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Title page

The Impact of Hypoglycaemia in Children and Adolescents with Type 1 Diabetes on Parental Quality of Life and Related Outcomes: A Systematic Review

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The Impact of Hypoglycaemia in Children and Adolescents with Type 1 Diabetes on Parental Quality of Life and Related Outcomes: A Systematic Review

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Author contributions

MB, JS, AS, AC, SH, BdG, CH and FP developed the search protocol. MVJ, MB, JS, HC, CH and FP completed the Prospective Register of Systematic Reviews Protocol. AS and AC conducted the systematic search. AS, AC, MVJ and HC screened the studies and extracted the data. MVJ wrote the manuscript. All authors reviewed and edited the manuscript for critical content and approved the final version.

Abstract

Aim To summarize and critically evaluate the current evidence regarding the impact of hypoglycaemia in children and adolescents with type 1 diabetes on parental quality of life.

Methods MEDLINE, PsycINFO, CINAHL and the Cochrane Library were searched. Inclusion criteria were: 1) quantitative design, 2) included parents of children or adolescents with type 1 diabetes, 3) assessment of hypoglycaemia in children/adolescents with type 1 diabetes, 4) assessment of parent quality of life (or related domains of life), and 5) analysis of the relationship(s) between the child's hypoglycaemia and parent's quality of life. The data were summarized in accordance with Synthesis Without Meta-Analysis Guidelines.

Results Twelve studies were included, reporting data from 1,895 parents across 6 countries. Ten studies were cross-sectional; two included prospective data. Evidence suggested that greater frequency and severity of hypoglycaemia was associated with greater parental fear of hypoglycaemia, emotional distress and family burden.

Conclusion Children's hypoglycaemia has a negative impact on the well-being of parents, but there is an absence of evidence regarding the impact on their overall quality of life. Research into the hypoglycaemia-specific quality of life of parents is needed to explore the impact on various areas, such as social and physical dimensions.

Keywords Systematic review, Quality of Life, Hypoglycaemia, Pediatric Diabetes, Parents, Type 1 diabetes

Introduction

Hypoglycaemia (low blood glucose) is a common side-effect of insulin therapy in children and adolescents with type 1 diabetes, which can result in significant physical and psychological symptoms that interfere with and disrupt daily activities [1-3]. Parents and caregivers (hereafter referred to as parents) typically play a crucial role in the daily diabetes care of their child(ren). Parents of younger children are responsible for performing or supervising daily insulin injections and glucose monitoring and are thus significantly involved in preventing and managing episodes of hypoglycaemia [4-6]. Parents of adolescents face different challenges. With the transition to self-management, parents may worry that the adolescents are less vigilant (than they would be) about low glucose levels, more so when in social situations with friends or when they engage in risk-taking behaviours [4-7].

It is estimated that children, adolescents and young adults with type 1 diabetes experience symptomatic episodes of hypoglycaemia 1-2 times a week [8]. While rates of episodes of severe hypoglycaemia have decreased, children remain at risk as they are often unable to communicate their symptoms [8]. Research has found associations between frequency of hypoglycaemia and parents' fear of hypoglycaemia [9, 10] and diabetes distress [11]. It has also been shown that parents' fear related to the risk of hypoglycaemia while the child is asleep is associated with significant disruptions to their own sleep [12]Parents with fear of hypoglycaemia, parenting and emotional stress, may be at increased risk for anxiety and depression [13, 14]. However, it is unclear how episodes of hypoglycaemia (self-treated and severe) impact on parents' quality of life.

The subjective and dynamic nature of the quality of life construct makes it challenging to assess all areas of potential importance to an individual [15]. Several studies have used person-reported outcome measures to assess concepts related to quality of life (i.e., psychological, social or physical functioning), which are insufficient to capture the entire concept, but remain useful in understanding an individual's quality of life.

Hypoglycaemic episodes in children may affect many areas of their parents' quality of life, and thus a comprehensive understanding is needed of whether (and if so: how) parents' overall quality of life is impacted by hypoglycaemia specifically. In the present review, quality of life is defined as a multi-dimensional construct comprising physical, social and psychological dimensions [15-16].

The aim of this systematic review was to summarize and critically evaluate quantitative studies examining relationships between children's experience of hypoglycaemia and parents' quality of life and related outcomes (such as fear of hypoglycaemia and diabetes distress).

Methods

Search Strategy

A systematic literature search was conducted as part of a single search strategy for five related reviews of the impact of hypoglycaemia on quality of life and related outcomes in various populations, as part of the Hypo-RESOLVE project [17]. Each review focused on a different population: 1) parents of children with type 1 diabetes (reported here); 2) family members of adults with type 1 or type 2 diabetes; 3) adolescents with type 1 diabetes; 4) adults with type 1 diabetes; 5) adults with type 2 diabetes. Reviews 2 and 4 are published [18, 19] and reviews 3 and 5 will be reported elsewhere.

MEDLINE, PsycINFO, CINAHL and Cochrane Library were searched, with no date of publication or language limiters. The search strategy was developed based on an adapted PICO strategy: 1) Population: people affected by diabetes; 2) Intervention/exposure: hypoglycaemia; 3) Comparator: none; and 4) Outcome: quality of life. Targeted inclusion and exclusion criteria for this review were applied in the screening and selection phases. The full MEDLINE search string for the present review can be seen in *Appendix 1.* The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42020154023).

Screening and Selection

Studies were included in the present systematic review when they: 1) used a quantitative study design, 2) reported on parents or caregivers of children/adolescents with type 1 diabetes, 3) included measures of hypoglycaemia in children/adolescents with type 1 diabetes, 4) included measures of parent/caregiver quality of life (or related concepts) as outcomes, and 5) analysed relationships between the child's hypoglycaemia and the quality of life or related outcomes of parents/caregivers. Studies with a qualitative design and systematic reviews were excluded.

After the systematic search, articles were imported into EPPI-Reviewer 4, where a subset of titles and abstracts were screened independently by three reviewers. Following this, one reviewer (AC) screened the remaining titles and abstracts, and two reviewers (MC & AS) checked each 5% of the articles screened at abstract level. Full-text article screening was completed by MVJ, and 10% of these were checked by a second reviewer (HC) with "substantial" agreement between reviewers (k: 0.62. Citation searching was conducted using the reference list of the included studies for backward chaining, and Google Scholar for forward chaining. See *Figure 1* for the PRISMA flow diagram.

Data Extraction and Synthesis

AS extracted the following data from each of the eligible studies: reference details, study details (i.e., design, setting, measures, objectives), sample characteristics (i.e., inclusion/exclusion criteria, demographic information, clinical information), statistical analyses, results, and author-reported limitations (AS). MVJ and a second reviewer (KM) independently checked 10% of the extracted data and reached consensus. Data from articles identified in citation searches were extracted by MVJ and checked by a second reviewer (KM).

Meta-analysis would have been ideal, but the heterogeneity in outcome measures made this impossible. Based on Synthesis Without Meta-Analysis (SWiM) guidelines [20], findings were grouped into categories according to the psychosocial outcome measure used to assess the impact of hypoglycaemia. A narrative synthesis was conducted of the findings of the included studies.

Cohen's *d* was calculated from study results reporting mean comparisons and interpreted as follows: d=0.2: small effect size; d=0.5: medium effect size; d=0.8: large effect size [21]. Studies reporting Pearson's correlation coefficients can be interpreted as follows: r=0.1: small effect size; r=0.3: medium effect size; r=0.5: large effect size [21]. The remaining results were reported using their original metric.

Quality Assessment

The quality of the included studies was assessed by MVJ using the Johanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies [22]. The quality checklist has eight questions assessing the study's methodology and analysis approach with four response options; *yes, no, unclear, not applicable.* The quality assessment was used to appraise the methodological quality of all included studies, and to aid the interpretation of the evidence.

Results

Systematic Search and Selection

Database searches retrieved 223 studies. After removal of duplicates, 126 studies were screened at title and abstract level. Ninety-four studies were eligible for full-text screening. Following full-text screening, nine studies met the inclusion criteria. Forward- and backward-chaining identified an additional three studies, resulting in 12 studies being included in the final review. Figure 1 shows the PRISMA flow diagram.

Characteristics of Included Studies

Of the 12 studies, ten had a cross-sectional design [9-11, 23-29]. While two studies employed a prospective design overall [30, 31], the results relevant to this review were cross-sectional. Studies were conducted in six countries: five in the USA [11, 27, 28, 30, 31], three in Norway [9, 10, 25], and one each in Australia [29], Iran [24], Poland [26] and Saudi-Arabia [23]. Two papers reported on the same Norwegian study [10, 25] but as they reported on different outcome measures, both were included. In eleven studies, parents were recruited through outpatient clinics where the children with type 1 diabetes were receiving treatment. In one study, parents were recruited through a local diabetes association database [23]. Sample sizes ranged from *N*=24 [31] to *N*=390 [24], with a total of N=1,895 parents across all 12 studies (excluding the second Norwegian publication from this calculation). Most (*n*=1,368; 72%) parents were women/mothers. Parents' mean±SD age ranged from 36±6 to 47±6 years. Six studies did not report parents' age [24, 27-31]. Nine of the 12 studies focused their analyses on parents and caregivers alone (reporting only demographic and clinical data from children) [9-11, 23-26, 30, 31], while three studies reported results from both parents and children [27-29]. The mean±SD age of children ranged from 5±2 to 15±2 years. Table 1 provides an overview of the sample characteristics of the studies.

Definition and Measurement of Hypoglycaemia

The occurrence or frequency of hypoglycaemia was proxy-reported by parents in ten studies [9-11, 23, 25-28, 30, 31], and was obtained via clinical records in two studies [24, 29]. The recall periods for hypoglycaemia episodes varied across studies, with the most common recall period being episodes in the past 12 months in five studies [9, 10, 25, 28, 29]. One study had a recall period of three months [23], and two studies had a six-month recall period [11, 27]. Four studies did not report recall periods for hypoglycaemic episodes [24, 26, 29, 30].

The definition of hypoglycaemia varied across the studies. Two studies used a biochemical definition of hypoglycaemia, as a blood glucose level of $\leq$60mg/dL (3.3 mmol/L) [30, 31]. In three papers (reporting on two studies), parents were asked about the frequency of what they perceived as "problematic hypoglycaemia" in the past year with no further definition [9, 10, 25]. Severe hypoglycaemia (SH) was defined in various ways. In one study, SH was defined as "episodes where the child required assistance from others" [11], and another study defined SH as episodes where the child had experienced seizures or unconsciousness, and where external assistance was needed [23, 27].. Two studies applied two categories of hypoglycaemia, defining both moderate and severe episodes [28, 29]. One study defined SH as episodes with unconsciousness and need of external assistance, and problematic hypoglycaemia as episodes requiring external assistance, but where the child was conscious [23]. However, the study reported only on results based on their definition of problematic hypoglycaemia.

Two studies did not provide a definition of or recall period for hypoglycaemia, and only reported on the frequency of hypoglycaemia [24, 26]. Table 2 summarizes the definitions and measures of hypoglycaemia.

Quality Assessment

Overall, included studies were of good quality (see Table 3). All studies described and defined their inclusion and exclusion criteria and recruited participants through pediatric diabetes clinics or a diabetes association, indicating objective, standardized classification of diabetes status. Eleven studies used psychological scales validated previously in a diabetes context [9-11, 23-25, 27-31]. Ten studies were marked as "unclear" for a valid measurement of the exposure (hypoglycaemia) [9-11, 23, 25-28, 30, 31]. This was due to the fact that no standardized definition or guideline for determining hypoglycaemia in children (e.g. ISPAD guidelines [8]) was used to obtain information on episodes of hypoglycaemia. Information on episodes of hypoglycaemia was obtained through parent report in 10 studies [9-11, 23, 25-28, 30, 31], and via medical records in two studies [24, 29].

Synthesis of Findings

Findings were grouped by parent-reported outcome, into three categories according to the attribution of the psychological measures: 1) hypoglycaemia-specific, 2) diabetes-specific, and 3) generic. The generic measures category was further divided into psychological functioning and parent/family functioning. Table 2 provides an overview of the main findings of the studies.

1. Assessing the impact of hypoglycaemia using hypoglycaemia-specific measures

None of the 12 studies identified used a measure of the impact of hypoglycaemia on parental quality of life. Eight studies assessed parental fear of hypoglycaemia, with a version of the Hypoglycaemia Fear Survey (HFS).

1a. Fear of hypoglycaemia

The Parent version of the HFS (HFS-P) was administered in six studies [9, 10, 23, 27-29] and the Parents of Young Children version (HFS-PYC) in two studies [30, 31]. The HFS-P is a 25-item questionnaire with two subscales: Worry (10 items) and Behavior (15 item). The items assess parents' fear of hypoglycaemia and behaviours related to avoidance of hypoglycaemia. Higher scores on the HFS-P indicate higher fear, with a maximum overall score of 125 [32]. The HFS-PYC is a version of the HFS-P where the items are adapted to be relevant for parents of young children [31]

Four of the six studies using the HFS-P reported a significant relationship between occurrence of problematic or SH episodes in children/adolescents and greater parental fear of hypoglycaemia [9, 10, 27, 29]. In Haugstvedt et al (2015), mothers who reported their child to have had $\geq$7 problematic episodes in the past year scored higher on both HFS-P subscales compared to mothers reporting no episodes, with medium effect sizes [9]. This was also the case in Haugstvedt et al (2010), where a significant association was found between occurrence of $\geq$7 parent-reported problematic hypoglycemic episodes in the past year and higher scores on the HFS-P Worry subscale (b=5.06, p=0.005) [10]. No association was reported for fathers [9].

Similarly, Marrero et al (1997) found that parents had a higher overall HFS-P score when their child had experienced at least one SH episode in the past year (*large effect size*), or ever since diagnosis (*medium-to-large effect*), compared to parents reporting no episodes in the past year or ever since diagnosis [27]. Although no recall period was reported, a similar association was found in Johnson et al (2013), where parents reporting a SH episode had a higher score on the overall HFS-P scale (6.3 points, p=.005) [29].

The baseline findings from the two studies using the HFS-PYC, found positive correlations between occurrence of hypoglycaemia seizures and scores on Worry subscale [30, 31]. In Patton et al (2007), parents of young children who had experienced a hypoglycaemia-related seizure in the past six months scored higher on the HFS-PYC Worry subscale, compared to parents whose child had not had seizures (*large effect*) [31]. Similarly, in Patton et al (2008) [30], mothers who reported that their child had a hypoglycaemic seizure, scored higher on the HFS-PYC Total Score, compared to mothers of a child who had never had a seizure (*small-to-medium effect*). Furthermore, the frequency of episodes where the child had a blood glucose of ≤60 mg/dL (3.3 mmol/L) positively correlated with mothers' scores on the Worry subscale (*small-to-medium effect*). No association was reported for fathers [30, 31].

In contrast to these positive associations, Gonder-Frederick et al [28] and Amiri et al [23], found no significant relationship between the number of moderate or SH/problematic hypoglycaemia in the past three or 12 months respectively, and fear of hypoglycaemia measured by the HFS-P. The differences in findings may be due to the age range of children included in the studies, as well as the varied definitions of hypoglycaemia and recall period across the eight studies using a version of the HFS-P.

Based on the included studies, the current evidence suggests that both frequency and severity of hypoglycaemia in children with type 1 diabetes is associated with a higher level of fear of hypoglycaemia in their parents – with as few as one SH episode leading to greater parental fear of hypoglycaemia.

2. Assessing the impact of hypoglycaemia using diabetes-specific measures

None of the 12 studies identified used a measure of the impact of diabetes on parental quality of life. One study [11] assessed parental diabetes distress, using the Parent Diabetes Distress Scale (PDDS), a measure of diabetes-specific emotional distress developed specifically for parents of adolescents with type 1 diabetes. This scale assesses four areas of distress that parents may experience (personal distress, distress about their adolescent's management of diabetes, distress about their relationship with the adolescent, and distress about the adolescent's healthcare team).

2a. Diabetes distress

Frequency of SH over a six-month period was positively associated with parents' overall diabetes-related distress (b=0.13, *p*=0.009) and personal distress (b=0.18, *p*=.001). Given this is just a single study, there is insufficient evidence to draw conclusions regarding the relationship between hypoglycaemia and parental diabetes distress.

3. Assessing the impact of hypoglycaemia using generic measures

None of the studies used a measure of generic quality of life, although three studies reported associations between hypoglycaemia and related psychological outcomes in parents [23-25]. Two studies examined the associations between hypoglycaemia and parent [26] or family (10) functioning.

3a. Psychological Functioning

Measures of psychological functioning included emotional distress and frequency and severity of stressful events. One study found a significant positive association between occurrence of nocturnal hypoglycaemia (in the past 12 months) and emotional distress as measured by the Hopkins Symptom Checklist (b= 0.11 p=0.012) [25].

Two studies administered the Pediatric Inventory for Parents (PIP) [23, 24]. The PIP examines the frequency and difficulty of a number of events that are usually considered stressful by parents of children with a chronic illness, for example *"arguing with family member"*, or *"helping my child with medical procedures"* [33]. For each item, the parents are asked two questions: *"how often has the event occurred?"* and *"how difficult was the event for you?"*. The first study reported a positive association between occurrence of hypoglycaemia more than once a week and the frequency of stressful events (*small-to-medium effect*) [24], while the other study found no significant association between occurrence of problematic hypoglycaemic episodes in the past three months and either the frequency or severity of stressful events [23].

However, as the study by Aldubayee et al, did not define hypoglycaemia or the recall period [24], conclusions cannot be drawn regarding the nature of the relationship between hypoglycaemia and the frequency of stressful events experienced in the sample. Thus, there is insufficient evidence to draw conclusions regarding the relationship between hypoglycaemia and parents' generic psychological functioning outcomes.

3b. Parent/Family Functioning

Two studies examined the association between hypoglycaemia and parent/family functioning. One study administered the Family Burden Scale [25]. The scale consists of five items that address parents' perceived burden in various areas (e.g. medical treatment and family disruption). For each item parents can indicate "*none*" to "*major burden*" on a five-point Likert scale [25]. The study found a significant association between the occurrence of $\geq$7 parent-reported perceived problematic hypoglycaemic episodes in the past year and increased family burden, as measured with the Family Burden Scale (b=1.78 p=0.002) [25].

Another study administered The Caregiver Burden Scale [26]. The scale consists of 22 items, and five subscales that address areas such as general strain and emotional involvement. Each item is rated on a four-point Likert scale [26]. The study found no correlation between frequency of episodes with a glucose level below 60mg/dL (3.3 mmol/L) and overall or sub-domain scores on The Caregiver Burden scale [26].

Due to divergent definitions of hypoglycaemia between the two studies, and the differences in outcome measures, it is not possible to draw conclusions regarding a relationship between episodes of hypoglycaemia and parent or family functioning.

Discussion

The present review identified 12 quantitative studies that examined the associations between the occurrence, frequency or severity of hypoglycaemia among children and adolescents with type 1 diabetes and parental psychological outcomes. None of the studies identified used a measure of the impact of the child's hypoglycaemia on parental quality of life. Eight of the 12 studies focused on parental fear of hypoglycaemia, with findings suggesting that both frequency and severity of hypoglycaemia in children with type 1 diabetes is associated with a higher level of fear of hypoglycaemia in their parents – with as few as one SH episode leading to greater parental fear of hypoglycaemia.

Across the studies that found a relationship between hypoglycaemia and parental fear (HFS-P or HFS-PYC) [9, 10, 27, 29-31], higher effect sizes were noted for the worry subscale relative to the behaviour subscale scores. This may be explained by inclusion of items in the behavior subscale that do not necessarily reflect problematic behaviours, but rather reflect appropriate management, such as the item: "*I reduce my child's insulin when I think his/her sugar is too low*" [9]. Another explanation could be that items on the behavior subscale relate more to parents of children of younger age than parents of adolescents. Parents might have less impact on the behaviors of adolescents (as compared to younger children), and thus items such as "*I have my child eat large snacks at bedtime*" might be more applicable to parents of younger children.

Outcomes related to quality of life, such as diabetes distress, (generic) psychological functioning, caregiver burden, and family burden, were each assessed in just one or two studies and thus no firm conclusions can be drawn. Despite variation in the outcome measures used, nine of the 12 studies reported a significant association between occurrence of and/or severity of hypoglycaemic episodes and worse parental psychological outcomes. The results suggest that the psychological dimension of parental quality of life (e.g. emotional well-being) is likely to be impacted negatively by the child's hypoglycaemia. None of the studies assessed other dimensions of life important for quality of life, such as physical and social aspects (e.g. sleep, work, or social life). Importantly, across all studies, there was lack of consistency in defining and measuring hypoglycaemia with negative implications for evidence synthesis.

Heterogeneity in Hypoglycaemia Definitions and Recall Periods

An important limitation of the evidence base lies in the significant heterogeneity in the definitions of hypoglycaemia across studies. Although studies presented some overlap in their descriptions of hypoglycaemia, eleven different definitions were identified across the twelve studies. Five studies used more than one definition of hypoglycaemia [23, 28-31], with two of these defining both moderate and SH [28, 29]. Five studies defined only SH (including parent's perception of a problematic episode) [9-11, 25, 27], and two studies reported no definition of hypoglycaemia [24, 26].

Overall, studies limiting the description of SH to seizures, coma or problematic hypoglycaemia (as perceived by parents), all found a positive association between SH and fear of hypoglycaemia in parents completing the HFS-P or HFS-PYC scales. In contrast, studies reporting on a broader definition of SH, such as problematic episodes with consciousness but needing external assistance

[23], or where SH included mental disorientation [28], did not find an association between these episodes and parental fear of hypoglycaemia.

This can potentially be explained by episodes with seizures and coma being more burdensome and upsetting to parents, compared to episodes where the child experienced hypoglycaemia but was conscious or able to self-treat. Furthermore, episodes resulting in seizures or coma are likely to be interpreted as *problematic hypoglycaemia* by parents, and thus parents might recall and report on episodes of seizures and coma when asked about their own perception of problematic hypoglycaemia. Overall, occurrence of seizure or coma, as well as the frequency of perceived problematic hypoglycaemia, is likely to be associated with higher levels of parental fear, as compared to other types of episodes.

An additional source of heterogeneity across studies was the recall periods for hypoglycaemia. Studies finding a significant association between episodes of hypoglycaemia and fear of hypoglycaemia all employed a recall period of a minimum of six months [9-11, 25, 27, 31]. As episodes of SH are relatively uncommon [34], it may be that short recall periods (e.g., three months) are not long enough to capture any episodes of SH, and therefore may not differentiate between children who do and do not experience SH. For future studies, researchers need to consider longer recall periods (at least six months).

Sample Heterogeneity

The age of the children in the included studies could also be a factor in explaining inconsistent findings. Studies with a majority of children in the older age group (12-15 years) were less likely to find a significant association between number or occurrence of hypoglycaemic episodes and parental outcomes [23, 26, 28]. Gonder-Frederick et al found that parental fear of hypoglycaemia was not related to episodes of hypoglycaemia, but rather related to their confidence in their child's ability to treat a hypoglycaemic episode. The mean age of the children in this study was 15 years [28]. In seven of the eight studies finding an association between episodes of hypoglycaemia and worse parental outcomes, the mean age of children was <12 years old [9, 10, 24, 25, 27, 29-31], with one including children as young as 12 months [10].

The stronger relationship observed in the review between hypoglycaemia and emotional reactions in parents of younger (compared to older) children could be explained by the significant involvement of parents in a child's (compared to an adolescent's) diabetes management. Younger children are less likely to be able to detect and communicate symptoms of hypoglycaemia, and are dependent on their parents to prevent, recognize and treat these episodes. Therefore, these parents may experience a greater negative impact of hypoglycaemia on their well-being, including higher fear of hypoglycaemia (e.g., worries about not being available to help their child, or the child being away from home when hypoglycaemia occurs,). Parental fear of hypoglycaemia is a complex construct. Predictors have been previously described to include personality, behavioral and situational factors [28].It is highly likely that various factors could impact on the relationship between frequency of episodes and fear of hypoglycaemia. However, future research should establish factors related to fear of hypoglycaemia, including age of the child, parents' confidence in managing hypoglycaemia, and time since diagnosis.

Finally, the studies in the review were published across more than two decades (from 1997 [27] to 2020 [24]), during which time diabetes management and technologies have changed substantially. However, most studies (*n*=7) included children using insulin pumps and multiple daily injections. There was no indication that mode of insulin administration affected the relationship between hypoglycaemia and parent-reported outcomes, although this could be explored in future studies.

Challenges with Parent-Reported Outcomes

None of the studies included in this systematic review used a validated measure of the impact of hypoglycaemia on quality of life. However, allowing inclusion of outcomes related to quality of life (i.e., psychological, social, or physical functioning) [35] enabled insight into how hypoglycaemia impacts substantially on parents' emotional well-being. Despite this, it should be noted that concepts that constituted "related outcomes" were defined by the authors. For optimal assessment of the impact of hypoglycaemia on parents' quality of life, there is a need for a measure that includes assessment of areas of life that are important for parents' quality of life, and enables attribution of those to the child's hypoglycaemia, i.e. a measure of hypoglycaemia-specific quality of life.

While some measures identified in this review were specific to hypoglycaemia (i.e. HFS-P and HFS-PYC), they are too specific to capture the full impact of hypoglycaemia on parents' quality of life, which includes a range of domains beyond emotional well-being. As emotional well-being is only one aspect of life contributing to the quality of life of a parent of a child with diabetes, it may be important to ask targeted questions about how hypoglycaemia impacts on various aspects of parents' lives.

Perspectives

To fully understand the impact of various experiences of a child's hypoglycaemia on parents' quality of life, future research needs to apply standard definitions of hypoglycaemic episodes that can reliably capture parents' proxy-report (e.g., a distinction between severe and less severe episodes as perceived by parents), also to allow for comparison across studies. In addition, as more studies use continuous glucose monitoring (CGM) for objective assessment of the depth and duration of hypoglycaemia, there is reason to hope that this aspect of the relationship may become clearer.

Clinical implications

This review showed that severe hypoglycaemia was associated with greater parental fear of hypoglycaemia. There are few evidence-based interventions aiming to reduce parental fear of hypoglycaemia (e.g. cognitive behavioural therapy interventions delivered to parents via telehealth [36]). This is an area for future research.

Technological advancements, such as CGM and hybrid closed loop systems, have been shown to reduce the rate of hypoglycaemia in children with type 1 diabetes [4, 37]. and the use of CGM has the potential to alleviate parents' fear of hypoglycaemia [38]. However, the use of CGM can also increase family conflict and cause "alarm fatigue" in parents [39]. Additionally, hybrid closed loop systems have been documented to decrease fear of hypoglycaemia in children with type 1 diabetes [40], and this might be the case for their parents as well. Due to these possible (dis)advantages of CGM, and limited understanding of the impact of hybrid closed loop systems on parental fear of hypoglycaemia, further research is needed to determine whether advanced diabetes technologies can minimise hypoglycaemia and its impact on parents' quality of life and related outcomes.

Future research

This systematic review has identified numerous measures used to assess the impact of hypoglycaemia on parental outcomes, such as emotional well-being. Further research and consensus is needed to establish a core set of questionnaires, which are the most acceptable to parents, psychometrically robust, and useful for determining the impact of hypoglycaemia on parents. Consensus has recently been established for adults with diabetes [41]. Furthermore, there is a need for suitable psychometric tools to assess how the child's risk and experiences of hypoglycaemia affects the parent's quality of life. We need to understand how quality of life domains such as work, social life and sleep, are affected by the child’s hypoglycaemia, as these have not been assessed in the studies identified in this systematic review.

As the evidence base consists of cross-sectional studies (and thus cannot provide evidence of temporality), alternative study designs are also needed to further understand how a child’s hypoglycaemia relates to parental outcomes. For example, longitudinal studies applying ecological momentary assessments (i.e. data collection of behaviour and experiences of a population in real time, for example using smart phones) alongside CGM could assess the direct impact of episodes of hypoglycaemia on parents’ daily lives. Likewise, to understand the complex impact of hypoglycaemia on a variety of areas of parents’ life, qualitative methods are crucial in capturing the lived experiences of parents.

Conclusion

The current evidence of the impact of a child’s hypoglycaemia on the quality of life of parents and caregivers remains limited by the small number of studies, the varied definitions and operationalisation of hypoglycaemia, and the absence of studies that have assessed the impact of hypoglycaemia on quality of life as a whole. The findings of the 12 studies in the present systematic review suggest that greater severity and frequency of hypoglycaemia are both associated with reduced parental psychological well-being, in particular greater fear of hypoglycaemia. However, most studies were cross-sectional and thus longitudinal research with hypoglycaemia-specific quality of life measures is needed to increase the understanding of how various aspects of parental quality of life are impacted by their child’s experience of hypoglycaemia.

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Table 1. Parents/Caregivers Characteristics of the Included Studies.

Reference and country	Parents (N)	Age of parent: years	Gender, *n*	Age of child: years
Aldubayee et al (2020) Saudi-Arabia [24]	390	Not reported	Females, 370 Males, 20	9.9 (3.1)
Amiri et al (2018) Iran [23]	105	Mothers: 36.2 (5.6), 25 – 49 Fathers: 36.2 (5.6), 30 – 58	Females, 60 Males, 45	9.2 (2), 6-12
Gonder-Frederick et al (2006) US [28]	39	Not reported	Females, 38 Males, 1	15.36 (1.5)
Haugstvedt et al (2010) Norway [10]	200	Mothers: 39.6 (5.7), 21–52 Fathers: 42.6 (6.4), 30–58	Females,103 Males, 97	10.6 (3.6), 1–15
Haugstvedt et al (2011) Norway [25]	200	Mothers: 39.6 (5.7), 21–52 Fathers: 42.6 (6.4), 30–58	Females,103 Males,97	10.6 (3.6), 1–15
Haugstvedt et al (2015) Norway [9]	176	Mothers: 40.2 (5.7) Fathers: 43.4 (6.3)	Females,91 Males,85	11.4 (2.9), 6-15
Hessler et al (2016) US [11]	322	All parents: 47.2 (5.86)	Females, 283 Males, 39	15.3 (2.2)
Johnson et al (2013) Australia [29]	325	Not reported	Females, 154 Males, 174	11.8 (3.7)
Kobos et al (2015) Poland [26]	112	Mothers only: 39.6 (6.8)	Females, 112	11.3 (3.6)
Marrero et al (1997) US [27]	61	Not reported	Females, 56 Males, 5	8.6 (3.4)
Patton et al (2007) US [31]	24	Not reported	Females, 20 Males, 4	5.7 (1.8)
Patton et al (2008) US [30]	145	Not reported	Females, 81 Males, 64	5.6 (1.6)

All data are mean (standard deviation), range

Table 2. Summary of the association between child's hypoglycaemia and parental outcomes (N=12 studies)

Reference and country	**Definition of Hypoglycaemia**	**Recall period**	**Child's experience of Hypoglycaemia**	**Parental Outcome measure**	**Main Findings**
Hypoglycaemia-Specific Measures: Fear of Hypoglycaemia					
Amiri et al (2018) Iran [23]	SH: Episodes where external assistance was required due to mental confusion or unconsciousness Problematic hypoglycaemia: episodes where the child was conscious but in need of parents' help	3 months	Problematic hypoglycaemia: *n*=59/61, Mean (SD) frequency =1.4 (5.4), range 0-36.	HFS-P	No significant associations between parents' fear of hypoglycaemia and episodes of children's problematic hypoglycaemia
Gonder-Frederick et al (2006), US [28]	MH: BG so low that it interfered with the adolescent's ability to function, but they did not become so mentally disoriented that self-treatment was not possible. SH: BG resulting in neuroglycopenia that interfered with the adolescent's ability to self-treat due to mental disorientation, unconsciousness, or seizure.	12 months	Mean (SD) frequency: MH: 6.74 (5.03) SH: 0.46 (2.11)	HFS-P	No significant association between HFS-P scores and the number of moderate or severe hypoglycaemia episodes.

Reference and country	**Definition of Hypoglycaemia**	**Recall period**	**Child's experience of Hypoglycaemia**	**Parental Outcome measure**	**Main Findings**
Hypoglycaemia-Specific Measures: Fear of Hypoglycaemia					
Haugstvedt et al (2010) Norway [10]	Problematic hypoglycaemic episodes: episodes perceived as problematic by parents	12 months	>7 problematic hypoglycaemia episodes in past 12 months: n=26/111 (23%) Hypoglycaemia with unconsciousness (ever): n=24/111 (21%) Hypoglycaemia during night (ever): n=79/113 (70%)	HFS-P	Association between problematic hypoglycaemia in past 12 months and HFS-P Worry subscale: ≥ 7 episodes vs. 0 episodes b= 5.06, CI= 1.50 - 8.61, *p*=.005
Haugstvedt et al (2015) Norway [9]	Problematic hypoglycaemic episodes: episodes perceived as problematic by parents	12 months	>7 problematic hypoglycaemia episodes in past 12 months n=22/99 (22%) Hypoglycaemia with unconsciousness (ever *n*=24/101 (24%) Hypoglycaemia during night (ever): n reports, *n*=71/100 (71%).	HFS-P	Mothers of a child reporting ≥ 7 episodes in the past year versus 0 episodes in the past year. Mean (SD) Worry subscale 42.1 (9.3) vs. 36.7 (10.3), *(d=0.55)* Behavior subscale 34.3(6.5) vs. 31.0 (5.8), *(d=0.53)*

Reference and country	**Definition of Hypoglycaemia**	**Recall period**	**Child's experience of Hypoglycaemia**	**Parental Outcome measure**	**Main Findings**
Hypoglycaemia-Specific Measures: Fear of Hypoglycaemia					
Johnson et al (2013) US [29]	MH: episodes requiring the assistance of another person for treatment SH: episodes with seizure or coma.	Not reported	SH: *n*=61/325 (18.8%)	HFS-P	Parents whose child had experienced a SH event had a 6.3-point higher fear-of-hypoglycaemia score *p*=.005
Marrero et al (1997) US [27]	Experience of seizures or loss of consciousness (SLC), due to hypoglycaemia that required second-party intervention.	Within past 12 months and since diagnosis of diabetes.	SLC in past 12 months*:* *n*=19/61 (30%) No SLC in past 12 months: *n*=43/61 (70%)	HFS-P	SLC in past 12 months vs. no SLC in past 12 months Mean (SD): HFS total score: 69.8 (15.1) vs. 58 (10.6) *p*= 0.005, (*d=0.9)* HFS Behaviour scale: 32.3 (6.8) vs. 28.8 (5.8) *p*=0.04, (*d=0.05)* HFS Worry scale: 37.6 (9.9) vs. 29.2 (7.2) *p*=0.003, (*d=0.9)* Mean (SD) for experience of SLC ever vs. no experience of SLC ever HFS total score: 64.9 (14.2) vs. 56.6 (10.1) *p*= 0.01, (*d=0.67)* HFS Behaviour scale: 31.1 (6.3) vs. 28.0 (5.8) *p*=0.05, (*d=0.51)* HFS Worry scale: 33.3 (9.6) vs. 28.7 (7.7) *p*=0.03, (*d=0.52)*

Reference and country	Definition of Hypoglycaemia	Recall period	Child's experience of Hypoglycaemia	Parental Outcome measure	Main Findings
Hypoglycaemia-Specific Measures: Fear of Hypoglycaemia					
Patton et al (2008) US [30]	*Baseline*: BG ≤ 60 mg/dL (3.3 mmol/L) Additionally, parents had to report whether the child had experienced a hypoglycaemia seizure	Not reported	Frequency BG ≤ 60 mg/dL (3.3 mmol/L), n (%) Once per day: 7 (9) 1–2 /wk: 27 (33) 3–5/wk: 31 (38) Once per month: 9 (11) Once every few months: 7 (9) History of hypoglycaemia seizure: Yes: 26 (32)	HFS-P-YC	Correlation between mothers' scores on the Worry subscale of the HFS-P-YC and the frequency of hypoglycaemic episodes: (r= .24, p < .05). Total HFS-P-YC scores for mothers of child who had a positive seizure history versus mothers of children who had never had a seizure: Mean (SD) 80.5 (17.7) vs. 72.4 (16.7), p=.05, (d=0.4)
	During the 2-weeks study period BG measurement at least 4 times daily for 2 weeks using a finger-prick BG monitoring device		*End of study period* Mean (SD) Number of BG checks below 60 mg/dl was 4.1 (6.3)		*End of study period* No significant correlations were found between mothers' HFS-PYC-Score and the number of BG checks below 60 mg/dl (3.3 mmol/L)

Reference and country	**Definition of Hypoglycaemia**	**Recall period**	**Child's experience of Hypoglycaemia**	**Parental Outcome measure**	**Main Findings**
Hypoglycaemia-Specific Measures: Fear of Hypoglycaemia					
Patton et al (2007) US	*Baseline*: BG ≤ 60 mg/dL (3.3 mmol/L) Additionally, parents had to report whether the child had experienced a hypoglycaemic seizure (HS)	6 months	Frequency of BG ≤ 0,60 mg/dL), Mean(SD): Once per day: 1(4) 1–2/wk.: 8(33) 3–5/wk.: 12(50) Once per month: 2(9) Once every few months: 1(4) Hypoglycaemic seizure: *n* (%) Yes: 6 (25) No: 18 (75)	HFS-P-YC	Parents of children with HS vs. vs. parents of children without HS. HFS-PYC Worry Subscale Mean (SD) (50.7 (12.6) vs. 41.7 (9.6), (d=0.8)
	During the 2-weeks study period BG measurement at least 4 times daily for 2 weeks using a finger-prick BG monitoring device		*End of study period* 5 ± 3% of tests below the target range of 70-200 mg/Dl.		*End of study period* No significant correlations between parents' HFS-PYC scores and the percentage of BG checks below the target range (70 mg-200 mg/dl).

Reference and country	**Definition of Hypoglycaemia**	**Recall period**	**Child's experience of Hypoglycaemia**	**Parental Outcome measure**	**Main Findings**
Diabetes-Specific Measures: Diabetes-specific Distress					
Hessler et al (2016) US [11]	SH: Where the adolescent required assistance from another.	6 months	Mean (SD) of low BG levels: 1.48 (2.64)	PDDS	Association between number of low BG levels and total parent stress: b=0.13 *p*=.009 Association between number of low BG levels and personal distress: b=0.18, *p*=.001
Generic Psychological Functioning					
Haugstvedt et al (2011) Norway [25]	Problematic hypoglycaemic episodes: episodes perceived as problematic by parents	12 months	≥7 problematic hypoglycemic episodes in the past year, n=29/115 (23%) Nocturnal hypoglycaemia (at least once): n=80/115 (69%) Loss of consciousness (at least once), n=24/115 (21%).	HSCL-25	Association between hypoglycaemia while asleep – yes vs. no and parents total score on the HSCL-25: b=0.11 *p*=.012
Aldubayee et al (2020) Saudi-Arabia [24]	Not reported	Not reported	Hypoglycaemia more than once\wk.: n=38/390 (9,9 %) Hypoglycaemia less than once/wk.: n=344/390 (90,1%)	PIP	Hypoglycaemia more than once/wk. and total frequency score vs. Hypoglycaemia less than once/wk. and total frequency score Mean (SD): 67.8 (12.3) vs 64.5 (6.8), *p* = 0.018, (*d*=0.33)

Reference and country	**Definition of Hypoglycaemia**	**Recall period**	**Child's experience of Hypoglycaemia**	**Parental Outcome measure**	**Main Findings**
Generic Psychological Functioning					
Amiri et al (2018) Iran [23]	SH: Episodes where external assistance was required due to mental confusion or unconsciousness Problematic hypoglycaemia: episodes where the child was conscious but in need of parents' help.	3 months	Problematic hypoglycaemia: *n*=59/61, Mean (SD) frequency =1.4 (5.4), range 0-36.	PIP	No significant associations between parents' stress measures and episodes of problematic hypoglycaemia.
Generic Parent and Family Functioning					
Haugstvedt et al (2011) Norway [25]	Problematic hypoglycaemic episodes: episodes perceived as problematic by parents	12 months	≥7 problematic hypoglycemic episodes in the past year, n=29/115 (23%) Nocturnal hypoglycaemia (at least once): n=80/115 (69%) Loss of consciousness (at least once), n=24/115 (21%).	FBS	Association between ≥7 episodes of hypoglycaemia vs. 0 episodes FBS score b=1.78 *p*=.002
Kobos et al (2015) Poland [26]	Not reported	Not reported	Glycaemia < 60 mg/dL: Few times/wk.: n =23/112 (20.4%) Every week: n=20/112 (17.9%)	CBS	No significant associations between frequency of glycaemia < 60 mg/dL and CBS scores.

Reference and country	**Definition of Hypoglycaemia**	**Recall period**	**Child's experience of Hypoglycaemia**	**Parental Outcome measure**	**Main Findings**
			Daily: n=8/112 (7.1%)		

CI= Confidence interval; SD= Standard deviation; *d*= Cohen's d;
BG= Blood Glucose; MH= Moderate hypoglycaemia; SH=Severe Hypoglycaemia;
CBS= Caregiver Burden Scale; FBS= Family Burden Scale; HS= Hypoglycaemic Seizure; HSCL-25= Hopkins Symptom Checklist-25 items; HFS-P= Hypoglycaemia Fear Survey - Parent version; HFS-P-YC = Hypoglycaemia Fear Survey – Parents of Young Children; PDDS = Parent Diabetes Distress Scale; PIP = Pediatric Inventory for Parents

Table 3. Overview of Quality Assessment

Reference	Aldubayee et al (2020)	Amiri et al (2018	Gonder-Frederick et al (2006)	Haugstvedt et al (2010)	Haugstvedt et al (2011)	Haugstvedt et.al (2015)	Hessler et al (2016)	Johnson et al (2013)	Kobos et.al (2014)	Marrero et al (1997)	*Patton et al (2007)	*Patton et al (2008)
Were the criteria for inclusion in the sample clearly defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the study subjects and the setting described in detail?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes
Was the exposure measured in a valid and reliable way?	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Unclear
Were objective, standard criteria used for the measurement of the condition?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were confounding factors identified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear
Were strategies to deal with confounding factors stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear
Were the outcomes measured in a valid and reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

*Although these studies employed a prospective design overall, the results relevant to this review were predominantly cross-sectional. Therefore, it was deemed appropriate to use the analytical cross-sectional study tool for these.

Figure legends

Appendix 1: Search String
Figure 1: PRISMA Flow Diagram

Appendix 1. Search string

1 exp Diabetes Mellitus, Type 1/
2 (("typ* 1" or "typ* I") adj2 diabet*).tw.
3 (IDDM or T1DM or T1D).tw.
4 (("insulin* depend*" or "insulin depend*") not ("non-insulin* depend*" or "noninsulin depend*")).tw.
5 1 or 2 or 3 or 4

11 exp Hypoglycemia/ or Blood Glucose Self-Monitoring/
12 (hypoglycemi* or hypoglycaemi* or hypo-glycemi* or hypo-glycaemi* or low blood sugar or low blood glucose or blood glucose monitor*).mp.
13 11 or 12
14 5 and 13 [T1DM + hypo]

16 ((psychological or psychosocial or psycho-social) adj3 outcome*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
17 ("level of independence" or self-efficacy or self-esteem or resilien* or ((social or friend* or marital or partner* or husband* or wife* or spous* or family or familial or families) adj3 relationship*) or social* isolat* or finances or sleep or "daytime functioning" or "cognitive function*" or productivity or (work adj2 absen*) or absenteeism or presenteeism or memory or mood or depress* or anxi* or ((fear or afraid or worr* or distress* or stigma* or impact*) adj3 (hypoglycaemi* or hypoglycemi*)) or "diabetes distress" or "diabetes stigma" or "diabetes burnout" or "psychological conflict").mp.
18 ("care needs" adj3 (express* or perception* or perspective* or judge* or (patient* adj2 view*) or "own assessment*")).mp.
19 Quality of Life/
20 quality of life.mp.
21 (hql or hqol or h qol or hrqol or hr qol).ti,ab,kf.
22 (life satisfaction or wellbeing or well-being).mp.
23 16 or 17 or 18 or 19 or 20 or 21 or 22 **[outcome / QoL terms]**
24 randomized controlled trial.pt. or randomized.mp. or placebo.mp.
[McMaster therapy filter]
25 meta analysis.mp,pt. or review.pt. or search:.tw. **[McMaster SR filter]**
26 ((("semi-structured" or semistructured or unstructured or informal or "in-depth" or indepth or "face-to-face" or structured or guide) adj3 (interview* or discussion* or questionnaire*)) or (focus group* or qualitative or ethnograph* or fieldwork or "field work" or "key informant")).ti,ab. or interviews as topic/ or focus groups/ or narration/ or qualitative research/
[University of Texas qualitative filter]
27 Epidemiologic studies/ or exp case control studies/ or exp cohort studies/ or Cross-sectional studies/

29 (longitudinal or retrospective or cross sectional).tw.
30 (cohort adj (study or studies)).tw.
31 (Follow up adj (study or studies)).tw.
32 (observational adj (study or studies)).tw.

34 (exp child/ not exp adult/) or (child* or adolescen* or teen* or schoolchild* or infant* or paediatric or pediatric).ti.
35 or/24-32 **[ALL eligible study types]**

37 14 and 23 and 34 and 35 **[Rev 1: T1DM + hypo + children]**

40 (parent* or carer* or caregiver* or father* or mother* or guardian*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
41 37 and 40 [**Rev 4: parents of children with T1DM]**

Figure 1. PRISMA Flow Diagram