the questionnaires were offered on-line using Qualtrics (www.qualtrics.com) as well as on paper. Recruitment was converted to virtual to remain compliant with Covid-19 restrictions.

Statistical analysis

To investigate 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 (18). The sample-to-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's alpha was calculated for each factor as a measure of internal consistency; >0.7 was considered adequate.

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, using 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's post-hoc test, adjusted 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% confidence intervals.

We employed 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 were centered and scaled before clustering, including a ranking step for HFS-II, A2A, and HAS due to skewed distributions, to improve balance between questionnaires. The Hartigan and Wong algorithm (19) 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 HbA1c, and use of diabetes

technologies. An individual was allocated to the cluster with the greatest similarity by Euclidian distance. Comparisons between clusters for HbA1c and severe hypoglycemia were performed with the Kruskal-Wallis test with Dunn's post-hoc test, adjusted for multiple comparisons with the Benjamini-Hochberg procedure.

All statistical computations were performed in R version 4.0.3 (2020-10-10) (20,21).

Results

The study cohort

One hundred and seventy-eight individuals returned questionnaires, 19 on-line. Their demographics are shown in Table 1, together with HbA1c, hypoglycemia awareness (Gold score), and diabetes technology used. Fifty-three individuals (30%) were using continuous subcutaneous insulin infusion *plus* either continuous glucose monitoring or isCGM, with 26 participants (15%) on CSII only, 52 (29%) using MDII *plus* either continuous glucose monitoring or isCGM, and 47 (26%) using multiple daily injections and intermittent finger-prick glucose monitoring. 57% of respondents reported at least one episode of severe hypoglycemia in the previous 12 months, and 49% reported recurrent severe hypoglycemia. The median (IQR, range) severe hypoglycemia count in 12 months was 1.0 (5.2, 0-365). Mean (SD) scores for the questionnaires are presented in Table 1.

Exploratory factor analysis of HFS-II

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, considering the cumulative variance explained, the degree of cross-loading and the item composition of each factor. We named the factors Restricted Activity, Ran High, Sought Safety, and Worry. . Calculated Cronbach's alphas indicated high internal consistency of the factors.

Associations between the HFS-II factors and problematic hypoglycemia

With increasing impaired awareness (Gold score), Fig. 1A, Worry ($p < 0.001$), Sought Safety ($p < 0.001$), and Restricted Activity ($p < 0.001$) scores increased (supplementary table S1). 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 ($p < 0.001$) scores, but not Ran High ($p = 0.440$) score (Fig. 1B).

Multivariate model of impaired awareness *and* recurrent severe hypoglycemia

In a multivariate logistic regression model of impaired awareness and recurrent severe hypoglycemia (supplementary Figure S1), Sought Safety had the largest association with both outcomes, odds ratios (95% CI) of 7.39 (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, odds ratios (95% CI) of 0.39 (0.22, 0.71) and 0.42 (0.24, 0.73), respectively, both $p < 0.001$. Restricted Activity was associated with impaired awareness, showing a 3.12 (95% CI 1.24, 7.85) times increased likelihood of impaired awareness, $p = 0.02$, but was not

associated with recurrent severe hypoglycemia, odds ratio 1.36 (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, odds ratio (95% CI) 1.49 (1.08, 2.04), p = 0.02 and recurrent severe hypoglycemia, odds ratio (95% CI) 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, Supplementary Tables S2 and S3).

Cluster 1, n = 52, was characterized by the lowest Gold score, low scores across HFS-derived variables, and the lower HAS. The median severe hypoglycemia count was 0 and mean HbA1c was 7.72%.

Cluster 2, n = 26, was characterized by low Gold scores and, relative to the other clusters, high PAID, Worry, Ran High, and HAS scores and relatively high A2A. The median severe hypoglycemia count was 0 and mean HbA1c was 8.03 %.

Cluster 3, n = 21, was characterized by high Gold score, high scores for A2A variables, in particular for Hyperglycemia Avoidance Prioritized, markedly low Ran High, and relatively low Restricted Activity and Sought Safety. The median severe hypoglycemia count was 3.5 (the highest among clusters) and mean HbA1c was 6.82 % (the lowest).

Cluster 4, n = 37, was characterized by the highest Gold score, high HFS factors, in particular Sought Safety; A2A scores were relatively low. The median severe hypoglycemia count was 3 and mean HbA1c was 7.19 %.

Statistical comparisons between clusters (Supplementary Table S2 for pairwise statistics) revealed significantly different SH count ($p < 0.001$), HbA1c ($p = 0.001$), and CGM usage ($p = 0.023$), but not pump usage ($p = 0.11$) or isCGM usage ($p = 0.065$).

Conclusions

In this examination of fear of hypoglycemia in adults with type 1 diabetes, we have demonstrated a four-factor structure of the Hypoglycemia Fear Survey-II (HFS-II): three factors were dominated by behaviors related to hypoglycemia (Sought Safety, Restricted Activity, and Ran High), and the other related to worry (Worry). Worry, Sought Safety, and Restricted Activity were positively related to both impaired awareness and recurrent severe hypoglycemia. The other factor, Ran High, did not increase with progressive impaired awareness. In a clustering analysis including 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 dominant (cluster 3) and one cluster in which fear was high and cognitive barriers 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 HbA1c outcomes revealed clear

demarcation between high and low severe hypoglycemia, and higher and lower HbA1c.

Factor analysis revealed four HFS-II factors

Sought Safety items were linked to worries and actions taken to mitigate the harm of significant hypoglycemia, particularly by 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”. 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”.

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 (15), 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 did not increase with progressive impaired awareness – those with hypoglycemia awareness had a similar Ran High scores to those with impaired awareness – and Ran High 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.

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 are 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 severe hypoglycemia (Sought Safety) and reactions to severe hypoglycemia (Felt Restricted), but not actions to prevent severe hypoglycemia (Ran High). In some individuals, this may reflect an acceptance of severe hypoglycemia, hampering the prevention of further episodes.

Cluster analysis

The clusters allow us to make clinically plausible speculations about the role of cognitive barriers, 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 expressed unhelpful health beliefs about the need to avoid hypoglycemia and 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 HbA1c. 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 HbA1c. People in this cluster may struggle to engage with conventional therapies to reduce their hypoglycemia risk unless their cognitive barriers are addressed (22). 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 may speculate that fewer cognitive barriers mean this group is amenable to conventional interventions such as education and diabetes technologies (continuous glucose monitoring, insulin infusion devices and hybrid closed loop systems): their worry and fear may help them engage with such strategies.

With preserved awareness of hypoglycemia, low cognitive barriers, and low fear, as in cluster 1, may be permissive of a relatively low HbA1c. The low worry about

hypoglycemia may be a realistic response to (relatively) low experience. However, cognitive barriers may exist even where hypoglycemia awareness is maintained, as in cluster 2. In this cluster, high cognitive barriers 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 by the 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 resembles the four groups identified by Anderbro et al. in a clinic-based study of the HFS (6). Our cluster 1 (n = 52, 38%) corresponds to the “low fear low risk” group (43% of population), cluster 2 (n = 26, 19% of population) to the “high fear low risk” (32% of population) group, cluster 3 (n = 21, 15%) to the “low fear high risk” (8%), and cluster 4 (n = 37, 27%) to the “high fear high risk” (17% of population). Importantly, in this study we were able to describe associated cognitive barriers, levels of diabetes distress and hyperglycemia avoidance for each cluster.

Previous factor structures of the HFS

Previous factor analysis of the HFS-II have shown the HFS-W subscale 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 study, with a different version of the HFS, Sought Safety shifts towards actions taken to avoid being alone, with the including 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. A study of the Norwegian HFS-II found a four-factor structure for the HFS, with three HFS-B factors (10). This factor structure was remarkably similar to our study, and the authors referred to the factors as “blood glucose-regulating behavior” (items 2, 3, 13, 14), “avoidance behavior” (items 6, 7, 8, 9, 10, 12), and “seeking support from others” (items 5, 11, 15).

Across studies, the ‘running blood glucose high’ factor is consistent. On the other hand, Sought Safety and Felt Restricted factors have been grouped as an ‘Avoidance’ factor. This may suggest that the most fundamental distinction between HFS-II behaviors is between actions taken to avoid low blood glucose, versus behaviors in response to the negative consequences of hypoglycemia. 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.

Limitations

Whilst this study had a favorable sample size for reliable factor analysis, exploratory factor analysis 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. 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 questionnaire which is relevant to our understanding of its link with severe hypoglycemia risk and even HbA1c. These HFS-II factors are linked to both impaired awareness of hypoglycemia and severe hypoglycemia. In particular, the lack of increase in Ran High 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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Authors' contributions

SAA, RHM, PJ and PC designed the study. RHM, SRH, ET, DK and AB collected the data; RHM and PJ, with LGF and NdeZ, conducted the data analyses; all the authors contributed to the data interpretation and all authors have reviewed and contributed to this manuscript.

Competing Interests

SAA has served on Advisory Boards for NovoNordisk and Medtronic in the past year and is a co-investigator on the EU IMI HypoRESOLVE programme. PC has received personal fees from Abbott, Dexcom. Insulet, Medtronic, Novo Nordisk, Lilly and Sanofi. SRH has served on Avisory Boards and Consulted with Eli Lilly, NovoNordisk, Zealand Pharma and served on speaker panels for NovoNordisk. He is a co-investigator on the EU IMI HypoRESOLVE programme. ET is a consultant to Medtronic; AB declares that he has received honoraria from Astra Zeneca and Sanofi for speaking at educational events and sponsorship from Lilly and Janssen to attend conferences. The other authors have no disclosures. LGF 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. There were no licensing fees for use of the HFS-II in this study.

References

1. Hendrieckx C, Gonder-Frederick L, Heller SR, Snoek FJ, Speight J. How has psycho-behavioural research advanced our understanding of hypoglycaemia in type 1 diabetes? Diabet Med. 2020;37(3):409–17.

2. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977.
3. Heller SR. Glucose concentrations of less than 3.0 mmol/L (54 mg/dL) should be reported in clinical trials: A joint position statement of the American diabetes association and the European association for the study of diabetes. Diabetes Care. 2017;
4. Cox DJ, Irvine A, Gonder-Frederick L, Nowacek G, Butterfield J. Fear of hypoglycemia: quantification, validation, and utilization. Diabetes Care. 1987;10:617-21.
5. Gonder-Frederick LA, Schmidt KM, Vajda KA, Greear ML, Singh H, Shepard JA, et al. Psychometric properties of the hypoglycemia fear survey-II for adults with type 1 diabetes. Diabetes Care. 2011;34:801–6.
6. Anderbro T, Gonder-Frederick L, Bolinder J, Lins PE, Wredling R, Moberg E, et al. Fear of hypoglycemia: relationship to hypoglycemic risk and psychological factors. Acta Diabetol. 2015;52:581–9.
7. Gonder-Frederick LA, Vajda KA, Schmidt KM, Cox DJ, Devries JH, Erol O, et al. Examining the Behaviour subscale of the Hypoglycaemia Fear Survey: An international study. Diabet Med. 2013;30:603–9.
8. Lam AYR, Xin X, Tan WB, Gardner DS, Goh SY. Psychometric validation of the Hypoglycemia Fear Survey-II (HFS-II) in Singapore. BMJ Open Diabetes Res

Care. 2017;5(1):e000329.

9. Mu C, Xing Q, Zhai Y. Psychometric properties of the Chinese version of the hypoglycemia fear survey II for patients with type 2 diabetes mellitus in a Chinese metropolis. PLoS One. 2020;1 2020;15:e0229562..
10. Graue M, Iversen MM, Wentzel-Larsen T, Rokne B, Haugstvedt A. Assessing fear of hypoglycemia among adults with type 1 diabetes - Psychometric properties of the Norwegian version of the Hypoglycemia fear survey II questionnaire. Nor Epidemiol. 2013;23(1):75–81.
11. Choudhary P, Rickels MR, Senior PA, Vantyghem MC, Maffi P, Kay TW, et al. Evidence-informed clinical practice recommendations for treatment of type 1 diabetes complicated by problematic hypoglycemia. Diabetes Care. 2015; 38:1016-29
12. Vallis M, Jones A, Pouwer F. Managing hypoglycemia in diabetes may be more fear management than glucose management: a practical guide for diabetes care providers. Curr Diabetes Rev. 2014;10:364-70.
13. Rogers HA, de Zoysa N, Amiel SA. Patient experience of hypoglycaemia unawareness in Type 1 diabetes: are patients appropriately concerned? Diabet Med. 2012; 29:321-7
14. Cook AJ, DuBose SN, Foster N, Smith EL, Wu M, Margiotta G, Rickels MR, Speight J, de Zoysa N, Amiel SA. Cognitions Associated With Hypoglycemia Awareness Status and Severe Hypoglycemia Experience in Adults With Type 1 Diabetes. Diabetes Care. 2019;42:1854-1864.
15. Pedersen-Bjergaard U, Pramming S, Heller SR, Wallace TM, Rasmussen ÅK,

Jørgensen H V., et al. Severe hypoglycaemia in 1076 adult patients with type 1 diabetes: Influence of risk markerts and selection. Diabetes Metab Res Rev. 2004;20(6):479–86.

16. Gold AE, Macleod KM, Frier BM. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. Diabetes Care. 1994 Jul 1;17(7):697–703.
17. Singh H, Gonder-Frederick L, Schmidt K, et al. Assessing hyperglycemia avoidance in people with type 1 diabetes. Diabetes Management 2014;4:263–71.
18. Costello AB, Osborne JW. Best practices in exploratory factor analysis: Four recommendations for getting the most from your analysis. Pract Assessment, Res Eval. 2005;10(7).
19. Hartigan JA, Wong MA. A *K*-means clustering algorithm. 1979. Journal of the Royal Statistical Society. 28: 100-108.
20. Koenker R. quantreg: Quantile Regression [Internet]. 2020. Available from: https://cran.r-project.org/package=quantreg
21. 2R Core Team. R: A language and environment for statistical computing. [Internet]. R Foundation for Statistical Computing, Vienna, Austria.; Available from: https://www.r-project.org/
21. De Zoysa N, Rogers H, Stadler M, Gianfrancesco C, Beveridge S, Britneff E, et al. A psychoeducational program to restore hypoglycemia awareness: The DAFNE-HART pilot study. Diabetes Care. 2014 Mar 1;37(3):863–6.
22. Anderbro T, Amsberg S, Wredling R, Lins PE, Adamson U, Lisspers J, et al.

Psychometric evaluation of the Swedish version of the Hypoglycaemia Fear Survey. Patient Educ Couns. 2008;73(1):127–31.

Table and Figure Legends

Table 1. The demographics and questionnaire scores of the study population.

Table 2. Exploratory factor analysis of the Hypoglycemia Fear Score-II (HFS-II) describing four factors. Cronbach's alpha >0.70 for each factor indicated adequate consistency. Factor loadings <0.4 are not presented.

Figure 1. Associations between HFS-II-derived factor scores and Gold score (panel A) and recurrent severe hypoglycemia, (recurrent SH, panel B). Dark grey bars = Restricted Activity; mid grey bars = Sought Safety; light grey bars = Ran High; open bars = Worry. Statistical analysis is given in supplementary table S1. *** $p < 0.001$; *NS* $p > 0.05$.

Figure 2. Cluster analysis of the cohort, showing four hypoglycemia subtypes. For each cluster, the cluster center with respect to each variable is presented. Black bars indicate values above the mean, grey bars values below the mean. The full statistical analysis is given in supplementary table S2.

Table 1: Participant characteristics

Age, years, mean (SD)		50.6 (14.2)
Diabetes duration, years, mean (SD)		32.5 (14.4)
Gender (% female)		56.7%
Ethnicity (%)		
	White	94.9%
	Black	1.1%
	Other	4.0%
HbA1c, %, 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 Prioritised	1.4 (0.6)
HAS score, mean (SD)		1.8 (0.5)
PAID score, mean(SD)		23 (15)

* CSII: continuous subcutaneous insulin infusion (pump therapy); CGM: continuous glucose monitoring; SAP: sensor augmented pump therapy, with automated suspend of insulin infusion features; isCGM: intermittently-scanned retrospective continuous glucose monitoring

Table 2: Exploratory factor analysis of the HFS-II questionnaire

Four factor solution*				
Question	Worry	Sought Safety	Restricted Activity	Ran High
To avoid low blood sugar and how it affects me, I…				
1. ate large snacks				
2. tried to keep my blood sugar above 8.3 mmol/L (150 mg/dl)				0.602
3. reduced my insulin when my blood sugar was low				
4. measured my blood sugar 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 sugar higher than usual in social situations				0.876
14. kept my blood sugar 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 sugar could go low, I worried about ...				
16. not recognising/realising I was having low blood sugar.				

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 hypoglycaemic 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 hypoglycaemic episode.		0.857		
24. having a hypoglycaemic episode while driving.	0.523			
25. making a mistake or having an accident.	0.701			
26. getting a bad evaluation or being criticised.	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 sugar interfering with important things I was doing.	0.667			
32. becoming hypoglycaemic 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's alpha	0.937	0.896	0.857	0.771

*Factor loadings <0.4 not presented.

Supplementary Data

Supplementary Table S1: Statistical analysis for associations between Gold score and HFS-II factors. Groupwise comparisons for each factor by Kruskal-Wallis test; pairwise comparisons by Dunn's post hoc test with adjustment for multiple comparisons. Statistical analysis for associations between recurrent severe hypoglycemia groups and HFS-II factors by Wilcoxon Rank Sum test.

	Worry	Sought Safety	Restricted Activity	Ran High
Gold score				
Kruskal-Wallis	<0.001	<0.001	<0.001	0.109
1 - 2	0.355	0.690	0.774	0.486
1 - 3	0.323	0.579	0.293	0.742
2 - 3	0.089	0.434	0.373	0.209
1 - 4	0.399	0.113	0.012	0.924
2 - 4	0.093	0.033	0.014	0.496
3 - 4	0.714	0.485	0.615	0.562
1 - 5	0.332	0.004	0.003	0.955
2 - 5	0.041	<0.001	0.004	0.439
3 - 5	0.720	0.163	0.618	0.454
4 - 5	0.987	0.412	0.967	0.977
1 - 6	0.004	<0.001	0.004	0.554
2 - 6	<0.001	<0.001	0.002	0.124
3 - 6	0.324	0.010	0.386	0.559
4 - 6	0.096	0.019	0.750	0.607
5 - 6	0.042	0.076	0.671	0.524
1 - 7	0.022	0.010	0.013	0.986
2 - 7	0.001	0.002	0.015	0.574

3 - 7	0.313	0.152	0.509	0.535
4 - 7	0.124	0.368	0.814	0.980
5 - 7	0.091	0.708	0.794	0.950
6 - 7	0.934	0.305	0.921	0.746
Recurrent severe hypoglycemia				
	<0.001	<0.001	<0.001	0.440

Supplementary Table S2: Statistical analysis comparing rate of severe hypoglycemia (column 2) and HbA1c (column 3) between the four clusters as shown in Fig. 2 of the main paper. Pairwise comparisons by Dunn's post hoc test with adjustment for multiple comparisons.

Cluster comparison	Severe hypoglycemia count (p value)	HbA1c (p value)
1 - 2	0.300	0.480
1 - 3	<0.001	0.006
2 - 3	<0.001	0.008
1 - 4	<0.001	0.035
2 - 4	<0.001	0.025
3 - 4	0.770	0.029
Kruskal-Wallis	<0.001	0.001

Supplementary Table S3. Summary of the cluster analysis, with interpretation of the key findings that define each cluster. * median values for questionnaire scores.

Cluster number	1	2	3	4
Cluster description	Response to lower severe hypoglycemia experience	High hypoglycemia fear and distress; lower severe hypoglycemia risk	High hyperglycemia avoidance; low hypoglycemia fear; high barriers	High hypoglycemia fear; lower barriers
A2A Avoid High*	1	1.6	2.3	1
A2A Minimise*	0.62	0.75	1	0.25
A2A Normalise*	0.25	0.75	0.75	0
Gold*	2	2	5	5
HAS*	1.54	2.17	1.96	1.83
HFS Ran High*	1.1	2	0.38	2
HFS Restricted*	0	0.46	0	0.85
HFS Sought Safety*	0.18	1.3	0.37	1.6
HFS Worry*	0.46	1.7	1.1	1.7
PAID*	12	40	14	22
HbA1c mean	7.72	8.03	6.82	7.19
SH median	0	0	3.5	3

Supplementary Figure S1. Forest plot presenting the logistic regression coefficients for the HFS-II factors and diabetes duration (top), against impaired awareness of hypoglycemia (open circles) and recurrent severe hypoglycemia (closed circles).

Supplementary Figure S2. Study recruitment flowchart, from consented participants up to questionnaire results available for analysis.