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RESEARCH ARTICLE

Hypoglycaemia symptom frequency, severity, burden, and utility among adults with type 1 diabetes and impaired awareness of hypoglycaemia: Baseline and 24-week findings from the HypoCOMPaSS study

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Abstract

Aims: To determine the frequency, severity, burden, and utility of hypoglycaemia symptoms among adults with type 1 diabetes (T1D) and impaired awareness of hypoglycaemia (IAH) at baseline and week 24 following the HypoCOMPaSS awareness restoration intervention.

Methods: Adults ($N = 96$) with T1D (duration: 29 ± 12 years; 64% women) and IAH completed the Hypoglycaemia Burden Questionnaire (HypoB-Q), assessing experience of 20 pre-specified hypoglycaemia symptoms, at baseline and week 24.

Results: At baseline, 93 (97%) participants experienced at least one symptom (mean ± SD 10.6 ± 4.6 symptoms). The proportion recognising each specific symptom ranged from 15% to 83%. At 24 weeks, symptom severity and burden appear reduced, and utility increased.

Conclusions: Adults with T1D and IAH experience a range of hypoglycaemia symptoms. Perceptions of symptom burden or utility are malleable. Although larger scale studies are needed to confirm, these findings suggest that changing

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the salience of the symptomatic response may be more important in recovering protection from hypoglycaemia through regained awareness than intensifying symptom frequency or severity.

KEYWORDS

diabetes, hypoglycaemia, impaired awareness, symptom burden

1 | INTRODUCTION

Symptomatic hypoglycaemia is a common side effect of insulin therapy, and hypoglycaemia symptoms provide important warning of impending low glucose. However, approximately 25%–40% of adults with type 1 diabetes (T1D) have impaired awareness of hypoglycaemia (IAH).[1] IAH is characterised by reduction in subjective recognition of hypoglycaemia, placing the individual at a 6- to 10-fold higher risk of severe episodes of hypoglycaemia, requiring assistance from others for recovery.[2] While continuous glucose monitoring (CGM) can provide technological warning of impending low glucose, this technology is not accessible to all,[3] and 70% of those with CGM use it less than 6 days per week.[4] Even when CGM is used, IAH can persist and remain associated with high risk of severe hypoglycaemia.[5] For many, symptoms remain central in detecting hypoglycaemia.

It is a common misconception that people with IAH do not experience symptoms of hypoglycaemia. However, it is more typical that they experience either a change in symptom type or intensity, or experience symptoms at lower glucose levels compared to those with intact awareness.[6] Measures of subjective awareness of hypoglycaemia enable assessment of IAH,[7] but do not explore the experience of symptoms. The 'Edinburgh Hypoglycaemia Scale' assesses the intensity of 11 hypoglycaemia symptoms, and factor analyses have identified three distinct symptom clusters: *neuroglycopenic*, *autonomic*, and *general malaise*.[8,9] However, there is limited understanding about how bothersome they are, or how useful they are as warning signs for detecting hypoglycaemia. Finally, it is unclear what a change in awareness status may mean in terms of symptom experience following an awareness restoration intervention.

HypoCOMPaSS was a 24-week randomised controlled trial (RCT) investigating whether IAH among adults with T1D could be reduced and recurrent severe hypoglycaemia prevented by avoiding biochemical hypoglycaemia.[10] A 2×2 design compared insulin pump with multiple daily injections and CGM with self monitoring of blood glucose (SMBG). Therapeutic targets, brief psycho-education (*my hypo compass*), and support were consistent across groups. The *my hypo compass* intervention is a brief psycho-educational programme focusing on how to minimise risk of dangerous hypoglycaemia, framed around four compass points, NESW: 'Now; No delay' (never delay hypoglycaemia treatment); 'Establish your Extra risks' (and times when risk is highest); 'Scan for Subtle Symptoms' (of hypoglycaemia); and 'be Wary even While asleep' (through watchful detection and active prevention of hypoglycaemia while asleep).[11] Participants were eligible if aged 18–74 years, with T1D (C-peptide negative) and IAH (Gold score ≥ 4[12]). Primary and secondary outcomes (at 24 weeks and 2 years) have been published.[10,11,13] Briefly, across groups at 24 weeks, there were significant reductions in time below range, severe hypoglycaemia, and fear of hypoglycaemia, alongside significant improvements in hypoglycaemia awareness.[10] Using the HypoCOMPaSS trial data set,[10] we examined the prevalence, frequency, severity, burden, and utility of hypoglycaemia symptoms among adults with T1D and IAH pre- and post-intervention using a novel measure: the Hypoglycaemia Burden Questionnaire (HypoB-Q).

What's new?

- The HypoCOMPaSS trial has previously shown reduction in time below range, improved awareness of symptoms, and changes in cognitions/attitudes regarding hypoglycaemia.
- This study highlights that adults with type 1 diabetes and impaired awareness of hypoglycaemia continue to experience hypoglycaemia symptoms, with variability in type, frequency, severity, and perception of burden/utility. Following the intervention, it appears that participants perceived their symptoms as less burdensome and more useful, suggesting that they may have reframed their perception of symptoms.
- Symptoms previously regarded as burdensome were reframed as helpful for managing falling glucose levels, suggesting that brief psycho-education may be a valuable clinical intervention.

2 | METHODS

Ethical approval for the HypoCOMPaSS study has been granted by the Sunderland Research Ethics Committee (09/H0904/63), and all study participants provided written informed consent.[14]

Developed for HypoCOMPaSS, the 'Hypoglycaemia Burden Questionnaire' was administered at baseline and week 24. The HypoB-Q was informed by the symptoms of the 'Edinburgh Hypoglycaemia Scale', targeted literature review, and exploratory interviews with $N=17$ adults with T1D and history of IAH.[15] An iterative process (described elsewhere[15]) was used to finalise the design, based on cognitive debriefing with the same adults with T1D and consultation with diabetologists. The HypoB-Q invites participants to indicate which of 20 prespecified symptoms they experience 'during a hypo' (response: yes/no). For the symptoms experienced, participants complete a further four items about that symptom's frequency, severity, burden, and utility (helpfulness to identify and treat the episode early), each reported on a 3-point Likert scale.

TABLE 1 Participants' characteristics at baseline.

	Baseline ($N=96$)
Women	61 (64%)
Age, years	49 ± 12
Type 1 diabetes duration, years	29 ± 12, 1 missing
HbA_{1c} (mmol/mol)	66 ± 12
(%)	8.2 ± 1.2
Impaired awareness of hypoglycaemia: Gold score ≥ 4	96 (100%)

Note: Data are *n* (%) or mean ± SD.

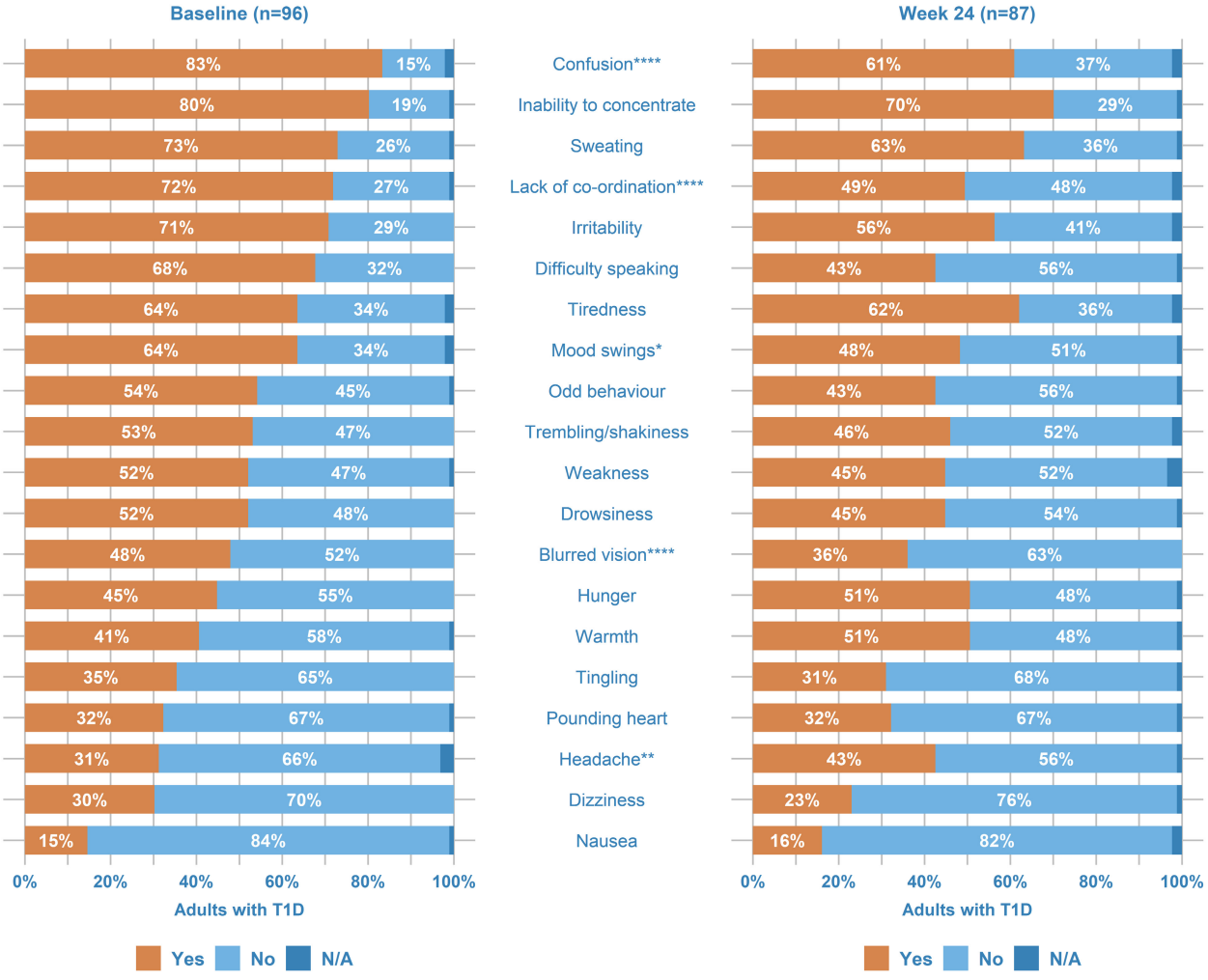

FIGURE 1 Percentage of adults with type 1 diabetes (T1D) self reporting experience of symptoms during hypoglycaemia, at baseline and week 24. HypoB-Q question 1 ("Do you have this symptom during a hypo?"). All symptoms were listed in the HypoB-Q. N/A indicates that the question was skipped/not answered. Symptoms are arranged by high to low percentage of participants experiencing the symptoms at baseline (orange category). *$p<0.05$, **$p<0.01$, ***$p<0.0025$, ****$p<0.001$ (McNemar's chi square test).

Descriptive statistics were used to characterise participants at baseline, and HypoB-Q responses at baseline and week 24. McNemar's chi-square test and Wilcoxon's signed-rank test were used for statistical testing of changes, with pair-wise deletion and a Bonferroni-corrected p-value < 0.0025 applied. These analyses were not pre-specified in the HypoCOMPaSS protocol or statistical analysis plan.

3 | RESULTS

A total of 96 adults with T1D and IAH were included (Table 1), with 24-week follow-up data available for $n = 87$ participants. Detailed sample characteristics are published.[10]

Figures 1–5 show response patterns for the 20 pre-specified hypoglycaemia symptoms in terms of frequency, severity, burden, and utility. At baseline, 93 (97%) of participants reported at least one symptom, with a mean ± SD of 10.6 ± 4.6 symptoms. The proportion recognising each specific symptom ranged from 15% to 83%. At baseline, the most reported symptom was 'confusion' (Figure 1), while 'inability to concentrate' was most frequently experienced 'almost always' (Figure 2). At 24 weeks, 'inability to concentrate' was both the symptom most commonly and most frequently ('almost always') experienced (Figures 1 and 2).

At 24 weeks, relative to baseline, the proportion of participants experiencing 'hunger', 'warmth', 'headache', and 'nausea' increased. For most symptoms, the proportion experiencing them was generally lower, and significantly so for 'confusion', 'lack of coordination', and 'blurred vision' (Figure 1). Likelihood of experiencing 'confusion' and 'difficulty speaking' during hypoglycaemia was lower 24 weeks after intervention (Figure 2). Participants appeared to report hypoglycaemia symptoms as less severe (Figure 3; not statistically significant) and less bothersome (Figure 4), with significantly fewer reporting 'yes, a lot' of burden from 'confusion' during hypoglycaemia.

Across the spectrum of symptoms, at 24 weeks, there appeared to be a trend for fewer participants to report hypoglycaemia symptoms as 'never' being helpful for recognition of hypoglycaemia, compared to baseline (Figure 5). Participants appeared to perceive certain symptoms ('trembling/shakiness', 'lack of coordination', and 'mood swings') as having increased utility, post-intervention, for facilitating early treatment of hypoglycaemia, although none reached the a priori agreed definition of statistical significance.

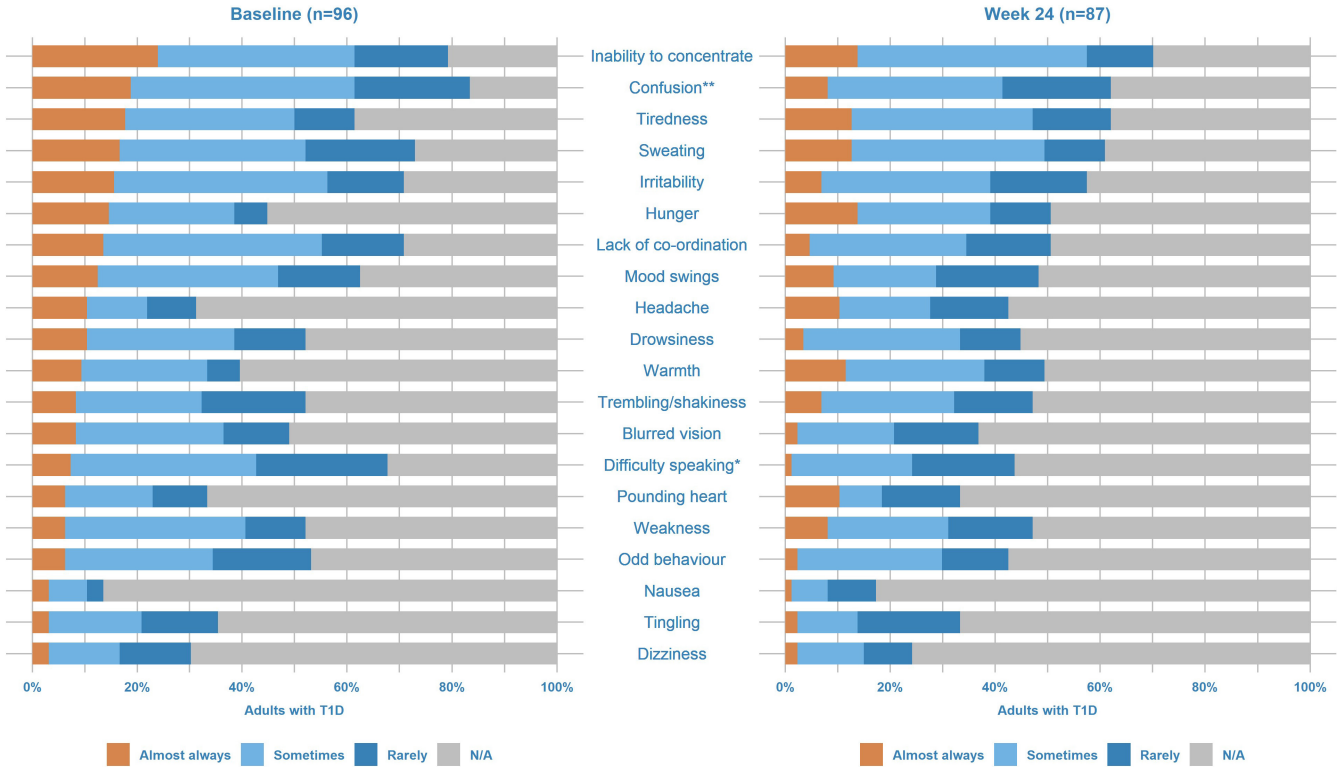

FIGURE 2 Frequency of symptoms experienced during hypoglycaemia by adults with type 1 diabetes (T1D). HypoB-Q question 2 ("How often does it happen?"). All symptoms were listed in the HypoB-Q. N/A indicates that the person either did not have the symptom or the response was missing. Symptoms are arranged by high to low percentage of how often participants experience the symptoms at baseline (orange category). *$p < 0.05$, **$p < 0.01$, ***$p < 0.0025$, ****$p < 0.001$ (Wilcoxon signed-rank test).

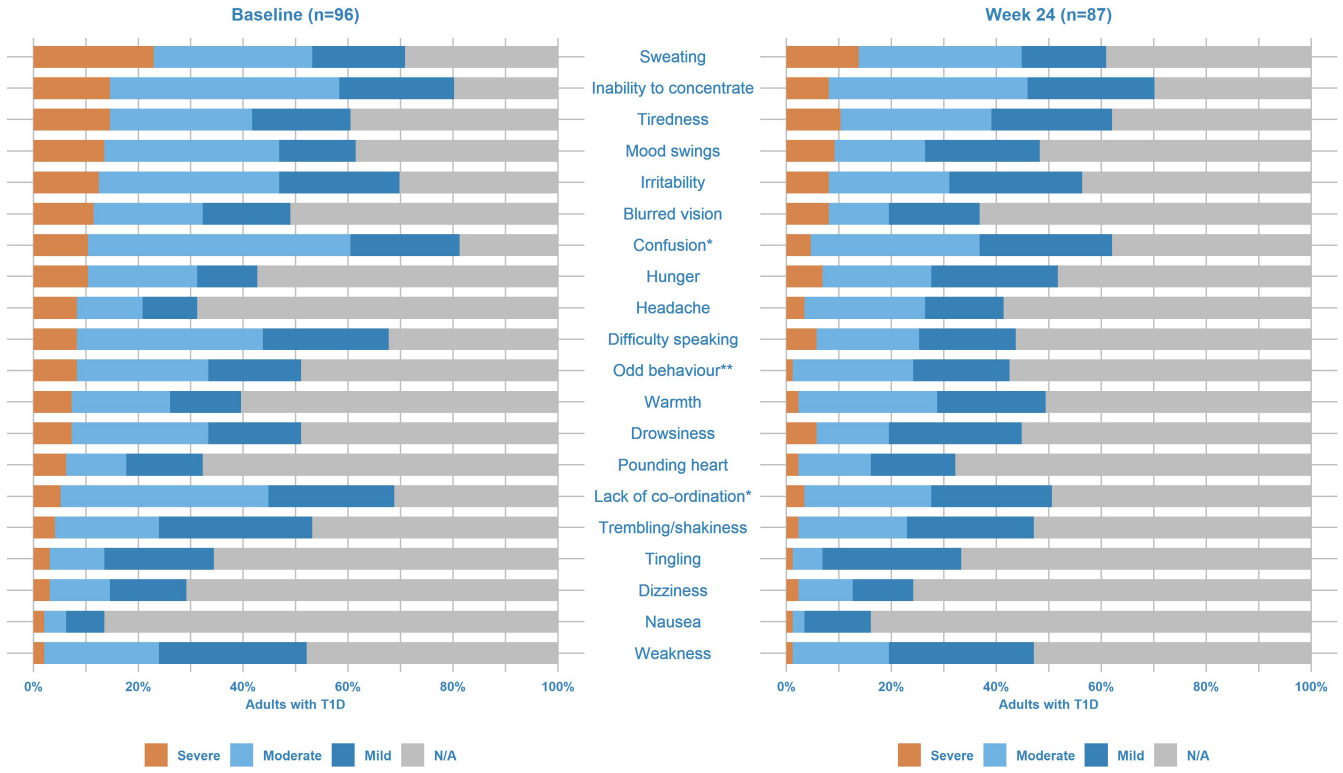

FIGURE 3 Severity of symptoms experienced during hypoglycaemia by adults with type 1 diabetes (T1D). HypoB-Q question 3 ("How severe is it?"). All symptoms were listed in the HypoB-Q. N/A indicates that the person either did not have the symptom or the response was missing. Symptoms are arranged by high to low percentage of how severe participants experience the symptoms at baseline (orange category). *$p < 0.05$, **$p < 0.01$, ***$p < 0.0025$, ****$p < 0.001$ (Wilcoxon signed-rank test).

4 | CONCLUSIONS

Using a novel questionnaire, this analysis demonstrates that almost all adults with long-standing C-peptide-deficient T1D, who were recruited to HypoCOMPaSS due to established IAH, continued to experience hypoglycaemia symptoms, and each symptom was reported by at least 15% of participants. However, their impaired awareness is corroborated by their inconsistent symptomatic recognition (fewer than 24% experienced any symptom 'almost always') and modest symptom intensity (fewer than 23% experienced any symptom as 'severe'). Following a hypoglycaemia awareness restoration intervention (including titration of insulin, brief 2-h psycho-education, and ongoing support over 24 weeks), it appears that participants perceived their symptoms as less burdensome and more useful, suggesting that they may have reframed their perception of symptoms, towards the goal of reducing hypoglycaemia frequency and severity.

Previous research has found that neuroglycopenic symptoms predominate in people with IAH,[8] while studies not stratifying on awareness status show neuroglycopenic and autonomic warning symptoms occurring at similar frequency.[16] Although 'inability to concentrate' and 'confusion' were most frequently experienced at baseline (Figure 2), autonomic symptoms (e.g. 'sweating') and symptoms such as 'tiredness' and 'irritability' also ranked highly, suggesting variability in the type of symptoms experienced by people with IAH. Hypoglycaemia symptoms have been described as idiosyncratic, with both between- and within-person variation.[17,18] As reported elsewhere, time below range decreased at 24 weeks,[10] and this analysis shows that autonomic symptoms (e.g. 'warmth') became more frequent.

At 24 weeks, participants were more inclined to use a gain-framing approach to characterise those symptoms, as opposed to loss-framing. In other words, it is likely that the brief, *my hypo compass* psycho-educational intervention was instrumental in assisting participants to perceive symptoms as useful, that is as a warning of impending low glucose and enabling them to recognise a window of opportunity to prevent severe hypoglycaemia. This reframing may be a more important factor in recovery from IAH than an increase in symptom severity or frequency, given that both of these seemed to reduce after the intervention, consistent with the reduction in hypoglycaemia and improvement in IAH reported for this intervention previously.[10] This is also consistent with other evidence from HypoCOMPaSS, showing a reduction post-intervention in attitudinal barriers to preventing severe hypoglycaemia,

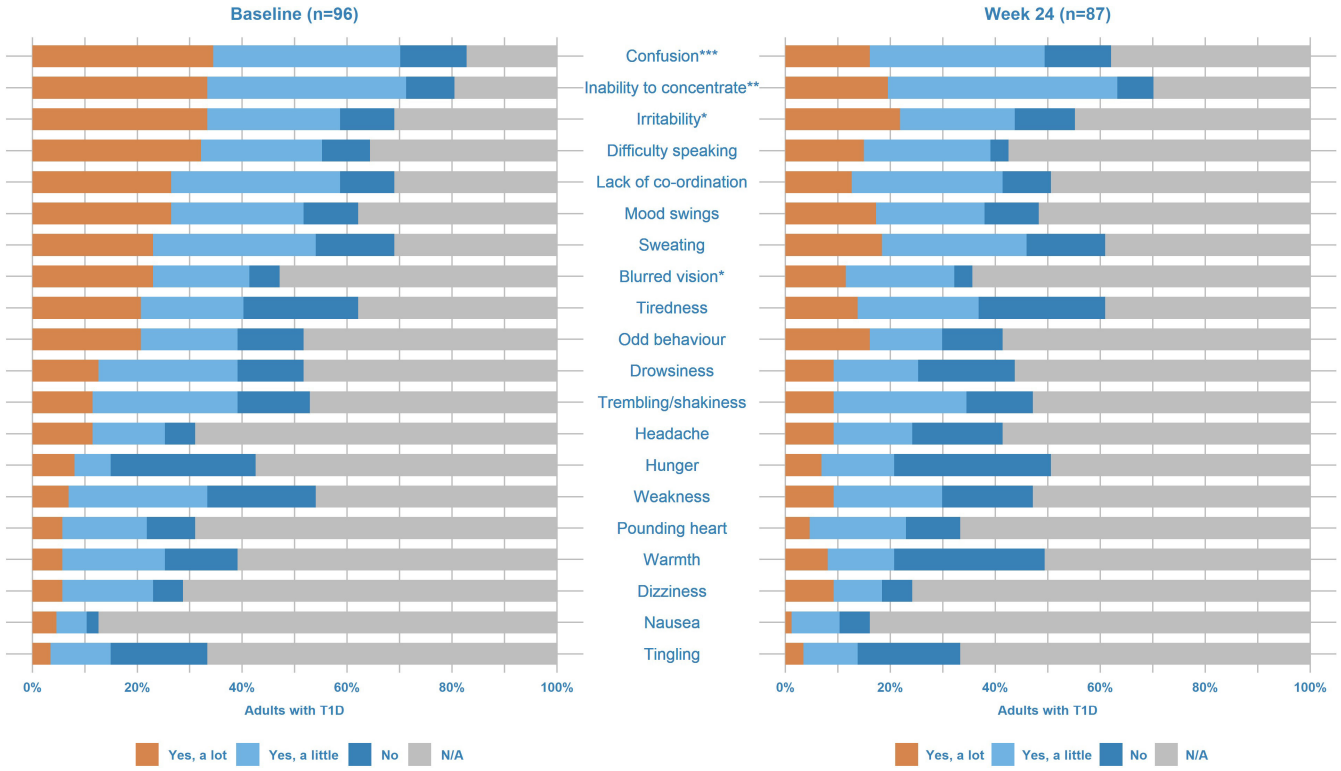

FIGURE 4 Burden of symptoms experienced during hypoglycaemia by adults with type 1 diabetes (T1D). HypoB-Q question 4 ("Does it bother you much?"). All symptoms were listed in the HypoB-Q. N/A indicates that the person either did not have the symptom or the response was missing. Symptoms are arranged by high to low percentage of how bothersome participants experience the symptoms at baseline (orange category). *$p < 0.05$, **$p < 0.01$, ***0.0025, ****$p < 0.001$ (Wilcoxon signed-rank test).

for example prioritising avoidance of hyperglycaemia.[11] The *my hypo compass* intervention is based around the bio-psychobehavioural model of severe hypoglycaemia risk.[19] It seeks to assist individuals to recognise subtle symptoms which may have been present previously but not considered mindfully ('Scan for Subtle Symptoms'); to increase their suspicion that these may be related to (impending) hypoglycaemia at times of (Extra) risk; to confirm that these are due to hypoglycaemia (Wary; Watchful); and to act immediately (Now; No delay). Each participant is encouraged to develop a personalised action plan enabling them to prioritise their own cues to reduce risk of dangerous hypoglycaemia, as opposed to being overburdened by didactic training around attention to all potential hypoglycaemic symptoms.

This study was not powered to determine correlations between HypoB-Q subscales, for example whether how much symptoms experienced by participants 'bothered' them was associated with the utility of these symptoms in 'identifying and treating hypos early'. Interestingly, 'inability to concentrate' and 'confusion' were in the top three symptoms cited as having highest burden and greatest utility at baseline. Following the intervention leading to a significantly improved Gold score, 'sweating', 'trembling/shakiness', and 'tiredness' were the top three ranked 'helpful' symptoms, with only 'sweating' being in the top three burdensome symptoms.

It is striking that despite all participants being identified as having IAH (by Gold score ≥ 4) at baseline, they also reported an average of more than 10 hypoglycaemia symptoms. The Gold score asks the single question 'Do you know when your hypos are commencing' with the respondent circling a number between 1 (always aware) and 7 (never aware).[12] Thus, a score of ≥4 is indicative of impaired awareness, not total unawareness. Our findings are consistent with this definition, and with previous evidence demonstrating that total loss of hypoglycaemia symptoms is rare, with most people with IAH retaining autonomic symptoms, perceived at relatively low glucose levels.[6] As in previous studies,[2] the Gold score at baseline and 24 weeks was associated with prevalence of severe hypoglycaemia[10] and thus remains a well-validated measure of 'awareness' in terms of risk of severe events and a useful brief screening tool for clinical practice. The additional data provided by HypoB-Q provide clear evidence that IAH does not designate an absence of symptoms. The five-item 'impaired awareness' subscale of the Hypoglycaemia Awareness Questionnaire (HypoA-Q)[15] has a newly validated cut-point for establishing 'impaired awareness',[20] which may provide a more robust measure

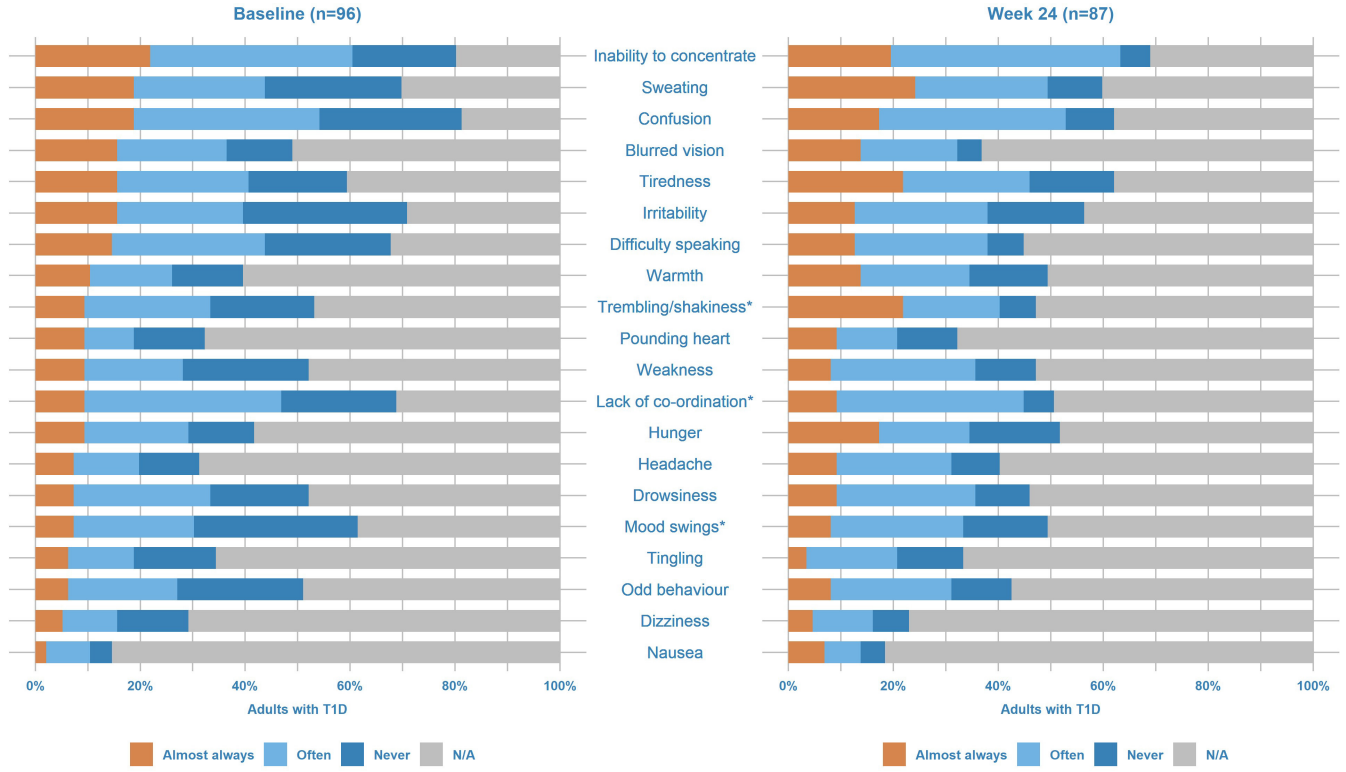

FIGURE 5 Utility of symptoms experienced during hypoglycaemia by adults with type 1 diabetes (T1D). HypoB-Q question 5 ("Does it help you to identify and treat your hypo early?"). All symptoms were listed in the HypoB-Q. N/A indiates that the person either did not have the symptom or the response was missing. Symptoms are arranged by high to low percentage of how helpful participants experience the symptoms at baseline (orange category). *$p < 0.05$, **$p < 0.01$, ***0.0025, ****$p < 0.001$ (Wilcoxon signed-rank test).

for the purposes of determining inclusion in future clinical trials.

Strengths of the study include the focus on adults with confirmed, C-peptide-deficient T1D and established IAH, and use of the novel HypoB-Q to provide a comprehensive assessment of hypoglycaemia symptom experience before and after a hypoglycaemia awareness restoration intervention. Despite visual inspection suggesting clinically relevant change, statistical testing is limited by insufficiently powered secondary analyses and small sample sizes for several comparisons (i.e. due to most participants not experiencing most symptoms). Although several of the potential changes in symptom scores after study intervention met a nominal significance level of $p < 0.05$, few comparisons attained significance following the Bonferroni adjustment for multiple comparisons. Analyses were conducted at a symptom level, and symptom clustering was not possible, as the sample size precluded factor analysis. Thus, further studies are needed with pre-specified power calculations to determine optimal sample size. Further psychometric testing will be important and could be bolstered through collection via the recently developed Hypo-METRICS smartphone app, enabling (multiple) daily and comprehensive assessments of hypoglycaemia symptoms.[21] Further studies are also needed to determine the utility of the HypoB-Q in adults without IAH and those with insulin-treated type 2 diabetes.

In summary, this study highlights that adults with T1D and IAH continue to experience hypoglycaemia symptoms, with considerable variability in type, frequency, severity, and perception of burden/utility. This supports use of the more accurate terminology of 'impaired awareness' rather than the misnomer 'unawareness'.[22,23] Further, while the HypoCOMPaSS trial has previously shown reduction in time below range and improved awareness of symptoms[10] and changes in cognitions/attitudes,[11] this analysis adds evidence of a shift in experiences of specific symptoms and perceptions of their burden/utility. Symptoms previously regarded as burdensome were reframed as helpful for managing falling glucose levels, suggesting that relatively brief psycho-education may be a valuable clinical intervention and that further study is warranted to confirm the role of perceptions of hypoglycaemia symptom burden and utility in the prevention of severe hypoglycaemia.

AUTHOR CONTRIBUTIONS

Jane Speight and James A. M. Shaw conceived the idea for the HypoB-Q as part of the HypoCOMPaSS study, and Jane

Speight undertook the development with contributions from James A. M. Shaw and other HypoCOMPaSS researchers. Jane Speight and US conceived the analysis plan, and US developed it with contributions from Jane Speight, James A. M. Shaw, Melanie Broadley, Stephanie A. Amiel, Pratik Choudhary, Christel Hendrieckx, and Elizabeth Holmes-Truscott. US undertook the data analysis and discussed presentation and interpretation of findings with Jane Speight, Elizabeth Holmes-Truscott, Melanie Broadley, Christel Hendrieckx, Pratik Choudhary, Stephanie A. Amiel, and James A. M. Shaw. US prepared the manuscript, and all the authors contributed to revisions and finalising the manuscript. All the authors approved the final version submitted.

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CONFLICT OF INTEREST STATEMENT

US is employed by Novo Nordisk A/S, which supports the Hypo-RESOLVE study, but had no role in the HypoCOMPaSS study. SAA has served on advisory boards for Novo Nordisk and Medtronic and has spoken at educational events sponsored by Novo Nordisk and Sanofi. FP has received unrestricted funding for research from Novo Nordisk, Eli Lilly, and Sanofi. EHT has undertaken research funded by an unrestricted educational grant from Abbott Diabetes Care, AstraZeneca, and Sanofi, Australia; received speaker fees (to her research group) from Novo Nordisk and Roche; and has served on an advisory board for AstraZeneca. JAMS has served on an advisory board for Mogrify. PC has received research support and personal fees from Novo Nordisk, Lilly, Sanofi, Medtronic, Abbott, Dexcom, Insulet, Vertex, and Glooko. JSp has served on advisory boards for Janssen, Medtronic, Omnipod, Roche Diabetes Care, and Sanofi Diabetes; received unrestricted educational grants and in-kind support from Abbott Diabetes Care, AstraZeneca, Medtronic, Roche Diabetes Care, and Sanofi Diabetes; received sponsorship to attend educational meetings from Medtronic, Roche Diabetes Care, and Sanofi Diabetes; and received consultancy income or speaker fees from Abbott Diabetes Care, AstraZeneca, Insulet, Medtronic, Novo Nordisk, Roche Diabetes Care, and Sanofi Diabetes. In all cases, JSp's research group (ACBRD) has been the beneficiary. JSp owns the copyright of the HypoB-Q. All other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ACCESS TO THE HypoB-Q

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