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Systematic Review or Meta-analysis

Impact of severe hypoglycaemia on psychological outcomes in adults with Type 2 diabetes: a systematic review

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What's new?

- This is the first systematic review examining the psychological impact of severe hypoglycaemia in adults with Type 2 diabetes.
- For the most part, severe hypoglycaemia is associated with greater fear of hypoglycaemia, impaired general emotional well-being and health status, and greater impairment of diabetes-specific quality of life.

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- The psychological impact of severe hypoglycaemia is not exclusive to those managing their diabetes with insulin.
- Health professionals need to actively assess and address the frequency and psychological impact of severe hypoglycaemia, minimize risk of exposure to severe hypoglycaemia, and provide support to the individual to deal with the psychological consequences.

Abstract

Aim Hypoglycaemia affects many people with Type 2 diabetes using insulin and other glucose-lowering therapies. This systematic review examined the impact of severe hypoglycaemia (episodes requiring external assistance) on psychological outcomes (e.g. emotional well-being, health status and quality of life) in adults with Type 2 diabetes.

Methods MEDLINE Complete, PsycINFO and CINAHL databases were searched for peer-reviewed empirical studies, published in English, reporting the occurrence and severity of hypoglycaemia and its relationship with patient-reported outcomes (PROs) in adults with Type 2 diabetes. Data were extracted from published reports and analysed.

Results Of 3756 potentially relevant abstracts, 29 studies met the inclusion criteria. Most reported cross-sectional data and sample sizes varied widely ($N = 71$ to 17 563). Although definitions of mild and severe hypoglycaemia were largely consistent between studies, additional non-standard categorizations (e.g. moderate, very severe) were apparent and recall periods varied. Overall, severe hypoglycaemia was associated with increased fear of hypoglycaemia and decreased emotional well-being, health status and diabetes-specific quality of life. Effect sizes show that the association with fear of hypoglycaemia was stronger than with general health status.

Conclusions Notwithstanding the limitations of the empirical studies, these findings indicate that severe hypoglycaemia in adults with Type 2 diabetes (insulin- and non-insulin-treated) is associated with impaired psychological outcomes. Healthcare professionals should address the psychological impact of severe hypoglycaemia during clinical consultations, to support individuals to minimize exposure to, and the psychological consequences of, severe hypoglycaemia.

<H1>Introduction

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Despite major advances in diabetes management in recent decades, hypoglycaemia remains a common and much feared side-effect of therapy that affects everyday life. Although more prevalent in Type 1 diabetes, hypoglycaemia also affects many people with insulin-treated Type 2 diabetes and those taking oral insulin secretagogues.

In adults with Type 2 diabetes, a recent meta-analysis reported a prevalence of self-treated hypoglycaemia of 45%, and 6% experiencing severe hypoglycaemia (i.e. any event requiring external assistance), with the highest prevalence occurring in those using insulin therapy [1]. Prevalence increases with duration of insulin therapy and eventually resembles rates observed in people with Type 1 diabetes [2,3]. Increasing duration of Type 2 diabetes is associated with progressive β -cell failure, necessitating initiation followed by intensification of therapy to maintain blood glucose within a target range. Hypoglycaemia remains a significant barrier to achieving and maintaining optimal glycaemic control. Self-adjustment of medication (principally reduction of insulin dosage) and defensive eating are common responses to experiencing both severe and non-severe hypoglycaemia to avoid further exposure [4]. Although these may be effective short-term strategies to minimize hypoglycaemia risk, in the longer term, this may lead to persistent hyperglycaemia, increasing the risk of developing complications and compromising health and quality of life (QoL). For some people, it is a compelling way of coping with their fear of hypoglycaemia. In particular, severe hypoglycaemia can have immediate and potentially devastating physical (e.g. loss of consciousness) and social consequences (e.g. embarrassment) that affect a person's well-being and QoL [5]. In addition, perceived risk in the absence of actual hypoglycaemia may provoke an emotional reaction [6] and for some may be a disincentive to treatment intensification [7].

The purpose of this systematic review was to investigate the association between severe hypoglycaemia and psychological well-being and QoL in adults with Type 2 diabetes. A true measure of these outcomes can be achieved only by obtaining first-hand reports from people living with Type 2 diabetes as to how hypoglycaemia affects various aspects of their lives; these are known collectively as 'patient-reported outcomes' (PROs).

<H1>Methods

<H2>Search strategy and selection criteria

A systematic search was conducted in May 2016 (updated 18 January 2018) to identify peer-reviewed, empirical papers published in English since 1966 that examined the association between hypoglycaemia and PROs. We developed a review protocol, which detailed the databases to be searched (MEDLINE Complete, PsycINFO, CINAHL complete), and used an exhaustive set of search terms relating to three themes: (1) Type 2 diabetes; (2) hypoglycaemia; and (3) PROs, combined using the Boolean operator 'and'. Full details are provided in Appendix S1. Hand-searching of reference lists was performed to source additional articles. The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

All abstracts were screened independently by NI and a second author (CH, HS or JS). CH and NI performed the full-text review of articles for eligibility that were retained following abstract screening. Discrepancies were identified and resolved by mutual assessment against an agreed protocol between CH and NI. When agreement could not be reached, a third author (JS) assisted to reach consensus.

Eligible studies: (1) involved adults with Type 2 diabetes; (2) reported the incidence and/or prevalence of hypoglycaemia; (3) examined the relationship between hypoglycaemia and PROs, including generic and diabetes-specific QoL, health status, and emotional well-being (e.g. fear, anxiety and depressive symptoms); and (4) were peer-reviewed. Studies were excluded if they: (1) focused solely on people with Type 1 diabetes or gestational diabetes; (2) included people with other types of diabetes and did not report the results separately; (3) were not published in English; (4) did not specifically address the relationship between hypoglycaemia and PROs; (5) had a qualitative study design; (6) included individuals aged < 16 years and did not report adult data separately; and (7) had ≤ 20 participants.

<H2>Data extraction and synthesis

Extracted data included author and year of publication (study acronym if available), country of origin, study design and method, sample size, diabetes characteristics (duration, HbA_{1c}, treatment), participant age and gender, hypoglycaemia categorization and occurrence, PROs (Appendix S2), and results. NI performed data extraction, with CH verifying the extracted data against the original papers. A narrative synthesis of the findings was conducted, focusing on the relationship between hypoglycaemia and PROs. This was necessitated by the variety of PRO measures used in the studies precluding meta-analysis. Effect sizes were calculated for studies that provided mean and standard deviation (SD) for the most commonly used PRO

measures, the Hypoglycaemia Fear Survey-version II (HFS-II), EuroQoL 5 Dimensions (EQ-5D) and EuroQoL Visual Analogue Scale (EQ-VAS).

<H2>Assessment of risk of bias

Study quality was evaluated using the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (<https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>).

<H1>Results

The search identified 3756 papers. Following initial screening, 882 duplicates were removed and 2597 papers were ineligible. Following screening of the full-text of the remaining 277 papers, 198 were ineligible (Fig. 1). Of the remaining 79 papers, 30 reported on severe hypoglycaemia (the focus of the current research question) and were subjected to data extraction and analysis. Two papers reported on the same population [8,9] and were treated as one study, with $N = 29$ studies included in the final review. Two papers reported on the same cohort of nine European countries [10,11], but reported different sample sizes, characteristics and statistical analyses, and so were not merged.

The 29 selected studies (Table S1) involved participants from 21 countries. Four included multiple countries in Europe [10–12] and Asia [13]. Sample sizes varied widely ($N = 71$ to 17 563), and the largest was a multicentre study in Germany [14]. Where reported, mean age was > 58 years, and two studies specifically recruited older participants [15,16]. Average diabetes duration (reported in 21 studies) varied between 3 and 18 years, and HbA_{1c} (reported in 21 studies) between 52 and 72 mmol/mol (6.9 and 8.7%), with 16 studies reporting an average HbA_{1c} of ≤ 58 mmol/mol ($\leq 7.5\%$). Eleven of the 29 studies included participants managing their Type 2 diabetes with oral hypoglycaemic agents (OHAs) only (including one study that is OHA or diet). The majority of studies (18 of 29) included participants managing their Type 2 diabetes with insulin, OHAs or injectables alone, or a combination of these. In almost all studies, those using OHAs outnumbered those using insulin (except two studies in which $> 50\%$ injected insulin) [17,18].

<H2>Assessment of risk of bias

Study designs were mainly cross-sectional. Although six studies were prospective [14,16,19–22], for most of these, only cross-sectional (baseline) data [14,19,20,22] were relevant to the aims of the current review. In 16 studies [9,11–13,17,19,23–32] the aim was to examine the

association between hypoglycaemia and PROs. One study established a minimum important difference [33] and another determined a clinically meaningful cut-off score for fear of hypoglycaemia [6]. For the remaining studies, hypoglycaemia had been included as a potential risk factor or complication of diabetes.

With regard to the overall quality of studies, research objectives and study populations were clearly defined (93%), validated PROs were used (93%), recall periods of severe hypoglycaemia were at least 6 months (69%), and analyses were controlled for multiple confounders (59%). Few studies reported participation rates (28%) and sample size calculations (59%).

<H2>Severity of hypoglycaemia

Frequency and severity of hypoglycaemia were self-reported (directly by the individual with diabetes completing a survey or indirectly via the physician) over a predefined timeframe (mostly 6–12 months). These self-reports were categorized into various severity levels. Overall, the definition of the severity levels was consistent among the studies: ‘mild’ was defined as self-treated/no interruption of activities; ‘moderate’ as self-treated/some interruption of activities; ‘severe’ as needing external assistance; and ‘very severe’ as requiring medical assistance / hospitalization. Although some studies had collected data on severity of hypoglycaemia to examine its association with the PROs, data were merged and often dichotomized because the number of participants experiencing hypoglycaemia was low, particularly in the (very) severe categories. Table S1 reports the results separately for studies comparing presence or absence of severe hypoglycaemia, and severity of hypoglycaemia (two or more categories).

<H2>Psychological outcomes

Table 1 shows that severe hypoglycaemia was associated with impaired psychological outcomes, including fear of hypoglycaemia, general emotional well-being, general health status and diabetes-specific quality of life. Appendix S2 provides details of the measurement of each outcome: fear of hypoglycaemia was typically assessed with HFS or HFS-II, but also with the Hypoglycaemic Attitude and Behaviour Scale (HABS), or a study-specific item; general emotional well-being (including symptoms of anxiety/depression) was assessed using a wide range of PRO measures: the Beck Depression Inventory (BDI), Centre of Epidemiological Studies Depression Scale (CES-D), Hospital Anxiety and Depression Scale (HADS), Hamilton Anxiety Rating Scale/ Hamilton Depression Rating Scale

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(HARS/HDRS), 7-item General Anxiety Disorder (GAD-7), State-Trait Anxiety Inventory (STAI), Well-Being Questionnaire-12 (W-BQ12), and the 5 items World Health Organization Well-being index (WHO-5); general health status was typically assessed using the EQ-5D and EQ-VAS, but also with the Short Form-36 Health Survey (SF-36) or the 12-item Short Form Medical Outcomes Study (MOS-SF12); diabetes-specific QoL was assessed with the Audit of Diabetes-Dependent Quality of Life (ADDQoL).

<H2>Severe hypoglycaemia and fear of hypoglycaemia

Nine studies (reported in 11 papers) compared level of fear of hypoglycaemia in those with, and without, severe hypoglycaemia (Table 1) [6,10,11,17,24,25,27–29,32,34]. Nine of the 11 studies reported significantly greater fear in those who experienced severe events compared with those who did not, with very large effect sizes ($d > 0.9$) in three of the four studies for which calculations could be made (Table 2). By contrast, one study [32] did not find a significant relationship with severe hypoglycaemia, at baseline or at 3 and 6 months after initiation of long-acting insulin. However, the number of severe episodes was low as were the levels of fear. In two studies using the HFS-II questionnaire (Worry subscale) [27,28] moderate and severe episodes were merged and compared with either no or mild hypoglycaemia (Table 1). Greater fear of hypoglycaemia was reported by Pagkalos *et al.* [27] in those with moderate/severe episodes, with a large effect size. Pettersson *et al.* [28] found a non-significant difference between groups. Two studies measuring fear of hypoglycaemia with a study-specific item [24,29] observed a significant association between fear and the occurrence of severe hypoglycaemia.

Only two studies investigated outcomes by treatment type. Polonsky *et al.* [17] found that severe hypoglycaemia (in the preceding 6 months) was associated with a significantly higher level of hypoglycaemia-associated anxiety (assessed with the HABS), only in those taking insulin. Dømgård *et al.* [24] did not observe any differences according to treatment modality (69% vs. 68%, insulin vs. non-insulin respectively).

Five studies reported on the association between worries about hypoglycaemia and levels of hypoglycaemia severity [8,9,13,27,30,33]. The hypoglycaemia reference period was 6 months and participants were not using insulin. For three of the five studies, effect sizes could be calculated. Significant differences in fear of hypoglycaemia were observed (medium-to-large effect sizes for six of the seven observations) between levels of

hypoglycaemia severity (Table S2). This association was confirmed after controlling for confounders [9,13,27,30].

<H2>Severe hypoglycaemia and general emotional well-being (including depression/anxiety symptoms)

The eight studies investigating the association between severe hypoglycaemia and general emotional well-being (including depression and/or anxiety symptoms) reported mixed findings (Table 1). Prevalence of severe hypoglycaemia was associated with greater severity of depressive symptoms (CES-D) after adjusting for clinical factors such as treatment, HbA_{1c} and diabetes duration [19]. This was confirmed in a subsample using sulfonylureas and/or insulin. The incidence of severe hypoglycaemia during a 4-year follow-up was associated with more depressive/anxiety symptoms (HADS) compared with people with no severe hypoglycaemia [16]. In the same cohort, lifetime history of severe hypoglycaemia was associated with anxiety, but not with depressive symptoms [20]. In contrast, severe hypoglycaemia was an independent predictor of (sub-)clinical depression, but not of anxiety [18]. Participants with severe hypoglycaemia had higher levels of anxiety symptoms (GAD-7), but after controlling for confounders, this relationship was no longer significant [25]. In a small study in an older population [15], those reporting severe hypoglycaemia had higher anxiety/depression scores (HARS/HDRS) compared with those reporting mild/moderate episodes. Severe hypoglycaemia was negatively associated with general emotional well-being (WHO-5) after adjusting for confounders in a large German sample [14], whereas no association was found in a small Dutch sample who were using oral agents alone [32]. Effect sizes could not be calculated and the range of measures used precludes robust comparisons between studies.

<H2>Severe hypoglycaemia and generic health status

Five studies (reported in six papers) compared individuals with, or without, severe hypoglycaemia in terms of health status (EQ-5D, EQ-VAS, MOS SF-12, SF-36) (Table 1) [10,11,23,25,28,35]. Five showed that those experiencing severe hypoglycaemia reported lower health status. However, after controlling for confounders, the earlier association (using EQ-VAS) reported by Simon *et al.* [11] was not confirmed by Bradley *et al.* [10]. Across the three studies where effect sizes could be calculated, the effects were small, medium and large (Table 2).

Ten studies examined the association between level of hypoglycaemia severity and health status (EQ-5D, EQ-VAS, MOS SF-12, SF-36). In seven studies [9,12,13,22,26,27,30], univariate analyses showed that greater severity of hypoglycaemia was associated with lower health status and this was confirmed by multivariate analyses in four studies [9,12,26,30]. Two studies [31,36] did not observe a difference comparing severity levels. In a 1-year prospective study [21], no significant differences in health status (EQ-5D) were observed between three (self-treated) levels of hypoglycaemia at baseline and follow-up. Effect sizes (Table S2, five studies) were mostly very small, with medium effects observed in two studies for the difference in health between moderate and severe hypoglycaemia [9,12]. With the exception of two studies [26,36], the participants were not taking insulin.

Three studies further explored the EQ-5D dimension scores. One observed significantly higher scores (poorer outcomes) for all five dimensions when comparing those with, and without, severe hypoglycaemia in the previous 6 months [25]. One study reported worse outcomes for pain/discomfort and anxiety/depression (comparing no/mild with moderate/severe episodes) [28] and one for pain/discomfort using a hypoglycaemia severity index with four levels of severity [36]. One study reporting on the SF-36 domains [23] showed that scores were lower for the severe hypoglycaemia group, compared with those with mild/moderate hypoglycaemia, except for the vitality/energy domain (significance not reported).

<H2>Severe hypoglycaemia and diabetes-specific quality of life

Severe hypoglycaemia was associated with lower diabetes-specific QoL (ADDQoL) in a multicentre European sample [11] and in the Spanish subsample [34] of the same study (Table 1). However, a subsequent analysis, which controlled for confounders, did not find this association to be significant [10].

<H1>Discussion

The findings of this systematic review indicate strong support for a relationship between severe hypoglycaemia and fear of hypoglycaemia, and also reduced general health status. In some, but not all studies, severe hypoglycaemia is associated with impaired psychological well-being (manifesting as the presence of depression/anxiety symptoms).

Adjusted multivariate analyses and effect sizes reveal that the associations observed between severe hypoglycaemia and fear of hypoglycaemia are mostly medium-to-large effects,

whereas the associations between severe hypoglycaemia and general health status are mostly small effects. This suggests that hypoglycaemia-specific measures are more sensitive to the impact of hypoglycaemia than generic measures. An important observation is that the within-measure and within-study effect sizes were broadly comparable, regardless of whether the comparison was mild vs. moderate hypoglycaemia or moderate vs. severe hypoglycaemia. For the most part, this suggests that various levels of hypoglycaemia severity represent very little perceived difference in impact to the person experiencing the hypoglycaemic episode. In addition, it seems that fear of hypoglycaemia is experienced at relatively low levels of severity, suggesting it may be the anticipation of experiencing a severe event (and not the event per se) that is the driving factor. This has considerable clinical implications, given that fear of hypoglycaemia drives strategies to avoid low glucose and may deter people from accepting further treatment intensification.

Although not an aim of this review, these findings suggest that irrespective of whether Type 2 diabetes is treated with insulin or OHAs, the emotional reactions experienced in response to severe hypoglycaemia are very similar. However, very few studies in this review have directly assessed the emotional impact of severe hypoglycaemia according to treatment type. It would be relevant to further investigate the association between emotional well-being and therapies that can provoke hypoglycaemia in adults with Type 2 diabetes.

The overall strength of the evidence is attenuated by heterogeneity of study design, sample size, lack of consistency in definitions and measurement of hypoglycaemia or varied measurement of psychological outcomes. For example, there was an assortment of definitions, severity ratings, frequency measures and symptoms of hypoglycaemia, all of which were based on self-report. Recall periods varied between studies, which may have implications for recall accuracy, and the overall prevalence of severe hypoglycaemia was low in the populations studied. Of note, the only study assessing fear of hypoglycaemia that did not find an effect was where severe hypoglycaemia affected only 3% of the study participants [32]. Furthermore, some studies combined severity ratings, with mixed findings; merging moderate and severe hypoglycaemia may have limited the ability to demonstrate an association with fear of hypoglycaemia [27,28]. This may also have influenced the observed effect sizes. It was therefore difficult to ascertain whether so-called 'very severe' episodes (those requiring active medical intervention or hospitalization) had a greater impact on emotional well-being than 'severe' events. The subdivision of severity into 'mild', 'moderate', 'severe' and 'very severe' is artificial and is not used in clinical practice where

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only 'non-severe' (mild) and 'severe' are used. This increases the complexity of the evidence and interpretation depends fundamentally on the way in which key variables were defined. Differentiating 'mild' from 'moderate' hypoglycaemia based on whether activities are interrupted or not is not a precise measure of severity and is open to subjective interpretation and the capacity of an individual to self-treat effectively. Ability to self-treat is the usual clinical method to assess the severity of hypoglycaemia. Many people with severe hypoglycaemia are treated at home or in the workplace by relatives or colleagues and emergency medical assistance is seldom sought. The latter is required in ~ 30% of those with insulin-treated Type 2 diabetes [37] and the need for this intervention may depend on circumstances or the inability of bystanders to treat hypoglycaemia effectively, rather than on actual severity. Hospital admission is much more commonly required for frail elderly people with multiple comorbidities [38], so may bias the assessment of a perceived effect of severity on emotional well-being in an older age-group.

The evidence is further limited by a preponderance of generic rather than diabetes- or hypoglycaemic-specific PROs. Of the 15 validated PROs identified, only four were diabetes specific (HFS-II, HABS, ADDQoL, W-BQ12). The most used measure, HFS-II, assesses only worries and avoidance behaviours, although hypoglycaemia can have a much broader impact on a person's life, for example, on sleep, relationships, work and social life [39]. The more recently developed HABS [17] incorporates assessment of confidence (a positive construct) in remaining safe from hypoglycaemia. Many studies assessed health status with generic measures and effect sizes were small. These may not be the most appropriate to assess the impact of hypoglycaemia and are known to capture the influence of comorbidities, a particular problem in Type 2 diabetes [40]. In particular, these measures may profoundly underestimate the impact of hypoglycaemia on QoL [41].

A major strength of this review is that the literature search was systematic and comprehensive; the majority of the included studies clearly described the research aims, the study populations, the applied definition of (severe) hypoglycaemia and assessed psychological constructs with well-validated measures. However, the evidence is limited by cross-sectional study designs, which do not allow conclusions to be drawn about causality. Although clinical trials were not excluded from this review, most did not fulfil the inclusion criteria. Although occurrence and frequency of hypoglycaemia were assessed as well as PROs, the direct relationship between these outcome variables was not examined in the trials. However, the strength of the studies in this review is that participants had reported on their

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personal everyday experience of hypoglycaemia while receiving routine care, rather than in trial settings. With respect to the adequacy of the current review, it is possible that studies were not identified because of the multiplicity of search terms, the inadequacy of reporting in published abstracts or publication bias. A further potential bias is introduced by excluding qualitative studies or those that are not published in English. It was not possible to conduct a meta-analysis because of the wide range of PROs.

In consideration of the limitations of this systematic review, further targeted research is required to understand the full psychological impact of hypoglycaemia in adults with Type 2 diabetes. Robust, well-designed prospective studies are needed, along with meaningful and consistent methods of measuring hypoglycaemia and its impact. Study designs and analyses must control for therapies and other confounding factors.

Despite the fragmentary nature of the data, we attest that the evidence is indicative of a negative effect of severe hypoglycaemia on psychological outcomes, which is strongest (in terms of effect size) and most consistent in relation to fear of hypoglycaemia. Although the negative psychosocial impact of hypoglycaemia appears to increase with severity of hypoglycaemia, given the high cultural heterogeneity of studies included in the review, the effect size (considering the level and the standard deviation of psychosocial outcomes) is a more appropriate measure of impact. Although hypoglycaemia is often reported as a 'safety' issue and an unwanted side-effect of specific treatment regimens, this review suggests that healthcare professionals, researchers, regulators and payers should appreciate that hypoglycaemia may have considerable psychological impact on those individuals in whom it is experienced. In view of the increasing prevalence of Type 2 diabetes and the paucity of research in this area, targeted research is essential.

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Competing interests

BMF has served on advisory boards for Novo Nordisk, Eli Lilly, Locemia Solutions and Zucara, and received honoraria as a speaker for Novo Nordisk, Lilly, Sanofi, Roche, MSD

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Author contributions

JS, BMF, CH designed the study. NI searched the literature and generated the figure. NI, CH, HS and JS reviewed the abstracts. NI and CH reviewed the full papers and generated the tables. CH wrote the first draft. CH, NI, HS BMF & JS contributed to discussion, reviewed and edited manuscript, approved the final version.

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FIGURE 1 PRISMA statement flow diagram: summary of systematic search and review process.

<H1>Supporting Information

Additional Supporting Information is available in the online version of this article:

Appendix S1. Search terms and search strategy.

Appendix S2. Summary of patient reported outcome measures included.

Table S1. Characteristics and key results of 29 studies selected for inclusion.

Table S2. Effect sizes for hypoglycaemia severity levels and (a) fear of hypoglycaemia (HFS and Worry subscale) and (b) generic health status (EQ-VAS and EQ-5D).

Table 1: Relationship between severe hypoglycaemia and psychological outcomes: fear of hypoglycaemia, general emotional well-being, general health status and diabetes-specific quality of life

Author (year)	Study design	Relationship between severe hypoglycaemia and psychological outcome
Study name	Sample size	
Fear of hypoglycaemia		
Bradley et al. (2018) [10] PANORAMA	Multicentre, cross-sectional, observational study N = 5813 (multicountry)	Yes. Multivariable analysis: severe hypoglycaemia associated with fear of hypoglycaemia (HFS-II Worry) ($P < 0.001$)
DePablos-Velasco et al (2014) PANORAMA	Multicentre, cross-sectional, observational study N = 751 (Spain only)	Yes. Severe hypoglycaemia group had significantly greater fear of hypoglycaemia (HFS-II Worry) than non-severe hypoglycaemia group ($P < 0.003$)
Dømggaard et al. (2015) [24]	Cross-sectional survey N = 2112	YES. severe hypoglycaemia group had greater fear of hypoglycaemia (study-specific item) than mild hypoglycaemia group ($P < 0.0001$); no association with treatment type (P-value NR)
Hajós et al. (2014) [6] ESPRIT & SPIRIT	Cross-sectional study N = 1530	Yes. severe hypoglycaemia group had significantly greater fear of hypoglycaemia (HFS Worry; 13-item) than non-severe hypoglycaemia group ($P < 0.001$)
McCoy et al. (2013) [25]	Cross-sectional postal survey N = 326	Yes. Multivariate analysis: severe hypoglycaemia group had greater fear of hypoglycaemia (HFS) than no/mild hypoglycaemia group ($P < 0.001$)
Pagkalos et al. (2018) [27] *	Multicentre, cross-sectional, observational study N = 383	Yes. Fear of hypoglycaemia (HFS-II Worry) to be higher in the moderate/severe hypoglycaemia group compared with the none/mild group ($P < 0.001$)
Pettersson et al. (2011) [28] * Exhype	Multicentre, cross-sectional, survey N = 430	Trend. Age-adjusted: trend for fear of hypoglycaemia (HFS-II Worry) to be higher in the moderate/severe hypoglycaemia group compared with the none/mild group ($P < 0.059$)

Polonsky et al. (2015) [17] TCOYD Research Registry	Cross-sectional online survey (validation study) N = 424	Yes. Insulin group: hypoglycaemic attitudes and behaviours positively correlated with severe hypoglycaemia (HABS Anxiety: $r = 0.49$, $P < 0.001$; HABS Avoidance: $r = 0.32$, $P < 0.001$). Non-insulin group: no differences
Sakane et al. (2015) [29]	Cross-sectional multicentre survey N = 355	Yes. Percentage severe hypoglycaemia was significantly higher in participants with fear of hypoglycaemia (17.3%) vs. those without fear of hypoglycaemia (7.8%, $P < 0.01$). Fear of hypoglycaemia assessed with one item (scored 1–5) with fear of hypoglycaemia defined as highest quintile (27.7%). Logistic regression: severe hypoglycaemia significant predictor fear of hypoglycaemia ($P = 0.034$)
Simon et al. (2015) [1] PANORAMA	Multicentre, cross-sectional, observational study N = 5783 (multicountry)	Yes. Severe hypoglycaemia group had significantly greater fear of hypoglycaemia (HFS-II Worry) than no severe hypoglycaemia group ($P < 0.001$)
Wieringa et al. (2018) [32] * SPIRIT	Cross-sectional study (secondary analysis of observational longitudinal data set) N = 911	No. No significant differences between groups (HFS-W)
General emotional well-being (including anxiety/depressive symptoms)		
Feinkohl et al. (2014) [16] ET2DS	Prospective observational study (baseline in 2011 and 4 years later) N = 831	Yes. Severe hypoglycaemia since baseline associated with greater anxiety and depression symptoms (HADS) than those without severe hypoglycaemia ($P < 0.001$)
Hermanns et al. (2005) [18]	Cross-sectional survey N = 245	Mixed results. Logistic regression: severe hypoglycaemia was significant, independent positive predictor of clinical and subclinical depression ($P < 0.01$, $P < 0.05$ respectively) but not of clinical/subclinical anxiety (BDI, CES-D and STAI, followed by diagnostic interview)
Kikuchi et al. (2015) [19]	Multicentre prospective study	Yes. Severity of depressive symptoms (CES-D) positively associated with severe hypoglycaemia (unadjusted and adjusted multivariate analyses) ($P < 0.0001$).

	N = 4218	Confirmed in subsample treated with sulfonylurea and/or insulin (N = 2756) (P < 0.001)
Labad et al. (2010) [20] ET2DS	Population-based prospective cohort study N = 1066	Mixed results. Multiple linear regression: severe hypoglycaemia was significant positive predictor of anxiety symptoms (HADS-A) (P < 0.001), but not of depression symptoms (HADS-D) (n.s.)
McCoy et al. [25] (2013)	Cross-sectional postal survey N = 326	No. Multivariate analysis: no differences for anxiety symptoms (GAD-7) but was significant before adjusting for age, gender, diabetes duration, comorbidity
Prinz et al. (2017) [14] DPV	Multicentre, prospective follow-up registry N = 17 563	Yes. Logistic regression: severe hypoglycaemia associated with depressed mood (WHO-5) (P < 0.001); after adjusting for age, gender, diabetes duration, region of residence (P < 0.01)
Ragonesi et al. (1998) [15]	Cross-sectional N = 71	Yes. Severe hypoglycaemia associated with significantly greater depression and anxiety symptoms than STH group (HDRS P < 0.002; HARS P < 0.001)
Wieringa et al. (2018) [32]* SPIRIT	Cross-sectional study (secondary analysis of observational longitudinal data set) N = 911	No. No significant differences between groups (WHO-5)
General health status		
Bourdel-Marchasson et al. (2013) [35] ENTRED 2007	Cross-sectional, postal survey N = 2832	Yes. Severe hypoglycaemia associated with lower mental health (SF-12 MCS) and physical health (SF-12 PCS) after controlling for age and sex (P < 0.001 both). Multivariate linear regression: relationship between severe hypoglycaemia and lower health status confirmed
Bradley et al. (2018) [10] PANORAMA	Multicentre, cross-sectional, observational study N = 5813	No. Multivariable analysis: severe hypoglycaemia not associated with generic health status (EQ-VAS)
Davis et al. (2005) [23]	Cross-sectional postal survey	Yes. Severe hypoglycaemia associated with lower health status (EQ-5D and SF-

	N = 590	36); statistics NR
McCoy et al. (2013) [25]	Cross-sectional postal survey N = 326	Yes. Multivariate analysis: severe hypoglycaemia group had lower health status (EQ-5D and dimensions) than no/mild hypoglycaemia group ($P < 0.001$)
Pettersson et al. (2011) [28] Exhype	Multicentre, cross-sectional, survey N = 430	Yes. Age-adjusted: moderate/severe hypoglycaemia group had significantly reduced health status (EQ-5D and dimensions) compared to none/mild group ($P < 0.001$); significant differences for Pain/discomfort ($P < 0.01$), Anxiety/depression ($P < 0.02$)
Simon et al. (2015) [11] PANORAMA	Multicentre, cross-sectional, observational study N = 5783 (multicountry)	Yes. Severe hypoglycaemia group had significantly lower health status (EQ-VAS and EQ-5D) than no severe hypoglycaemia group (both $P < 0.001$)
Diabetes-specific quality of life		
Bradley et al. (2018) [10] PANORAMA	Multicentre, cross-sectional, observational study N = 5813	No. Multivariable analysis: severe hypoglycaemia not associated with diabetes-specific QoL (ADDQoL)
DePablos-Velasco et al. (2014) PANORAMA	Multicentre, cross-sectional, observational study N = 751 (Spain only)	Yes. Severe hypoglycaemia group had significantly greater negative impact of diabetes on QoL (ADDQoL) than non-SH group ($P < 0.049$)
Simon et al. (2015) [11] PANORAMA	Multicentre, cross-sectional, observational study N = 5783 (multi-country)	Yes. Severe hypoglycaemia group had significantly greater negative impact on diabetes-specific QoL (ADDQoL) than no SH group ($P < 0.001$)

*Participants managing Type 2 diabetes with oral hypoglycaemic agents only.

n.s., Not significant; ADDQoL, Audit of Diabetes-Dependent Quality of Life; BDI, Beck Depression Inventory; CES-D, Centre of Epidemiological Studies Depression Scale; EQ-5D, EuroQoL 5 Dimensions; EQ-VAS, EuroQoL Visual Analogue Scale; GAD-7, 7-item General Anxiety Disorder; HABS, Hypoglycemic Attitudes and Behavior Scale; HADS, Hospital Anxiety and Depression Scale; HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; HFS-II, Hypoglycaemia Fear Survey-version II; HFS-W, Hypoglycaemia Fear Survey-Worry; MOS SF-12, 12-item Short Form Medical Outcomes Study; SF-36, Short Form-36 Health Survey; STAI, State-Trait Anxiety Inventory; WHO-5, 5 items World Health Organisation Well-being index.

Table 2 Effect sizes of differences between severe hypoglycaemia (including moderate) vs. no hypoglycaemia (including mild) groups for fear of hypoglycaemia (HFS II and Worry subscale) and generic health status (EQ-VAS and EQ-5D)

Author (year)	Recall period (months)	Severe hypoglycaemia Yes/No (N, %)	Mean	SD	HFS II (Worry scale) P-value	Effect size (95% CI)
Fear of hypoglycaemia						
Depablos-Velasco et al. (2014)	12	Yes (14, 1.9%)	24.1	22.1	< 0.003	0.91 (0.38, 1.44)
		No (737, 98.1%)	10.9	14.4		
McCoy et al. (2013) [25]	6	Yes (55, 16.9%)	28.7	13.2	< 0.001	1.12 (0.82, 1.43)
		No (271, 83.1%)	14.7	12.3		
Pagkalos et al. (2018) [27]*	6	Yes: moderate/severe (83, 21.8%)	26.5	15.1	< 0.001	1.32 (1.06, 1.58)
		No/mild (300, 78.3%)	9.3	12.4		
Pettersson et al. (2011) [28] *	6	Yes: moderate/severe (80, 19.4%)	7.96	10.93	0.059	0.31 (0.06, 0.55)
		No/mild (332, 80.6%)	4.93	9.55		
Author (year)	Recall period	Severe hypoglycaemia Yes/no (N, %)	Mean	SD	EQ-VAS P-value	Effect size (95% CI)
General health status						
Pettersson et al. (2011) [28]*	6	Yes (80, 18.6%)	0.71	0.18	0.014	-0.30 (-0.55, -0.06)
		No (332, 77.2%)	0.76	0.16		
Author (year)	Recall period	Severe hypoglycaemia Yes/no (N, %)	Mean	SD	EQ-5D P-value	Effect size (95% CI)
McCoy et al. (2013) [25]	6	Yes (55, 16.9%)	0.70	0.24	< 0.001	-0.83 (-1.13, -0.53)
		No (271, 83.1%)	0.84	0.15		
Pagkalos et al.	6	Yes: moderate/severe (83,	0.7	0.2	< 0.061	-0.50 (-0.75, -0.25)

(2018) [27]*		21.8%)				
		No/mild (300, 78.3%)	0.8	0.2		
Pettersson et al.	6	Yes: moderate/severe (80,	0.81	0.26	< 0.001	-0.35 (-0.11, -0.6)
(2011) [28]*		19.4%)				
		No/mild (332, 80.6%)	0.88	0.18		

*All participants managing Type 2 diabetes with oral hypoglycaemic agents.

Figure 1:

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