



Quality of life of Children with Hypoglycemia in Type 1 diabetes: A systematic review

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ABSTRACT

Management of chronic diseases such as diabetes mellitus (DM) is difficult. People living with chronic diseases face challenges related to knowledge deficiencies, inability to sustain lifestyle modifications, and scarce access to specialists for timely advice. Although rates of SH in children and adolescents have decreased significantly in the past two decades, due to improvements in insulin administration and monitoring technologies. The review aims to summarize and critically appraise the evidence regarding the association between hypoglycemia and QoL (and related outcomes) in children and adolescents with type 1 diabetes. The PubMed, CINAHL and EBSCO database were searched for studies. The articles were searched by following inclusion and exclusion criteria. The articles published in English are considered. The journals which are peer reviewed are considered and included to manage the trustworthiness of the evidence. The articles published in the last 10 Years were considered. Out of 270 articles total 8 articles finalised. The findings showed that No hypoglycemia-specific measures of QoL were identified. Evidence for an association between SH and (domains) of generic and diabetes-specific QoL was too limited to draw conclusions, due to heterogenous definitions and operationalizations of hypoglycemia and outcomes across studies. SH was associated with greater worry about hypoglycemia, but was not clearly associated with diabetes distress, depression, anxiety, disordered eating or posttraumatic stress disorder. Although limited, some evidence suggests that more recent, more frequent, or more severe episodes of hypoglycemia may be associated with adverse outcomes and that the context in which hypoglycemia takes places might be important in relation to its impact.

INTRODUCTION

Management of chronic diseases such as diabetes mellitus (DM) is difficult. People living with chronic diseases face challenges related to knowledge deficiencies, inability to sustain lifestyle modifications, and scarce access to specialists for timely advice. In addition, people with DM need to master reading and mathematics skills to effectively incorporate the

principles of basal, bolus, and correction insulin doses to effectively manage their disease(Klonoff, 2013)

Type 1 diabetes is one of the most common chronic conditions among children and adolescents and requires a demanding treatment regimen (e.g., insulin administration several times a day, monitoring of glucose levels and regulation of food intake and physical activity) (DiMeglio *et al.*, 2018). The goal of diabetes management is to achieve and maintain recommended glycemic levels to prevent/delay acute and long-term complications (Cryer, Davis and Shamoon, 2003) However, treatment with insulin can lead to hypoglycemia (low blood glucose level) . Hypoglycemia can cause immediate uncomfortable symptoms (e.g., shakiness, dizziness), and in severe cases lead to confusion, seizures and coma, where self-treatment is not possible. In addition, recurrent episodes of severe hypoglycemia (SH) have been associated with neurocognitive impairments, especially in young children(Perantie *et al.*, 2008)

Although rates of SH in children and adolescents have decreased significantly in the past two decades, due to improvements in insulin administration and monitoring technologies (e.g., continuous subcutaneous insulin infusion and continuous glucose monitoring) , a recent systematic review still reported an incidence of 1.21–30 events per 100 person-years in young people with type 1 diabetes (Clements *et al.*, 2019). Hypoglycemia is particularly challenging and complex to manage in children and adolescents with type 1 diabetes for several reasons: this group has less predictable eating, activity, and sleep patterns relative to adults; children's diabetes is often (co-)managed by the parent; and young children may be unable to communicate their symptoms and needs (Maahs *et al.*, 2014). Among adolescents, both hormonal changes leading to insulin resistance and developmental changes, such as seeking independence from parents, that add to the burden of self-management, can lead to greater fluctuations in glucose levels and increase the risk of hypoglycemia (Haynes *et al.*, 2017)

It has been argued that, to understand the impact of a condition on QoL, we need to ask people how satisfied they are with the areas of life that are important to them for their overall QoL, and then ask how these areas are affected by the condition, such as diabetes or, more specifically, hypoglycaemia (St-Onge, Keller and Heymsfield, 2003) . It is therefore important to critically examine the range of patient-reported outcomes (PROs) used in studies, and to determine which are measuring the impact on QoL, (Coolen *et al.*, 2021)and which are measuring related outcomes (such as diabetes-specific emotional distress or health status) rather than QoL . Synthesis of the current evidence base is needed to determine the relationship between hypoglycemia and QoL-related outcomes(Alberti, Zimmet and Shaw, 2005).

Therefore, our aim was to conduct a systematic review to summarize and critically appraise the evidence regarding the association between hypoglycemia and QoL (and related outcomes) in children and adolescents with type 1 diabetes.

METHODS

The articles were searched by following inclusion and exclusion criteria. The articles published in English are considered. The journals which are peer reviewed are considered and included to manage the trustworthiness of the evidence. The articles published in the last 10 Years were considered

| Inclusion Criteria | Exclusion Criteria |
|-------------------------------------|-------------------------------------|
| Articles written in English | Non Peer Reviewed articles |
| Full Text articles | Paid articles |
| Articles Published in last 10 years | Articles written in other languages |

Search Strategy

This article reviews DM Type I in children that are commercially available and have had clinical outcomes data published in peer-reviewed literature in the past 10 years. The PubMed, CINAHL and EBSCO database were searched for studies based on randomized controlled trials (RCTs), observational studies, post hoc analyses, and survey studies. The articles examining the impact of hypoglycemia in various populations were searched. Search terms included free-text and subject heading terms relating to the following concepts, separated by the Boolean operator “and”: (1) type 1 diabetes, (2) children and adolescents, (3) hypoglycemia and (4) QoL and related outcomes. These databases were searched as most appropriate for the review

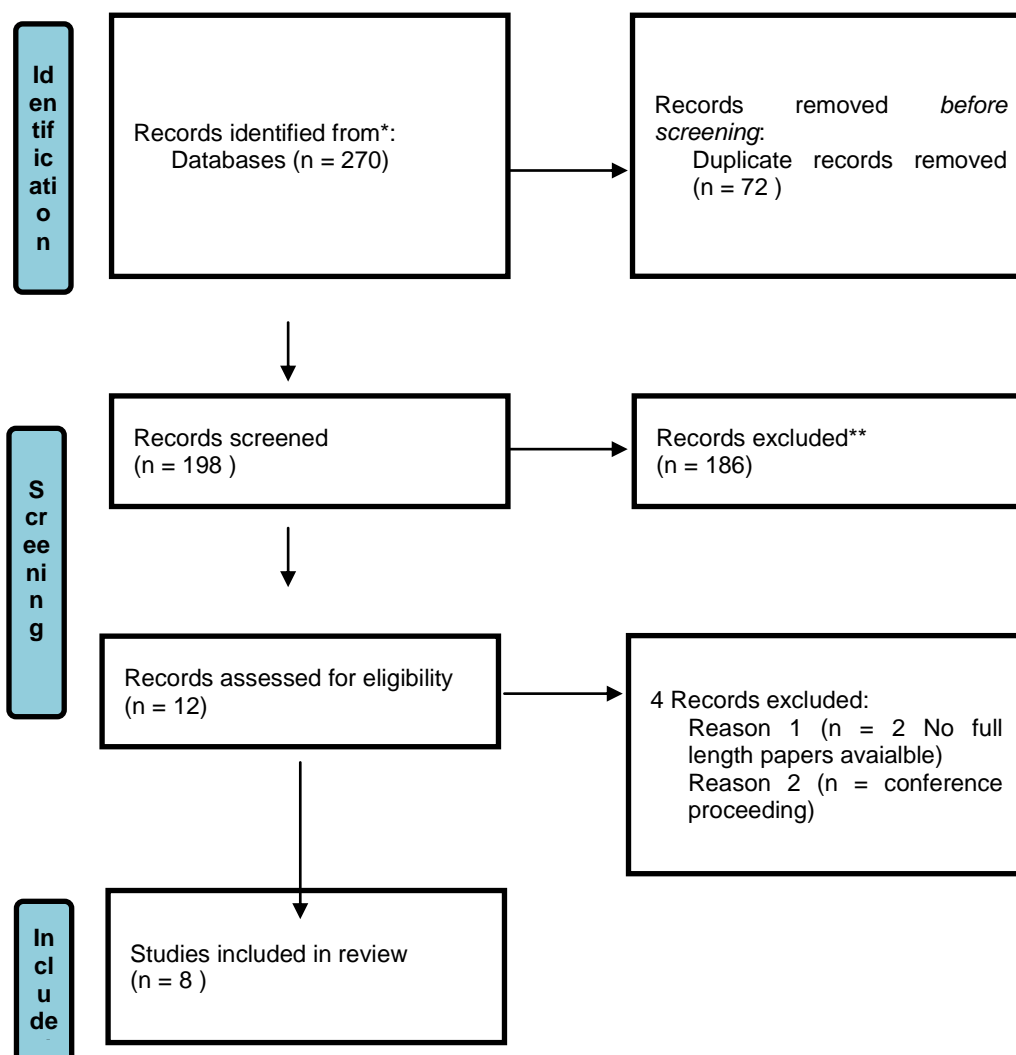
Inclusion and exclusion criteria were applied. (1) included children and/or adolescents with type 1 diabetes, majority aged ≤ 18 years, (2) assessed the history of hypoglycemia, (3) included outcomes of generic, diabetes-specific or hypoglycemia-specific QoL (or domains of QoL) or related outcomes (e.g., fear of hypoglycemia, depression, diabetes distress), (4) examined the association between hypoglycemia and QoL or related outcomes, (5) had a quantitative design, (6) were published in a peer-reviewed journal with full text available in English. Studies were excluded if they: (1) focused on cognitive functioning or neurodevelopmental disorders, or (2) only included proxy-report (e.g., by parents) of outcomes. The duplicate articles were removed. Total 270 articles were extracted. After applying the filters the remaining articles were screened by the titles and full text. The remaining articles were fully read and additional articles were fully retrieved. The final 6 articles were extracted and charted as follows

Risk of bias assessment

Risk of bias was assessed (MC) by the analytical cross-sectional studies critical appraisal tool from the Joanna Briggs Institute (JBI). Risk of bias assessment was not used to exclude studies but was discussed and summarized to aid interpretation of the quality of the evidence base

Data Extraction

The study design, Time period, participant characteristics, description and limitations were all gathered using a standard proforma. Inclusion and exclusion criteria were applied. The duplicate articles were removed. Total 270 articles were extracted . After applying the filters the remaining articles were screened by the titles and full text. The remaining articles were fully read and additional articles were fully retrieved. The final 8 articles were extracted and charted as follows

Table 2: PRISMA FLOWCHART

Results

| Author | Design | Sample size | Key findings |
|---|------------------------|--------------------|---|
| Al Hayek et al (Al Hayek <i>et al.</i> , 2015) | Cross Sectional | 187 | significant differences were observed in those with high frequencies of hypoglycemia, passing out, hypoglycemia while asleep and awake, and hypoglycemia in front of friends and at school. |
| Amiri (Amiri, Vafa and Gonder-Frederick, 2015) | Cross Sectional | 61 | The association between greater self-efficacy and lower fear of hypoglycemia |
| Coolen et al (Coolen <i>et al.</i> , 2021) | Cross Sectional | 96 | Fear of hypoglycaemia was the only factor independently associated with diabetes-specific quality of life, |
| Gallen et al (Galler <i>et al.</i> , 2021) | observational | 75258 | Children, adolescents, and young adults with type 1 diabetes and anxiety disorders had worse glycemic |

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|---|------------------------|------------|--|
| | | | control, higher rates of DKA, and more hospitalizations compared to those without anxiety disorders. |
| Hassan et al (Hassan <i>et al.</i> , 2017) | Cross Sectional | 150 | Adolescents with poor QoL had generally lower educational level |
| Johnson et al (Johnson <i>et al.</i> , 2013) | Cross Sectional | 196 | Fear of hypoglycaemia and not episodes of hypoglycaemia per se is associated with increased psychological burden for children with Type 1 diabetes |
| Adler et al (Adler <i>et al.</i> , 2017) | Cross Sectional | 45 | sleep disorders among most of the young T1D patients was no higher than in the nondiabetic population. Studies using objective sleep measures are warranted to further assess sleep quality in T1D patient |
| Caferoglu et al (Caferoglu <i>et al.</i> , | Cross Sectional | 70 | lower number of hypo- and |

| | | | |
|-------|--|--|---|
| 2016) | | | hyperglycaemic episodes were associated with an increase in psychosocial health scores and physical health scores as well as an increase in the total score for parents' proxy-reports. |
|-------|--|--|---|

(Al Hayek *et al.*, 2015) conducted cross-sectional study was conducted among 187 adolescents (aged 13-18 years; 92 males, 95 females) with T1DM at the Diabetes Treatment Center, Prince Sultan Military Medical City, Riyadh, Saudi Arabia, from June 2013 to February 2014. The participants were interviewed using FOH and Screen for Child Anxiety-Related Disorders (SCARED) scales. Females had significantly higher scores on all FOH and SCARED subscales compared to males. The mean scores for many subscales of FOH and SCARED were higher in the older age group (16-18 years), in those under multiple-dose injection (MDI) treatment (compared with the insulin pump treatment), and in those with a longer duration of T1DM. Similarly, significant differences were observed in those with high frequencies of hypoglycemia, passing out, hypoglycemia while asleep and awake, and hypoglycemia in front of friends and at school. Regression analysis revealed that higher age, female gender, MDI treatment, longer duration of T1DM, higher frequencies of hypoglycemia, passing out, hypoglycemia while asleep and awake, and hypoglycemia in front of friends and at school were the risk factors associated with the majority of the FOH and SCARED subscales. The behavior of the FOH subscale correlated with all the subscales of SCARED except the subscale of generalized anxiety disorder. Similarly, the FOH subscale of worry significantly correlated with all the subscales of SCARED.

(Amiri, Vafa and Gonder-Frederick, 2015) test the reliability of a Persian version of 2 questionnaires to assess the level of fear of hypoglycemia (FoH) and self-efficacy in diabetes management and their association with glycated hemoglobin (A1C) and parents' demographic characteristics in a sample of children with type 1 diabetes. The internal consistency of the Persian version of HFS-C and SED-C were very good. Our results showed that children older than 10 years of age report lower levels of FoH, which are related to higher levels of self-efficacy ($r=-.30$, $p=0.025$ and $r=-.30$, $p=0.02$, respectively). Of the children, 42.3% of girls and 31.4% of boys reported that low blood sugar is a big problem for them. These findings suggest that FoH is a significant concern for this target group. Only 19.7% of children had controlled diabetes based on A1C levels. There was no significant association between higher A1C levels and other variables, including HFS-C, SED-C and parents' demographic

characteristics. The Persian version of HFS-C and SED-C are reliable and valid measures of the fear of hypoglycemia and of self-efficacy in children with type 1 diabetes, and these questionnaires could be used in our country for identifying those children who may need diabetes education and other supports. The association between greater self-efficacy and lower fear of hypoglycemia suggests that addressing self-efficacy in diabetes education courses may be effective in helping to overcome FoH

(Coolen *et al.*, 2021) examined whether frequency, perceived severity and fear of hypoglycaemia are independently associated with diabetes-specific quality of life in adolescents with type 1 diabetes. Adolescents (12-18 years; $n = 96$) completed questionnaires. In the first three steps, female gender ($p < 0.05$), higher HbA_{1c} ($p < 0.05$), higher frequency of severe hypoglycaemia ($p < 0.05$) and higher perceived severity of severe ($p < 0.05$) and self-treated hypoglycaemia ($p < 0.001$) were significantly associated with lower diabetes-specific quality of life (β ranging from 0.20 to 0.35). However, in the final model only fear of hypoglycaemia was significantly associated with QoL ($p < 0.001$). Adolescents with greater fear reported lower diabetes-specific quality of life, with 52% explained variance. This pattern was observed across subdomains of diabetes-specific quality of life. Fear of hypoglycaemia was the only factor independently associated with diabetes-specific quality of life, whereas frequency and perceived severity of hypoglycaemia were not. These findings highlight the importance of awareness and assessment of fear of hypoglycaemia in clinical practice.

(Galler *et al.*, 2021) explored the metabolic characteristics and outcome parameters in youth with type 1 diabetes and anxiety disorders. HbA_{1c} levels, rates of severe hypoglycemia, diabetic ketoacidosis (DKA), and hospital admission in children, adolescents, and young adults with type 1 diabetes and an anxiety disorder from 431 diabetes-care-centers participating in the nationwide German/Austrian/Swiss/Luxembourgian diabetes survey DPV were analyzed and compared with youth without anxiety disorders. Children, adolescents, and young adults with type 1 diabetes and anxiety disorders ($n = 1325$) had significantly higher HbA_{1c} (8.5% vs. 8.2%), higher rates of DKA (4.2 vs. 2.5 per 100 patient-years), and higher hospital admission rates (63.6 vs. 40.0 per 100 patient-years) than youth without anxiety disorders (all $p < 0.001$). Rates of severe hypoglycemia did not differ. Individuals with anxiety disorders other than needle phobia ($n = 771$) had higher rates of DKA compared to those without anxiety disorders (4.2 vs. 2.5 per 100 patient-years, $p = 0.003$) whereas the rate of DKA in individuals with needle phobia ($n = 555$) was not significantly different compared to those without anxiety disorders. Children, adolescents, and young adults with anxiety disorders other than needle phobia had higher hospitalization rates (73.7 vs. 51.4 per 100 patient-years) and more inpatient days (13.2 vs. 10.1 days) compared to those with needle phobia (all $p < 0.001$). Children, adolescents, and young adults with type 1 diabetes and anxiety disorders had worse glycemic control, higher rates of DKA, and more hospitalizations compared to those without anxiety disorders. Because of the considerable

consequences, clinicians should screen for comorbid anxiety disorders in youth with type 1 diabetes.

(Hassan *et al.*, 2017) assessed the QoL in adolescents with T1D and assess the applicability of the use of the "Quality of Life for Youth" questionnaire at the Diabetes, Endocrine and Metabolism Pediatric Unit (DEMPU) clinic. One hundred and fifty adolescents (82 males and 68 females) (10-18 years), with T1D of at least 1 years' duration, completed the questionnaire that evaluated symptoms related to diabetes, treatment, activities, parent issues, worries about diabetes and health perception. Higher scores indicated a more negative impact of diabetes and poorer QoL. Males showed a significantly better mean QoL score than females ($p=0.004$). Different age groups showed different QoL scores ($p=0.047$). Urban adolescents had a better QoL than rural counterparts ($p=0.02$). Adolescents with poor QoL had generally lower educational level ($p=0.02$). Better metabolic control was associated with a better QoL ($p=0.01$). However, duration of diabetes and body mass index (BMI) had no statistically significant effect on QoL. QoL had a variable significant association with certain socio-demographic and clinical characteristics of diabetics (sex, residence, educational level as well as metabolic control).

(Johnson *et al.*, 2013) evaluate the association between fear of hypoglycaemia, episodes of hypoglycaemia and quality of life in children with Type 1 diabetes and their parents. This was a cross-sectional, population-based study of 325 children with Type 1 diabetes and their parents. The children were aged 2-18 years. A total of 325 parents of the patients aged 2-18 years and 196 of the patients themselves (aged 8-18 years) completed questionnaires including the PedsQL Diabetes Module, the Hypoglycaemia Fear Survey and Clarke's hypoglycaemia awareness questionnaire. Data were compared with HbA1c results and the history of severe hypoglycaemia episodes.

Parents with the highest levels of fear of hypoglycaemia reported that their children had a reduced quality of life ($P < 0.001$). Similarly children with the greatest fear also reported a reduced quality of life ($P < 0.001$); however a history of severe hypoglycaemia was not associated with the child's quality of life as perceived by the child or parent. Episodes of severe hypoglycaemia were associated with an increased fear of hypoglycaemia for the parents ($P = 0.004$) but not the children. Children in the highest fear quartile also had a higher HbA(1c) concentration compared with those in the lowest fear quartile [increase in HbA(1c) 7 mmol/mol (0.6%), $P < 0.01$]. Fear of hypoglycaemia and not episodes of hypoglycaemia per se is associated with increased psychological burden for children with Type 1 diabetes. Interventions to reduce fear of hypoglycaemia in these families may improve their quality of life.

(Adler *et al.*, 2017) assessed sleep characteristics in T1D patients and the possible association between sleep disturbances and diabetes-related variables. In a cross-sectional study in 154 young patients with T1D and 154 age-range-matched nondiabetic controls subjective sleep characteristics were assessed using validated questionnaires: Sleep Disturbance Scale for Children (SDSC), Adolescent Sleep-Wake Scale (ASWS), Pittsburgh Sleep Quality Index

(PSQI), Epworth Sleepiness Scale (ESS). Clinical and disease-related variables were obtained from medical charts. Sleep disorders were frequent in all age groups, with no significant difference in prevalence or total scores of the SDSC, ASWS, PSQI, or ESS between the patients and the controls. In T1D children, SDSC score was significantly higher in those using continuous glucose monitoring (CGM) vs glucose meters ($P = .042$). The score of disorders related to "initiating and maintaining sleep" was significantly higher in those treated with pumps vs patients treated with injections ($P = .014$), in those using CGM vs glucose meters ($P = .02$), and in those with nocturnal hypoglycemia vs those without ($P = .023$). The percentage of children with excessive daytime sleepiness was significantly lower in patients vs controls ($P = .035$). No significant differences were found in the other two age groups. The prevalence of sleep disorders among most of the young T1D patients was no higher than in the nondiabetic population. Studies using objective sleep measures are warranted to further assess sleep quality in T1D patients.

(Caferoğlu *et al.*, 2016) evaluated the HRQoL of Turkish children and adolescents with T1DM and to assess the correlation of HRQoL subscales (including physical and psychosocial health) with metabolic control, and particularly with hypo- and hyperglycaemic episodes. This cross-sectional study included 70 participants with T1DM aged between 8 and 18 years (study group) and 72 healthy controls who were matched to the study group in terms of age, gender, and sociodemographic characteristics (control group), and their parents. HRQoL was determined by the Pediatric Quality of Life Inventory. As an indicator of metabolic control, the most recent hemoglobin A1c (HbA1c) levels were obtained and the number of hypo- and hyperglycaemic episodes over the past one month were checked. The study group had similar HRQoL scores for children's self-reports and parents' proxy-reports to the control group apart from a decreasing psychosocial health score for parents' proxy-reports in the study group. Although HbA1c level was not related to HRQoL scores, lower number of hypo- and hyperglycaemic episodes were associated with an increase in psychosocial health scores and physical health scores as well as an increase in the total score for parents' proxy-reports. Although there was no correlation between metabolic control and HRQoL in children's self-reports, the improving HRQoL levels in parents' proxy-reports were associated with good metabolic control.

DISCUSSION

Results of this review show that evidence regarding an association between SH and (domains of) generic QoL is inconclusive, while the evidence suggests no association between NSH and generic QoL. For diabetes-specific QoL, the evidence was too limited to draw conclusions. None of the studies used hypoglycemia-specific QoL measures to explore the association between hypoglycemia and QoL (Mayfield and White, 2004). In addition, there was some evidence suggesting an association between SH in the past 12 months and greater worries about hypoglycemia, and no association between NSH and diabetes distress (Amiri, Vafa and Gonder-Frederick, 2015) There was insufficient evidence to draw conclusions regarding the relationship between hypoglycemia and diabetes distress (for SH),

FoH worries (for NSH), FoH-related behaviors and total FoH, anxiety, depression, disordered (Speight *et al.*, 2020)

A possible explanation for inconsistent findings is the heterogeneity in definitions of and recall periods for hypoglycemia and measures used to assess QoL across studies. This variation limits the ability to compare studies and draw conclusions (Cherubini *et al.*, 2014). Several key limitations of the existing evidence base were identified, such as cross-sectional designs, low statistical power, lack of reporting of effect sizes (and thus limited information on the clinical value of the observed statistically significant differences), lack of information on the definition or frequency of hypoglycemia, and the self-report of hypoglycemia over several months or even back to diagnosis, which might have led to recall bias (Jones and Davis, 2003). The key recommendation for future studies is to use a definition of hypoglycemia as recommended by current guidelines. Future studies should also use longitudinal /prospective study designs and modern methods, such as continuous glucose monitoring, for a more objective assessment of hypoglycemia that does not rely on recall of episodes, to determine the direct, day-to-day impact of hypoglycemia on various domains of QoL in children and adolescents with type 1 diabetes. Although emerging evidence shows the importance of self-treated hypoglycemia in relation to QoL and related outcomes in adults with diabetes (Nip *et al.*, 2019), current evidence on this relationship in youth with type 1 diabetes suggested no association between NSH and QoL (J *et al.*, 2021). However, this should be interpreted with caution, as these studies are limited by the use of generic and diabetes-specific QoL questionnaires, while hypoglycemia-specific QoL measures may be more sensitive to the impact of NSH. Different research designs, that minimize recall bias and assess the impact closer to the occurrence NSH are needed to understand the association between NSH and QoL. In addition, this review identified only one study that explored the association between hypoglycemia while asleep and sleep quality (Hanberger, Ludvigsson and Nordfeldt, 2009). This highlights the need for more studies that investigate such relationships.

The majority of studies included in this review pooled children and adolescents together when examining the link between hypoglycemia and QoL or related outcomes. Although these studies usually included age-appropriate assessments of outcomes, the impact of hypoglycemia on these outcomes might be different for children and adolescents. While younger children often rely on their parents for decisions about diabetes management, these responsibilities are usually transferred to the child during adolescence

Strengths and Limitations

Strengths of this review include the systematic and comprehensive search of multiple databases, and the application of a conceptual framework of QoL to categorize outcome measures in order to critically appraise the evidence. This allows for a more detailed understanding of the various ways in which hypoglycemia can impact on QoL and related outcomes and highlights the gaps in the evidence base. This review also has some limitations. Although the inclusion of a wide range of outcomes provided an overview of all the available evidence related to the impact of hypoglycemia on QoL, it also made it difficult to compare studies directly. Further, the heterogeneity across studies and the lack of effect sizes reported

in studies, precluded the possibility of meta-analysis. The inclusion of only quantitative studies that were published in English may have introduced some bias, although only six studies were excluded for this reason.

CONCLUSION

This systematic review shows that there is insufficient evidence on the relationship between hypoglycemia and (domains of) generic and diabetes-specific QoL in children and adolescents with type 1 diabetes. This is largely because heterogeneity and methodological limitations across studies hamper the ability to draw strong conclusions. Importantly, none of the studies used a measure designed specifically to assess the impact of hypoglycemia on QoL. Additionally, there seems to be an association between SH and greater worry about hypoglycemia, while the evidence is too limited for other related outcomes. Although limited, some evidence suggests that issues such as timing and context of hypoglycemia might influence its impact. Future research should focus on the development of measures that can assess the impact of hypoglycemia in children and adolescents with type 1 diabetes and use agreed definitions of hypoglycemia that increase comparability between studies.

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