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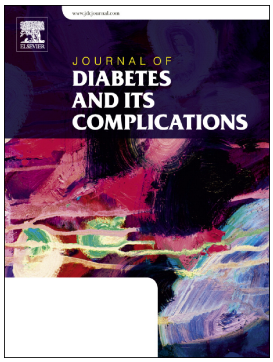

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The impact of hypoglycaemia on quality of life among adults with type 1 diabetes: Results from "YourSAY: Hypoglycaemia"

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Abstract

Aims: Research on hypoglycaemia and quality of life (QoL) has focused mostly on severe hypoglycaemia and psychological outcomes, with less known about other aspects of hypoglycaemia (e.g., self-treated episodes) and impacts on other QoL domains (e.g., relationships). Therefore, we examined the impact of all aspects of hypoglycaemia on QoL in adults with type 1 diabetes (T1DM).

Methods: Participants completed an online survey, including assessment of hypoglycaemia-specific QoL (12-item Hypoglycaemia Impact Profile). Mann-Whitney U tests examined differences in hypoglycaemia-specific QoL by hypoglycaemia frequency, severity, and awareness. Hierarchical linear regression examined associations with QoL.

Results: Participants were 1,028 adults with T1DM (M±SD age: 47±15 years; diabetes duration: 27±16 years). Impaired awareness and severe and self-treated hypoglycaemia negatively impacted on overall QoL and several QoL domains, including leisure activities, physical health, ability to keep fit/be active, sleep, emotional well-being, spontaneity, independence, work/studies, and dietary freedom. Diabetes distress was most strongly associated with hypoglycaemia-specific QoL, followed by generic emotional well-being, fear of hypoglycaemia, and confidence in managing hypoglycaemia. Hypoglycaemia frequency and awareness were no longer significantly associated with QoL once psychological factors were considered.

Conclusions: Hypoglycaemia negatively impacts on several QoL domains. Psychological factors supersede the effect of hypoglycaemia frequency and awareness in accounting for this negative impact.

Keywords: Hypoglycaemia, quality of life, T1DM, well-being, fear of hypoglycaemia, psychological functioning

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Hypoglycaemia remains the main side effect of intensive insulin therapy and a major concern for adults with type 1 diabetes (T1DM), despite the use of advanced insulin treatment and glucose monitoring methods (1). Past exposure to hypoglycaemia and fear of future episodes are associated with several adverse outcomes, including impaired emotional well-being, sleep quality, work productivity, and driving freedom (2-4). Thus, hypoglycaemia can impair an individual's quality of life (QoL) (5). While some studies have shown large negative impacts of hypoglycaemia on QoL and related outcomes (6, 7), other studies have found no significant association (8, 9). A systematic review reports that conclusions differ depending on the aspect of hypoglycaemia (e.g., frequency, severity, timing, and context) and outcome(s) assessed (10). Past research has focused almost exclusively on psychological outcomes and largely ignored other domains of QoL (10, 11). Little is known about which QoL domains are affected most negatively by hypoglycaemia. Most studies have focused on the impact of severe hypoglycaemia, with less known about self-treated hypoglycaemia, which occurs more frequently and affects virtually everyone with T1DM (10). In addition, few studies have investigated the impact of impaired awareness of hypoglycaemia (IAH), which affects approximately 25% of adults with T1DM (12). Further research is needed to examine how QoL is affected by aspects of hypoglycaemia beyond severe episodes.

Until recently, no validated measure assessing the impact of hypoglycaemia on QoL domains existed. Moreover, it has been argued that past research on hypoglycaemia and QoL has been limited by the suitability and interpretation of certain person-reported outcome measures (PROMs) in assessing the impact on QoL (13). For example, generic PROMs more accurately measure health status and treatment satisfaction, rather than general QoL (13). While these outcomes can potentially influence QoL, they do not comprehensively assess QoL and do not ask about the impact of hypoglycaemia (10). This may indicate that PROMs are not comprehensive enough to fully capture the impact of hypoglycaemia on QoL, which could explain mixed evidence

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reported in previous studies. A COSMIN review shows that existing PROMs lack evidence to support content validity in assessing the impact of hypoglycaemia on QoL and that new instruments are needed to assess this impact (14, 15).

Therefore, the aim of this study was to address knowledge gaps using a novel measure that assesses the impact of hypoglycaemia on QoL among adults with T1DM. Specific research questions were: 1) How do experiences with and worries about hypoglycaemia impact on QoL domains? 2) Does the impact of hypoglycaemia on QoL differ by hypoglycaemia frequency, severity, and awareness? 3) What is the association between hypoglycaemia-specific QoL and hypoglycaemia frequency, severity, awareness, fear, and confidence? 4) Which variables are most strongly associated with hypoglycaemia-specific QoL?

Methods

Design

The "*YourSAY (Self-management And You): Hypoglycaemia"* Study is a cross-sectional, multi-country, web-based survey investigating the impact of hypoglycaemia on QoL among people with T1DM or type 2 diabetes and partners of people with diabetes, conducted within the Hypo-RESOLVE Project (www.hypo-resolve.eu) (16). The data reported here focuses on adults with T1DM only. Ethics approval was granted by the University of Southern Denmark's Research Ethics Committee (#21/8758).

Participants & Recruitment

Eligible participants were adults (18+ years) with T1DM for at least 6 months who were able to complete the survey in English. Participants were recruited between 1st May and 1st

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August 2021 via social media (including Facebook, Twitter, Instagram, diabetes blogs, and online articles) and e-newsletters distributed by diabetes organizations (e.g., Diabetes UK and diaTribe).

Measures

The survey consisted of several PROMs (described below) and 18 questions assessing self-reported demographic and clinical information.

Hypoglycaemia awareness, frequency, and severity. The Gold score (17) was administered to categorize participants by hypoglycaemia awareness status, where scores of ≥4 indicate IAH and scores of ≤3 indicate intact awareness. The Hypoglycaemia Awareness Questionnaire (HypoA-Q) assesses hypoglycaemia frequency, severity, and awareness. Respondents indicate how often they have experienced hypoglycaemia of any severity in the past week, and the frequency of self-treated and severe hypoglycaemia while awake and while asleep in the past year. The 5-item *"Impaired Awareness"* (IA) subscale of the HypoA-Q assesses the extent to which individuals experience problems detecting symptoms of hypoglycaemia on a 5-point Likert-type scale. Item scores on the IA subscale are summed, with higher scores indicating greater IAH.

Hypoglycaemia-specific QoL. The 12-item Hypoglycaemia Impact Profile (HIP12) (18) assesses the impact of experiences with and worries about hypoglycaemia on 12 domains of QoL, including physical health, financial situation, relationships, leisure activities, work/studies, emotional well-being, dietary freedom, sleep, sex life, independence, and the ability to be spontaneous and keep fit/be active. Respondents rate the impact of hypoglycaemia on domains on a 7-point scale, from 1 (*Very positive impact*) to 7 (*Very negative impact*). Alternatively, participants can select "not applicable". Item scores are averaged to produce a composite score, with higher scores indicating a greater negative impact of hypoglycaemia. Psychometric validation

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demonstrates that the HIP-12 is an acceptable, internally consistent, and valid measure of the impact of hypoglycaemia on QoL among adults with T1DM (18).

Fear of hypoglycaemia. The 6-item "Worry" subscale of the Hypoglycaemia Fear Survey-Short Form (HFS-SF) (19) assesses fear of hypoglycaemia over the past six months. Respondents indicate how frequently they have worried about aspects of hypoglycaemia (e.g., passing out in public) on a 5-point scale, from 0 (*Never)* to 4 (*Almost always)*. Item scores are summed, with higher scores indicating higher fear of hypoglycaemia.

Confidence in managing hypoglycaemia. The 9-item Hypoglycaemia Confidence Scale (HCS) (20) assesses the degree to which individuals feel confident in their ability to manage hypoglycaemia in various situations (e.g., when alone and in social situations). Respondents rate their confidence on a 4-point scale, from 1 (*Not confident at all)* to 4 (*Very confident)*. Item scores are averaged, with scores ≥3 indicating at least moderate confidence (20).

Diabetes-specific emotional distress. The 5-item "Emotional Burden" subscale of the Diabetes Distress Scale (DDS) (21) assesses the perceived burden of diabetes (e.g., feeling overwhelmed by the demands of diabetes) over the past month. Respondents rate the extent to which diabetes-related concerns have been a problem for them on a 6-point scale, from 1 *(Not a problem)* to 6 *(A very serious problem)*. Item scores are averaged, with scores 2.0-2.9 and ≥3 indicating moderate and high distress, respectively (22).

Generic emotional well-being. The 5-item World Health Organisation-Five Well-being Index (WHO-5) (23) assesses generic emotional well-being over the past two weeks. Respondents indicate how often they have experienced emotional states (e.g., "calm and relaxed"). Items are scored on a 6-point scale, from 0 (*At no time*) to 5 (*All the time)*. Item scores are summed, with higher scores indicating better general emotional well-being and scores <13 indicating likely depression (24).

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Demographic and clinical information. Questions were related to age, gender, country of residence, birth country, native language, education level, employment status, financial status, living situation, comorbid diagnoses, age at diabetes onset, diabetes duration, treatment regimen, main glucose monitoring method, glucose checking frequency, and most recent HbA_{1c}.

Procedure

The survey was hosted via Qualtrics (Provo, Utah, USA) and accessible via computer, smartphone, or tablet. After responding to eligibility questions, participants reviewed an information sheet, provided informed consent, and proceeded to the survey. With the exception of eligibility questions, participants could skip any items they did not wish to answer.

Statistical Analyses

G*Power Version 3.1.9.7 (25) was used to perform a priori power analysis. A minimum sample of *N*=139 was required to detect medium-sized effects ($f^2 = 0.15$; $\alpha = 0.50$) between 15 explanatory variables and the primary outcome (i.e., hypoglycaemia-specific QoL), with a power of 0.80. We recruited beyond this minimum target to maximize sample diversity and allow for additional subgroup analyses.

Analyses were conducted in SPSS Version 28.0. Demographic, clinical and HIP12 variables were examined using descriptive statistics. Internal consistency was satisfactory (α=0.85-0.94) for all PROMs. Mann-Whitney U tests compared HIP12 scores between participants who: 1) had experienced severe hypoglycaemia while awake in the past year versus those who had not; 2) had experienced severe hypoglycaemia while asleep in the past year versus those who had not; 3) had experienced ≥1 episode of self-treated hypoglycaemia per week versus participants who had experienced less than weekly episodes; and 4) had impaired versus intact hypoglycaemia

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awareness. Rank biserial correlation coefficients determined the magnitude of effects, where r=0.1, r=0.3, and r=0.5 indicated small, medium, and large effects, respectively (26). One-way ANOVAs were performed to compare HIP12 scores between glucose monitoring methods (continuous glucose monitoring [CGM], intermittently-scanned/flash glucose monitoring, and self-monitoring of blood glucose [SMBG]).

A four-step hierarchical linear regression examined associations between HIP12 scores and hypoglycaemia awareness, frequency/severity, fear, and confidence. Bivariate correlations examined multicollinearity (r>0.8) between variables. Variables were entered stepwise as follows: 1) demographic variables (age, gender, education, and financial status) and clinical variables (diabetes duration, treatment regimen, monitoring method, number of diabetes complications, and depression/anxiety); 2) hypoglycaemia awareness (HypoA-Q IA) and frequency variables (episodes of any severity in the past week and severe episodes in the past year); 3) generic emotional well-being (WHO-5) and diabetes distress (DDS); 4) fear of hypoglycaemia (HFS-SF) and confidence in managing hypoglycaemia (HCS). Variables uniquely accounting for the largest proportion of the variance in hypoglycaemia-specific QoL were identified by comparing squared semi-partial correlations.

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Results

Of the 1,305 adults with T1DM who gave consent, 81% (n=1,057) reached the end of the survey. Twenty-two records were excluded due to ≥7 items missing on the HIP12 (18) and/or missing data on the HypoA-Q. Seven records were excluded from analyses due to concerns with response validity including inconsistent responses to HypoA-Q questions about hypoglycaemia frequency (see Appendix 1). Participants were 1,028 adults with T1DM, with 35% recruited via

diabetes organization e-newsletters, 25% via Facebook, and 11% via Twitter. Table 1 presents characteristics of the participants. Forty-four percent were using multiple daily injections (MDI), 40% an insulin pump, and 16% artificial pancreas/closed-loop systems (CLS). Approximately half (49%) were using CGM (including CLS users). One-third (33%) self-reported impaired awareness of hypoglycaemia (Gold score ≥4) and 22% had experienced at least one episode of severe hypoglycaemia (i.e., needed help/were unable to treat themselves) in the past year. Forty-two percent had a WHO-5 score <13, indicating likely depression, and 43% reported high diabetes distress (DDS score ≥3). Mean HCS scores indicated moderate confidence in managing hypoglycaemia.

Table 1. Sample Demographic and Clinical Characteristics.

Demographic Characteristics	
Age, years	47±15 (18-86)
Gender	
Female	71% (729)
Male	28% (285)
Non-binary	1% (10)
Other/Prefer not to say	0.4% (4)
Native language	
English	86% (882)
Other	14% (146)
Country of residence	
United States of America	31% (319)
United Kingdom	30% (305)

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Australia	10% (103)
Republic of Ireland	7% (75)
Canada	6% (63)
Other	16% (163)
Employment status[a]	
Full-time employment	48% (490)
Retired	19% (192)
Part-time employment	16% (160)
Student	8% (84)
Home duties	8% (77)
Not working but not retired	7% (70)
Other	7% (71)
Financial difficulties in the past year[b]	20% (202)
Living situation[a]	
With partner/spouse	67% (685)
With child(ren)	30% (303)
With others	20% (204)
Alone	16% (166)
Highest level of education	
Secondary education or lower	11% (114)
Post-secondary vocational education	13% (136)
University (Bachelor's level) education	39% (405)
Postgraduate (Master's or PhD level) education	32% (324)
Other	2% (22)

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Clinical Characteristics	
Age of T1DM onset, years	16 [9-30]
T1DM duration, years	25 [14-39]
Primary diabetes management regimen	
Multiple daily injections	44% (447)
Insulin pump	40% (409)
Artificial pancreas/closed-loop systems (CLS)	16% (166)
Main glucose monitoring method	
Continuous glucose monitoring (including participants using CLS)	49% (507)
Intermittently-scanned/flash glucose monitoring	33% (336)
Finger-prick self-monitoring of blood glucose	18% (183)
Most recent HbA_{1c}, self-reported	
mmol/mol	51 [44-57]
%	6.8 [6.2-7.4]
≤58 mmol/mol (7.5%)	71% (734)
Hypoglycaemia awareness status	
HypoA-Q Impaired Awareness subscale	9±4 (1-18)
Gold score	3±2 (1-7)
Impaired awareness (Gold score ≥4)	33% (342)
Hypoglycaemia frequency	
Number of episodes of any severity in the past week	3 [2-5]
Severe hypoglycaemia (needing help from others) in past year (≥1 event)	22% (223)
Diabetes complications[a]	36% (368)

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Retinopathy	21% (211)
Neuropathy	13% (136)
Sexual dysfunction	11% (108)
Nephropathy	6% (66)
Cardiovascular disease	5% (48)
Number of diabetes complications	0 [0-1]
None	64% (660)
1-2	31% (320)
3+	5% (48)
Other comorbidities[a]	66% (681)
Anxiety	29% (293)
Depression	22% (223)
Chronic pain	13% (129)
Gastroparesis	6% (66)
Sleep apnea	6% (60)
Celiac disease	5% (53)
Other	7% (74)
Psychological Characteristics	
Fear of hypoglycaemia: HFS-SF[c]	9.4±5.0 (0-24)
Confidence in managing hypoglycaemia: HCS[d]	3.0±0.7 (1-4)
Diabetes distress: DDS[e]	3.0±1.4 (1-6)
High diabetes distress (DDS score ≥3.0)	43% (440)
Generic emotional well-being: WHO-5[f]	52±21 (0-100)
Likely depression (WHO-5 score <13)	42% (431)

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Reported as M±SD (Range), Mdn [IQR], % (*n*). *n's* do not always sum to 100% due to missing data. [a]Participants could select more than one response option. [b]Financial difficulties defined as not being able to pay for things on time (e.g., rent/mortgage, bills), not being able to buy important things (e.g., food, clothing), or not being able to afford services (e.g., healthcare). [c]Scores can range from 0-24, where higher scores reflect higher fear. [d]Scores ≥3 reflect moderate confidence. [e]Scores 2.0-2.9 reflect moderate distress and scores >3.0 reflect high distress. [f]Scores <50 indicate likely depression.

Impact of Hypoglycaemia on QoL

The mean composite score indicates that, on average, participants reported a *"slightly negative impact"* of hypoglycaemia on overall QoL (Table 2). Figure 1 shows that, for 9 of the 12 QoL domains, the most common response was a *"slightly negative impact"* of hypoglycaemia (i.e., on leisure activities, physical health, ability to keep fit/be active, sleep, emotional well-being, spontaneity, independence, work/studies, and dietary freedom). For the remaining 3 domains (i.e., financial situation, relationships, and sex life), the most common response was *"no impact"* of hypoglycaemia. The QoL domain most frequently rated as negatively impacted by hypoglycaemia was sleep (84%), and the domain least frequently rated as negatively impacted was financial situation (24%) (see Appendix 2). The QoL domain most frequently rated as positively impacted by hypoglycaemia was dietary freedom (8%), and the domain least frequently rated as positively impacted was financial situation (1%).

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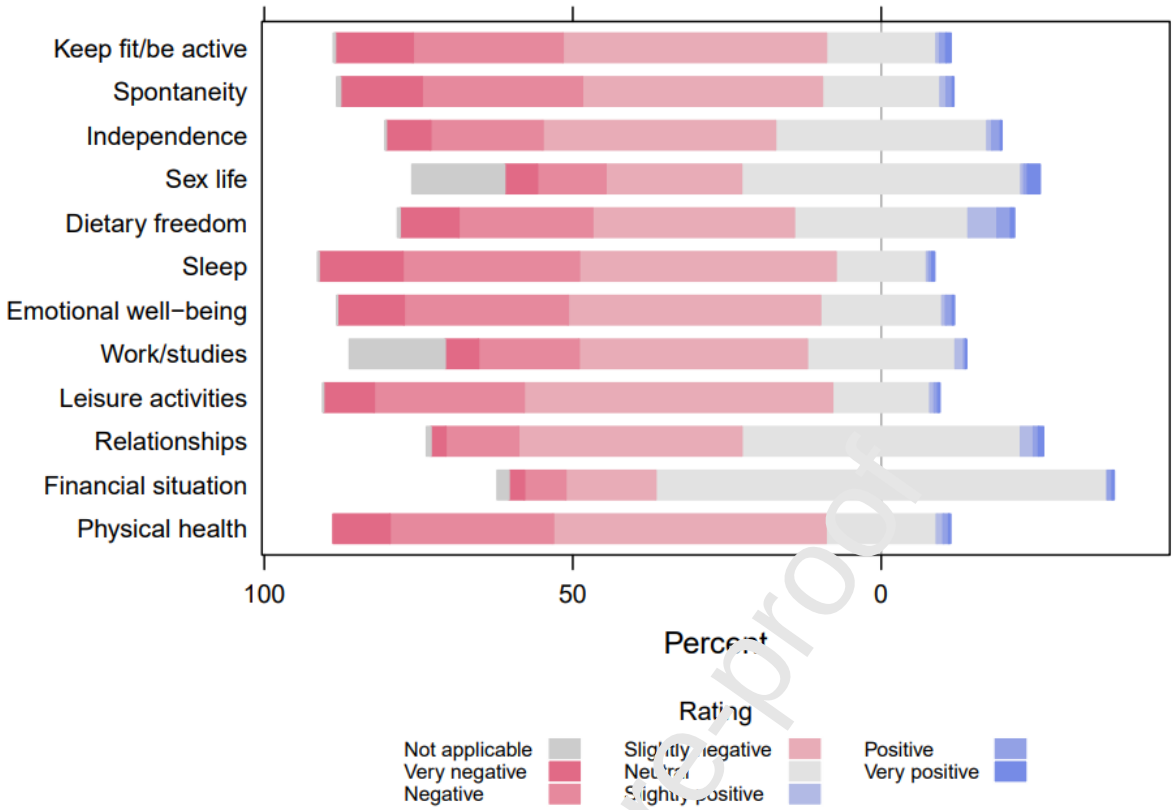

Figure 1. Impact of hypoglycaemia on QoL domains (HIP-12 scores).

Impact of Hypoglycaemia on QoL by Hypoglycaemia Awareness, Frequency, and Severity

Overall hypoglycemia-specific QoL. Table 2 presents mean HIP12 scores by hypoglycaemia awareness, frequency, and severity. Participants with IAH reported a significantly greater negative impact of hypoglycaemia on their overall QoL, compared to participants with intact awareness. Similar trends were observed for participants who experienced ≥1 episode of severe hypoglycaemia in the past year and participants who experienced ≥1 episode of self-treated hypoglycaemia per week. Effect sizes were small, with the largest observed for differences in hypoglycaemia-specific QoL between participants with IAH versus intact awareness (r=0.213).

Hypoglycaemia awareness. Across all QoL domains, participants with IAH reported a significantly greater negative impact of hypoglycaemia than participants with intact awareness.

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The largest between-group differences were for the impact on independence (r=0.236), followed by physical health (r=0.191) and relationships (r=0.164).

Severe hypoglycaemia while awake. Participants who had experienced severe hypoglycaemia while awake reported a significantly greater negative impact of hypoglycaemia on 10 of the 12 QoL domains than participants who had not. However, effects sizes are small. The largest between-group differences were for the impact on financial situation (r=0.177), followed by independence (r=0.166) and relationships (r=0.155). There were no between-group differences in dietary freedom or spontaneity.

Severe hypoglycaemia while asleep. Participants who had experienced severe hypoglycaemia while asleep reported a significantly greater negative impact of hypoglycaemia on 9 of the 12 QoL domains than participants who had not, but with small effects sizes. The largest between-group differences were for the impact on financial situation (r=0.180), followed by sleep (r=0.148) and relationships (r=0.136). There were no between-group differences in dietary freedom, spontaneity, or ability to keep fit/be active.

Self-treated hypoglycaemia. Participants who had experienced ≥1 episode of self-treated hypoglycaemia per week reported a significantly greater negative impact of hypoglycaemia on 10 of the 12 QoL domains than participants who experienced less than weekly self-treated hypoglycaemia, albeit with small effect sizes. The largest between-group differences were for the impact on spontaneity (r=0.198), followed by ability to keep fit/be active (r=0.144) and leisure activities (r=0.132). There were no between-group differences in financial situation or sex life.

Glucose monitoring method. CGM users reported a significantly greater negative impact of hypoglycaemia on their ability to keep/fit be active compared to flash glucose monitoring users (see Appendix 3). There were statistically significant differences in the impact of hypoglycaemia on sleep and spontaneity between monitoring methods, though post-hoc

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comparisons did not show any significant comparisons. There were no further differences in hypoglycaemia-specific QoL between glucose monitoring methods.

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Table 2. Impact of hypoglycaemia on QoL (HIP12 scores) by hypoglycaemia awareness, frequency, and severity.

Impact of hypoglycaemia on…	Total Sample (*N*=1,028)	**Hypoglycaemia awareness status (Gold scores)**			**Severe hypoglycaemia *while awake* in past year (HypoA-Q Item 4b)**			**Severe hypoglycaemia *while asleep* in past year (HypoA-Q Item 16a)**			**Self-treated hypoglycaemia in past year (HypoA-Q Item 4a)**		
		Intact (*n*=678)	Impaired (*n*=342)	Effect size	0 episodes (*n*=807)	≥1 episode (*n*=219)	Effect size	0 episodes (*n*=829)	≥1 episode (*n*=191)	Effect size	Less than weekly (*n*=294)	≥1 episode per week (*n*=734)	Effect size
Overall QoL (composite score)	5.01±0.69	4.91±0.63	5.18±0.75	.213***	4.95±0.65	5.19±0.78	.149***	4.96±0.64	5.19±0.83	.138***	4.84±0.73	5.07±0.66	.160***
Physical health	5.21±0.97	5.09±0.96	5.44±0.94	.191***	5.15±0.95	5.44±1.02	.129**	5.15±0.94	5.46±1.03	.134***	5.10±0.99	5.25±0.96	.081**
Financial situation	4.34±0.77	4.26±0.66	4.49±0.93	.131***	4.27±0.71	4.59±0.91	.177**	4.26±0.68	4.64±1.03	.180***	4.29±0.80	4.36±0.76	.042
Relationships	4.61±0.90	4.53±0.81	4.78±1.02	.164***	4.55±0.85	4.84±1.03	.155***	4.56±0.81	4.85±1.18	.136***	4.50±0.96	4.66±0.87	.083**
Leisure activities	5.21±0.90	5.15±0.85	5.32±0.98	.100**	5.16±0.87	5.37±1.00	.091**	5.18±0.87	5.32±1.03	.069*	5.01±0.94	5.28±0.87	.132***
Work/studies	4.99±0.92	4.93±0.89	5.13±0.97	.103**	4.95±0.89	5.12±1.00	.084*	4.95±0.89	5.19±0.99	.107**	4.82±0.91	5.05±0.92	.115***
Emotional well-being	5.23±1.01	5.14±0.96	5.39±1.07	.130***	5.17±0.98	5.46±1.08	.123***	5.17±0.94	5.45±1.21	.126***	5.06±1.07	5.30±0.97	.108***
Sleep	5.37±0.98	5.27±0.92	5.57±1.07	.158***	5.32±0.95	5.56±1.07	.113***	5.31±0.92	5.62±1.17	.148***	5.19±1.07	5.45±0.94	.113***
Dietary freedom	4.94±1.17	4.83±1.13	5.15±1.19	.138***	4.92±1.14	5.02±1.26	.038	4.94±1.12	4.97±1.32	.026	4.75±1.15	5.02±1.17	.110***
Sex life	4.68±0.97	4.60±0.91	4.85±1.03	.124***	4.63±0.91	4.83±1.10	.090**	4.63±0.92	4.88±1.09	.093**	4.58±0.99	4.72±0.95	.065
Independence	4.92±1.00	4.75±0.91	5.24±1.03	.236***	4.83±0.94	5.24±1.14	.166***	4.85±0.94	5.20±1.16	.126***	4.76±0.99	4.93±0.99	.100**
Ability to be spontaneous	5.28±1.03	5.19±1.00	5.47±1.07	.128***	5.25±1.01	5.38±1.11	.059	5.26±1.00	5.38±1.16	.051	4.96±1.06	5.41±1.00	.198***
Ability to keep fit/be active	5.25±1.05	5.19±1.01	5.36±1.11	.086**	5.21±1.02	5.37±1.16	.075*	5.24±1.02	5.28±1.15	.025	5.01±1.01	5.34±1.05	.144***

***p<.001 **p<.01 *p<.05. Data are reported as M±SD. Scores range from 1 (*Very positive impact*) to 7 (*Very negative impact*), with higher scores reflecting greater negative impact of hypoglycaemia on QoL.

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Associations with Hypoglycaemia-Specific QoL

Bivariate correlations indicated no multicollinearity between variables (see Appendix 4). There were significant (albeit small) univariate associations between hypoglycaemia-specific QoL and frequency of severe hypoglycaemia in the past year (r=.169, p<.001), frequency of any hypoglycaemia in the past week (r=.221, p<.001), and HypoA-Q IA scores (r=.237, p<.001). Univariate associations between hypoglycaemia-specific QoL and psychological variables were all moderate to strong (r=.443-.595, p<.001). Table 3 shows that all steps of the regression contributed significantly to the model. Demographic and clinical variables (step 1) accounted for 10.4% of the variance in hypoglycaemia-specific QoL. Hypoglycaemia frequency and awareness (step 2) explained an additional 5.4% of the variance. More frequent hypoglycaemia (including any hypoglycaemia in the past week and severe hypoglycaemia in the past year) and greater IAH were significantly associated with greater impairment of hypoglycaemia-specific QoL. Generic emotional well-being and diabetes distress (step 3) explained an additional 23.6% of the variance.

In the final step, fear of hypoglycaemia and confidence in managing hypoglycaemia explained an additional 3.2% of the variance. Overall, the final model accounted for 42.5% of the variance in hypoglycaemia-specific QoL, with six variables remaining significant. Greater negative impact of hypoglycaemia on QoL was associated with having university level education (<1%), using CGM (<1%), and reporting lower generic emotional well-being (2%), greater diabetes distress (5%) and fear of hypoglycaemia (1%), and lower confidence in managing hypoglycaemia (1%). Hypoglycaemia awareness and frequency were not significantly associated with hypoglycaemia-specific QoL in the final model.

Table 3. Variance in hypoglycaemia-specific QoL explained by demographic, clinical, and psychological variables (four-step hierarchical linear regression).

	Model 1			Model 2			Model 3			Model 4		
	β	*t*	*p*	β	*t*	*p*	β	*t*	*p*	β	*t*	*p*
Step 1: F (8, 980) = 14.16, p < .001, R^2 = .104												
Age, years	**-.075**	**-2.02**	**.044**	**-.076**	**-2.10**	**.036**	**.06(**	**2.11**	**.035**	.060	1.91	.057
Gender: Female	**.082**	**2.67**	**.008**	**.062**	**2.08**	**00.**	.019	0.74	.457	.007	0.27	.791
Education: University	.028	0.89	.372	.024	0.78	.435	**.056**	**2.15**	**.032**	**.058**	**2.28**	**.023**
Financial hardship: Yes	**.120**	**3.74**	**<.001**	**.0[illegible]1**	**2.90**	**.004**	.015	0.57	.567	-.004	-0.14	.889
Diabetes duration, years	-.038	-1.01	.313	-.061	-1.65	.099	-.030	-0.96	.377	-.009	-0.30	.764
Monitoring method: CGM	**.065**	**2.11**	.035	.032	1.04	.298	**.074**	**2.83**	**.005**	**.084**	**3.30**	**.001**
Number of diabetes complications	**.102**	**3.04**	**.002**	**.068**	**2.07**	**.039**	.013	0.47	.636	.014	0.53	.599
Depression and/or anxiety: Yes	**.107**	**6.19**	**<.001**	**.187**	**6.06**	**<.001**	-.008	-0.27	.786	-.010	-0.37	.710
Step 2: F (11, 977) = 16.59, p < .001, R^2 = .15[illegible] R^2_{change} = .054												
Frequency of any hypoglycaemia past week				**.114**	**3.81**	**<.001**	.046	1.81	.071	.031	1.22	.223
Frequency of severe hypoglycaemia past year				**.093**	**3.11**	**.002**	**.057**	**2.23**	**.026**	.030	1.17	.241
HypoA-Q Impaired Awareness				**.166**	**5.27**	**<.001**	**.102**	**3.79**	**<.001**	.034	1.24	.216
Step 3: F (13, 975) = 48.65, p < .001, R^2 = .393, R^2_{change} = .236												
Generic emotional well-being (WHO-5)							**-.225**	**-7.08**	**<.001**	**-.189**	**-6.04**	**<.001**

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Diabetes distress (DDS)							**.438**	**13.68**	**<.001**	**.326**	**9.34**	**<.001**
Step 4: F (15, 973) = 48.01, p < .001, R^2 = .425, R^2_{change} = .032												
Fear of hypoglycaemia (HFS-SF)										**.145**	**3.84**	**<.001**
Confidence in managing hypoglycaemia (HCS)										**-.131**	**-3.62**	**<.001**

CGM: Continuous glucose monitoring. DDS: Diabetes Distress Scale. HCS: Hypoglycaemia Confidence Scale. HFS-SF: Hypoglycaemia Fear Survey–Short Form. MDI: Multiple daily injections. Significant associations are in bold

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Discussion

This multi-country cross-sectional study examined the impact of hypoglycaemia on QoL among adults with T1DM, using a comprehensive approach involving a novel and validated measure of hypoglycaemia-specific QoL. Whereas past research has focused on the impact of hypoglycaemia on psychological outcomes (10), this study provides a broad assessment of the impact across multiple QoL domains and presents new evidence regarding the independent impact of hypoglycaemia awareness, frequency, severity, fear, and confidence. This study found that hypoglycaemia negatively impacts on overall QoL and most QoL domains, including leisure activities, physical health, ability to keep fit/be active, sleep, emotional well-being, spontaneity, independence, work/studies, and dietary freedom. This is consistent with qualitative research demonstrating the multi-faceted impact of hypoglycaemia on several QoL domains (5, 27). This study highlights domains that are most negatively affected by hypoglycaemia, including sleep, where four out of five adults with T1DM reported a negative impact.

Consistent with previous studies (6, 28), participants who experienced severe hypoglycaemia in the past year reported a greater negative impact of hypoglycaemia on overall QoL and several QoL domains. Moreover, this study addressed gaps in the current evidence relating to the impact of IAH and self-treated hypoglycaemia. Past research has examined relationships between IAH and fear of hypoglycaemia (29, 30), whereas little was known about the impact of IAH on other aspects of QoL and overall QoL. The current study revealed that participants with IAH reported a greater negative impact of hypoglycaemia on all QoL domains compared to participants with intact awareness. For seven of the 12 domains, effect sizes were larger (albeit small) for comparisons between hypoglycaemia awareness groups compared to effect sizes for comparisons between hypoglycaemia frequency/severity groups. Given that 66% of participants

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with IAH had not experienced severe hypoglycaemia in the past year, this finding suggests that IAH has an impact on QoL beyond the experience of hypoglycaemia.

Participants who experienced weekly self-treated hypoglycaemia reported a greater negative impact of hypoglycaemia on overall QoL and on 10 of the 12 QoL domains, compared to participants experiencing less frequent self-treated hypoglycaemia. While past research has shown that sleep, physical activity, and work can be negatively impacted by self-treated hypoglycaemia (31, 32), the current study suggests that this impact extends to relationships, emotional well-being, dietary freedom, independence, spontaneity, and ability to keep fit/be active. Even among participants with less frequent self-treated hypoglycaemia, mean HIP-12 scores were within the negative range for several QoL domains, which indicates that QoL can be impaired even among individuals who experience self-treated episodes less frequently. The results provide additional insights into how certain QoL domains are impacted by various aspects of hypoglycaemia, including financial situation being most impaired by severe episodes, spontaneity most impaired by self-treated episodes, and independence most impaired by IAH. However, all effect sizes were small (r=.069-.236).

The regression models advance our understanding of how various aspects of hypoglycaemia are related to QoL. Hypoglycaemia awareness and frequency were significantly associated with hypoglycaemia-specific QoL, though explained a relatively small amount of the variance in QoL after accounting for demographic, clinical, and psychological factors. Diabetes distress uniquely accounted for the largest proportion of variance in hypoglycaemia-specific QoL, followed by generic emotional well-being, fear of hypoglycaemia, and confidence in managing hypoglycaemia. This finding suggests that variance in the impact of hypoglycaemia on QoL is better explained by how an individual feels about and perceives hypoglycaemia than by the frequency of hypoglycaemia or magnitude of hypoglycaemia awareness. The negligible impact of

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hypoglycaemia frequency and awareness on hypoglycaemia-specific QoL is consistent with past research showing that some adults with T1DM report high fear of hypoglycaemia despite no recent history of severe hypoglycaemia (33). Furthermore, this finding indicates that hypoglycaemia frequency is not a suitable proxy for the impact of hypoglycaemia on QoL. Interestingly, CGM use was associated with impaired hypoglycaemia-specific QoL, which could be explained by the impact of CGM alarms, distress caused by having access to real-time glucose data, and history of problematic hypoglycaemia warranting CGM as an intervention (34).

A strength of this study was the large and geographically diverse sample. This study provides a broad assessment of QoL and examines the independent effects of hypoglycaemia awareness, frequency, and severity. This study involved development and validation of the HIP12, a measure that enabled us to examine how experiences with/worries about hypoglycaemia impacts on QoL domains, which led to several novel findings summarized above. Nevertheless, this study has some limitations. As with any survey, the results could have been affected by recruitment and self-selection bias. The survey was advertised as a study focused on the impact of hypoglycaemia; thus, there was likely an over-representation of participants concerned with hypoglycaemia. However, rates of IAH were typical of people attending specialist diabetes clinics (35) and rates of severe hypoglycaemia were lower than in a previous population study (36). It is notable that there was a high use of technology in this sample, which may have been prescribed due to concerns about hypoglycaemia and/or IAH. Previous studies have shown that CLS and CGM use is associated with improved glycaemia and QoL (37, 38), which may have ameliorated the impact of hypoglycaemia on QoL. Finally, HbA_{1c} was lower, depression and anxiety rates were higher, and there were larger proportions of women and people with university-level education, compared to past research (39-42).

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While an online survey made it possible to recruit participants from 28 countries, this method may have minimized access to the views of adults with T1DM from deprived communities and ethnic minorities. Participants were largely native English speakers from high-income countries, which was expected given that the study was advertised specifically in these countries and the survey was available only in English. Further research is needed to investigate the impact of hypoglycaemia among socioeconomically and culturally diverse populations using validated translations of the HIP12. This study relied on self-report of hypoglycaemia frequency which is known to be affected by recall bias (43), though this is a valid reflection of the individual's experience of hypoglycaemia. Response validity checks revealed that a few participants likely interpreted items of the HypoA-Q differently. Future studies should combine self-report of hypoglycaemia frequency with CGM-derived data, where possible. Nonetheless, each method contributes uniquely to our understanding of the impact of hypoglycaemia.

The findings of this study have several clinical implications. It is notable that both self-treated hypoglycaemia and IAH, and not just severe hypoglycaemia, had a negative impact on several QoL domains. Therefore, it is important that clinicians and educators pay attention to all facets of the experience of hypoglycaemia in adults with T1DM. Clinical priority should be to reduce the incidence of self treated events and restore awareness, and not just to avoid severe hypoglycaemia. Psychological factors were most strongly associated with hypoglycaemia-specific QoL, which indicates that asking adults with T1DM about the incidence of hypoglycaemia is no substitute for asking people how much it bothers them and how it is affecting their QoL. Some adults with T1DM could benefit from educational and psychological strategies to target perceptions of hypoglycaemia (e.g., perceived controllability) and reduce the impact of hypoglycaemia on QoL. While this study provides novel insights into cross-sectional associations between hypoglycaemia and QoL, prospective assessment could lend further insight into temporal relationships between

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variables, including whether fear of hypoglycaemia and/or confidence in managing hypoglycaemia mediate the associations between hypoglycaemia frequency and QoL. This investigation could elucidate which intervention approaches are most effective for reducing the impact of hypoglycaemia.

In conclusion, this study provides several novel insights that contribute to a more nuanced and comprehensive understanding of the impact of hypoglycaemia on QoL among adults with T1DM. These findings demonstrate that hypoglycaemia impacts negatively on several QoL domains, with sleep the most negatively affected domain, as well as on overall QoL. Participants who had experienced severe hypoglycaemia, more frequent self-treated hypoglycaemia, and IAH, reported a greater negative impact of hypoglycaemia on QoL. Severe hypoglycaemia most negatively affected financial situation, whereas self-treated hypoglycaemia most negatively affected spontaneity, and IAH most negatively affected independence. Psychological factors are most strongly associated with hypoglycaemia-specific QoL, which suggests that some adults with T1DM could benefit from educational and psychological strategies to preserve QoL. Experiences with and worries about hypoglycaemia need to be addressed in clinical care to reduce the impact of hypoglycaemia on QoL among adults with T1DM.

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Highlights

- Hypoglycaemia can affect several domains of quality of life
- Quality of life is worse among those experiencing more frequent/severe hypoglycaemia
- Psychological factors explain most of the variance in the impact of hypoglycaemia
- Clinicians should ask about experiences with and worries about hypoglycaemia

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