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The impact of hypoglycaemia on quality of life in children and adolescents with type 1 diabetes

PhD Thesis – Manon Coolen

University of
Southern Denmark

HYPO
RESOLVE

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The end of one journey means the beginning of another one. I am excited to see where my next journey will take me!

Manon
Odense - November 2021

Outline of this thesis

The present thesis is structured in four chapters based on three studies. Chapter 1 gives a general introduction into the research field and describes the aims and objectives of this thesis. Chapter 2 provides an overview of the different methodologies that are used in the studies. Chapter 3 summarizes the most important results from the respective studies. These results are then discussed and integrated on an overall level in Chapter 4. This chapter also presents methodological considerations, clinical implications, directions for future research and final conclusions.

List of papers included in the thesis

1. **Coolen M**, Aalders J, Broadley, M, Aanstoot HJ, Hartman EE, Hendrieckx C, Nefs G, & Pouwer F. Hypoglycaemia and diabetes-specific quality of life in adolescents with type 1 diabetes. Diabetic Medicine. 2021;38(8):1-9. DOI: 10.1111/dme.14565

2. **Coolen M**, Broadley M, Hendrieckx C, Chatwin H, Clowes M, Heller S, de Galan BE, Speight J, & Pouwer F, for the Hypo-RESOLVE Consortium. The impact of hypoglycemia on quality of life and related outcomes in children and adolescents with type 1 diabetes: a systematic review. PLOS ONE. [under review]

3. **Coolen M,** Broadley M, Axelsen, JL, Carlton J, Heller S, Amiel SA, de Galan BE, Hermanns N, Finke-Gröne K, Hendrieckx C, Pouwer F, & Speight, J, for the Hypo-RESOLVE consortium. ‘I don't want to stand out and be different’. A multi-country, web-based qualitative study of the impact of hypoglycaemia on quality of life among adolescents with type 1 diabetes. [Submitted for publication]

English summary

Type 1 diabetes (T1D) is one of the most common chronic illnesses in paediatric populations, affecting more than one million children and adolescents (0-18 years old) worldwide. As there is no cure for diabetes yet, management of diabetes requires demanding and complex self-care tasks, including administration of insulin (with multiple daily injections or an insulin pump) and monitoring of glucose levels multiple times per day. This can be challenging and have an impact on the quality of life (QoL) of children and adolescents with diabetes. Moreover, treatment with insulin can lead to hypoglycaemia (low blood glucose level), which can involve symptoms including tiredness, confusion, and shakiness, and in severe cases, can result in loss of consciousness, coma, and, rarely, death. Even though there have been technological developments, such as continuous glucose monitoring devices, that may help to prevent or reduce hypoglycaemia, many young people with T1D still experience multiple episodes of hypoglycaemia on a weekly basis. In addition, they have to deal with the constant threat of having hypoglycaemia. This can be stressful and frightening for them and their families and can have a huge impact on their lives. Although the physical consequences of hypoglycaemia are well documented, it is not yet clear how hypoglycaemia affects QoL of children and adolescents with T1D.

Therefore, the aim of this thesis was to examine the impact of hypoglycaemia on QoL in children and adolescents with T1D. To address this research question, three studies with different designs and methodologies were conducted.

The first study was a cross-sectional quantitative study involving 96 adolescents with T1D, that examined independent associations between frequency of hypoglycaemia, perceived severity of hypoglycaemia and fear of hypoglycaemia and QoL. In the first steps of the model, female gender, higher HbA_{1c}, higher frequency of severe hypoglycaemia, and higher perceived severity of severe and self-treated hypoglycaemia were significantly associated with lower diabetes-specific QoL. However, in the final model, fear of hypoglycaemia was the only significant independent predictor of diabetes-specific QoL. Adolescents with greater fear reported lower diabetes-specific QoL. These results highlight the importance of examining subjective experiences with hypoglycaemia when investigating the impact of hypoglycaemia on QoL.

The second study was a systematic review that evaluated previous studies that examined the association between hypoglycaemia and QoL and related outcomes. Results of this review indicated that the evidence for an association between severe hypoglycaemia and generic and diabetes-specific QoL was inconclusive. Severe hypoglycaemia was associated with greater worries about hypoglycaemia, but there was inconclusive evidence for diabetes distress, depression, anxiety, disordered eating, or posttraumatic stress disorder. The different methodological approaches that have been used for the measurement of hypoglycemia and psychological outcomes might have contributed to discrepant findings across studies. This highlights the importance of developing new tools to

measure the impact of hypoglycaemia on QoL in children and adolescents with T1D. These tools should be age appropriate and allow adolescents to indicate personal preferences regarding what is important for their QoL.

The third study was a qualitative web-based multi-country study that explored the impact of hypoglycaemia on QoL in 75 adolescents with T1D. To address the limitations of previous studies, a novel, individualized approach to measure QoL was used. Participants reported that both hypoglycaemia and living with the risk of hypoglycaemia impacted on various, important domains of their QoL, such as friends, family, school, sports, and sleep. Hypoglycaemic episodes had a physical, emotional, social, cognitive, and behavioural impact on different domains of QoL. The risk of hypoglycaemia had an impact on QoL through worries, reduced freedom, and sub-optimal glucose management. Future studies should investigate whether interventions aimed at reducing this impact could help to improve QoL in adolescents with diabetes.

The findings of this thesis illustrate that hypoglycaemia can impact on QoL in young people with T1D, not only through experiences of hypoglycaemia episodes per se, but also via worries or fear about hypoglycaemia. This highlights the importance of further exploring the impact of hypoglycaemia on QoL using appropriate measures, and the need to address this impact in individualized clinical care, in order to minimize the burden of hypoglycaemia for young people with T1D.

Danish summary

Type 1-diabetes (T1D) er en af de mest almindelige kroniske sygdomme i pædiatriske populationer, der påvirker mere end en million børn og unge (0-18 år) i verden. Da der endnu ikke findes nogen kur mod diabetes, indebærer behandling af diabetes krævende og komplekse egenomsorgs-opgaver, herunder administration af insulin (med flere daglige injektioner eller en insulinpumpe) og overvågning af glukose-niveauer flere gange dagligt. Dette kan være udfordrende og påvirke livskvaliteten for børn og unge med diabetes. Derudover er hypoglykæmi (lavt blodsukker) en komplikation til behandling med insulin, som kan involvere symptomer såsom træthed, forvirring og rysten, og i alvorlige tilfælde kan resultere i bevidsthedstab, koma eller død. Selvom der har været en udvikling på flere teknologiske områder, for eksempel kontinuerlig blodsukker-måling, der kan hjælpe med at forebygge eller reducere hypoglykæmi, oplever mange børn og unge med T1D stadig flere episoder af hypoglykæmi om ugen. Derudover skal de leve med den konstante risiko for at få hypoglykæmi. Dette kan være stressende og skræmmende for de unge og deres familier, hvilket kan påvirke deres livskvalitet negativt. De fysiske konsekvenser af hypoglykæmi er veldokumenterede, men der er begrænset forskning i hypoglykæmis påvirkning af livskvaliteten for børn og unge med T1D.

Derfor er formålet med denne PhD. at undersøge, hvordan hypoglykæmi påvirker livskvaliteten for børn og unge med T1D. For at besvare forskningsspørgsmålet er der blevet udført tre undersøgelser med forskellige designs og metoder.

Det første studie var en tværsnitsundersøgelse, der involverede 96 unge med T1D. Her blev der undersøgt sammenhænge mellem frekvensen af hypoglykæmi, selv-rapporteret sværhedsgrad af hypoglykæmi, frygt for hypoglykæmi og de unges livskvalitet. I de første trin af analysen var det kvindelige køn, højere HbA1c, højere frekvens af svær hypoglykæmi og højere oplevet sværhedsgrad af svær og selv-behandlet hypoglykæmi signifikant associeret med ringere diabetes-specifik livskvalitet. I den endelige model var frygt for hypoglykæmi den eneste uafhængige prædiktor for diabetes-specifik livskvalitet. Unge med højere frygt rapporterede ringere diabetes-specifik livskvalitet. Disse resultater fremhæver vigtigheden af at fokusere på subjektive oplevelser med hypoglykæmi, når man undersøger hypoglykæmis indvirkning på livskvaliteten.

Det andet studie var et systematisk review som evaluerede tidligere studier, der undersøgte sammenhængen mellem hypoglykæmi og livskvalitet og relaterede psykologiske områder. Resultaterne af dette systematiske review indikerede, at sammenhængen mellem alvorlig hypoglykæmi og generel og diabetes-specifik livskvalitet endnu er uafklaret. Alvorlig hypoglykæmi var associeret med flere bekymringer om hypoglykæmi, men der var uafklarede beviser for diabetes-relateret stress, depression, angst, spiseforstyrrelser eller posttraumatisk stresslidelse. De forskellige metoder, som var blevet anvendt til at måle hypoglykæmi og dets psykologiske konsekvenser, kan have bidraget til de forskellige resultater, som eksisterer i litteraturen. Dette understreger vigtigheden

af at udvikle nye værktøjer til at undersøge effekten af hypoglykæmi på livskvalitet for børn og unge med T1D. Disse værktøjer skal være alders-egnede og give unge mulighed for selv at indikere personlige præferencer for, hvad der har betydning for deres livskvalitet.

Det tredje studie var et kvalitativt, webbaseret multinationalt studie, der undersøgte hypoglykæmis påvirkning på livskvalitet hos 75 unge med T1D. For at imødekomme begrænsningerne set i tidligere undersøgelser, blev der brugt et nyt individualiseret værktøj til at måle livskvaliteten. Deltagerne rapporterede, at både hypoglykæmi og at leve med risikoen for hypoglykæmi påvirkede forskellige vigtige områder i deres liv, såsom venner, familie, skole, sport og søvn. Hypoglykæmiske episoder havde en fysisk, emotionel, social, kognitiv og adfærdsmæssig påvirkning på forskellige områder af unges livskvalitet. Risikoen for hypoglykæmi havde en indvirkning på livskvaliteten gennem bekymringer, nedsat frihed og suboptimal glukose-styring. Fremtidige studier bør undersøge, om interventioner rettet mod at reducere denne påvirkning kan bidrage til at forbedre livskvaliteten hos børn og unge med T1D.

Resultaterne af denne afhandling illustrerer, at hypoglykæmi kan påvirke livskvaliteten for børn og unge med T1D, ikke kun gennem oplevelser af episoder med hypoglykæmi, men også via bekymringer eller frygt for hypoglykæmi. Dette understreger vigtigheden af yderligere at undersøge hypoglykæmis påvirkning af livskvaliteten for børn og unge ved hjælp af passende værktøjer, samt behovet for at adressere denne påvirkning i en individualiseret behandling, for dermed at forsøge at minimere udfordringen ved hypoglykæmi for børn og unge med T1D.

Abbreviations

CGM	Continuous Glucose Monitoring
CSII	Continuous Subcutaneous Insulin Infusion
FoH	Fear of Hypoglycaemia
HbA$_{1c}$	Glycated haemoglobin
HFS-C	Hypoglycaemia-Fear Survey Child version
HFS-SF	Hypoglycaemia Fear Survey- Short Form
HypoA-Q	Hypoglycemia Awareness Questionnaire
Hypo-RESOLVE	Hypoglycemia – REdefining SOLutions for better liVEs
IAH	Impaired Awareness of Hypoglycemia
ISPAD	International Society for Paediatric and Adolescent Diabetes
JBI	Johanna Briggs Institute
MC	Manon Coolen
MDI	Multiple Daily Injections
PedsQL-DM	Paediatric Quality of Life Inventory – Diabetes Module
QoL	Quality of Life
SAP	Sensor Augmented Pump
SH	Severe Hypoglycaemia
SPSS	Statistical Package for the Social Science
T1D	Type 1 Diabetes
WP6	Work Package 6

Key defintions

Key definitions of important concepts in the present thesis	
Diabetes distress	• Negative emotions related to living with and managing diabetes
Fear of hypoglycaemia	• Elevated level of worries and/or fear related to (the consequences of) hypoglycaemia
Impaired awareness of hypoglycaemia	• Loss of warning symptoms to recognize hypoglycaemia
Non-severe hypoglycaemia	• Hypoglycaemia episodes that involve unpleasant symptoms such as hunger, sweatiness, shakiness, or confusion, but can often be self-treated by the young person with diabetes or their parents (depending on the age of the child)
Severe hypoglycaemia	• Hypoglycaemia episodes involving cognitive impairment such as loss of consciousness, seizures or coma that require assistance from others to recover
Quality of life	• A subjective, multidimensional, and dynamic construct

Chapter 1

Introduction

Introduction

In the following chapter, a general introduction to type 1 diabetes (T1D) and hypoglycaemia is given, followed by issues specific to children and adolescents. Following this, an overview of the psychosocial impact of T1D and hypoglycaemia is presented. Finally, the aims and objectives of the present thesis are presented.

Understanding type 1 diabetes and its treatment

Although there are several types of diabetes, including T1D, type 2 diabetes and gestational diabetes, the present thesis focuses on T1D, which accounts for approximately 5-10% of all people diagnosed with diabetes (1). In paediatrics however, T1D it is the most common form of diabetes, accounting for more than 85% of cases (2, 3). Approximately 1.1 million children and adolescents worldwide are affected by T1D (4).

T1D is an autoimmune disease where the β-cells in the pancreas (which produce insulin) are inactivated or destroyed (5). As a result, most people with T1D have an absolute deficiency of insulin (5). Insulin is necessary for glucose uptake in the cells to be used for energy. Without insulin, cells are unable to use glucose, causing blood glucose levels to rise (6). The body then starts to break down fat as an alternative source of energy, resulting in the production of ketones, which can lead to diabetic ketoacidosis which, if not treated, can result in coma or even death (7). People with T1D therefore need intensive treatment with insulin for survival (2, 6).

One of the goals of diabetes management is to keep glucose levels within target ranges to prevent short and long-term complications (8). Short-term complications include diabetic ketoacidosis or hypoglycaemia (low blood glucose). Hypoglycaemia can involve self-treated episodes with unpleasant symptoms such as shakiness, dizziness, sweatiness, blurred vision, concentration problems, mood changes or hunger (9). In (younger) children with T1D, the most common hypoglycaemia symptoms are behavioural symptoms, such as irritability (9-11). These day-to-day episodes are usually managed by the young person with diabetes or their parents, depending on the age of the child (9, 12). In more severe cases, hypoglycaemia can lead to impaired cognitive functioning, ranging from confusion to loss of consciousness, seizures, or coma where assistance of others is required to recover (9). Long-term complications include both microvascular complications, such as neuropathy and retinopathy, and macrovascular complications, such as cardiovascular disease (13).

Keeping glucose levels within target range requires a demanding treatment regimen, including insulin administration through multiple daily injections (MDI) or insulin pump therapy (continuous subcutaneous insulin infusion; CSII), self-monitoring of glucose levels multiple times per day, counting carbohydrates, and regulating food intake and exercise (14). In addition, environmental and biological factors such as stress, temperature, insulin absorption rates (depending on the injection site), other medications, or illness can also impact on glucose levels and should thus be considered when interpreting glucose levels and calculating insulin doses (15, 16). Finally, diabetes self-care behaviours involve healthy coping, problem-solving skills to set goals and transfer knowledge into action and engagement in behaviours that reduce risk of short and long-term complications (17). While parents often bear responsibility for the management of the child's diabetes during (early) childhood, this responsibility is usually transferred to the child during adolescence (12). Diabetes education plays an important role in supporting young people with T1D (and their parents) to engage in effective diabetes management and implement the necessary diabetes self-care skills into their lives (18). Several structured diabetes education programmes are available that focus on increasing knowledge and skills required for diabetes self-care, including minimizing and preventing hypoglycaemia (9, 19).

Given the myriad of factors that can affect blood glucose levels (15, 16), it is recommended that people with T1D check their glucose levels six to ten times per day in order to undertake the necessary self-care behaviours to keep glucose levels within target range (14). Glucose levels can be measured by a finger prick, which measures blood glucose at intermittent times throughout the day, or with a continuous glucose monitoring (CGM) device, which measures interstitial glucose levels every 1-5 minutes through a sensor that is placed under the skin and is connected to a monitoring device or a smartphone app, which displays the glucose levels and enables observation and reflection on glucose profiles (14, 20). Many such devices can be set up to alarm when glucose levels go above or below certain pre-set thresholds (14, 20). Other recent technological developments include sensor augmented pump (SAP) systems that can automatically suspend administration of insulin when a CGM detects that glucose levels are decreasing (20). In all these cases, there is an 'open loop system', in which the child/adolescent with T1D or their families have to make decisions about when to measure glucose levels and/or how to use the information to adjust glucose levels. There are recent, promising, developments towards 'closed-loop systems' that employ algorithms to automatically adjust insulin administration on the pump based on real time CGM glucose levels. However, these systems are not yet widely (commercially) available, and more research is needed to better assist young people with T1D and their families in adopting such systems (20).

The current guidelines of the International Society for Pediatric and Adolescent Diabetes (ISPAD) recommend that diabetes care for children and adolescents with T1D should include regular visits (i.e., every 3 months) to the multidisciplinary diabetes care team, including endocrinologists, nurses, social workers, and psychologists for ongoing evaluation of diabetes management and (psychosocial) health (8). Glycosylated haemoglobin (HbA_{1c}) levels give an impression of the average blood glucose levels in the past two to three months and are used as an index to evaluate diabetes management. For children and adolescents with diabetes, HbA_{1c} targets of <7.5% (58mmol/mol) are recommended as these are predictive of fewer diabetes-related microvascular and macrovascular complications later in life (14, 21). The most recent ISPAD guidelines reduced the HbA_{1c} target to <7.0% (53mmol/mol) for children and adolescents with access to comprehensive care (14). However, these targets should always be individualized and balanced against the individual's risk of hypoglycaemia (14).

Insulin: a blessing and a curse?

Although people with T1D are dependent on insulin for survival, the most common side effect of insulin treatment is hypoglycaemia (22). When blood glucose levels fall in people *without* diabetes, counter-regulatory mechanisms inhibit the secretion of insulin and release glucose from the liver, thus protecting the individual from hypoglycaemia. However, in people *with* T1D, these defence mechanisms are compromised, and glucose levels will drop further until insulin is completely absorbed (23). Therefore, they have to rely on recognizing hypoglycaemia warning symptoms, such as hunger, shakiness, sweatiness or confusion, and/or information about glucose levels derived from glucose monitoring devices, to confirm hypoglycaemia. Consequently, they have to take behavioural actions, such as taking exogenous glucose (e.g., a sugary drink), in order to restore glucose levels (9, 23).

As stated in the position statement of the American Diabetes Association, hypoglycaemia is "an abnormally low plasma glucose concentration that exposes the individual to potential harm" (24 p1246). However, it is difficult to define a single threshold glucose level that defines hypoglycaemia, as biochemical measures of hypoglycaemia do not always correspond to the experiences of hypoglycaemic symptoms, and the threshold for warning symptoms varies greatly between individuals (9, 25). Despite these differences, the current ISPAD guidelines recommend that hypoglycaemia in children and adolescents should be treated at a glucose level of ≤3.9 mmol/L (70 mg/dL), to prevent further dropping of glucose levels (9). In addition, these guidelines define clinically important hypoglycaemia as glucose levels <3.0 mmoL/L (54 mg/dL), and severe hypoglycaemia (SH) as an event including cognitive impairment, such as coma or convulsions where external assistance is required to recover (9).

Although the use of technological devices such as CSII, CGM, or SAP has the potential to prevent and reduce rates of SH (20, 26), some studies did not report any differences in rates of SH between those who used such devices and those who did not (27, 28). Furthermore, although the use of these devices in paediatric diabetes care has increased in the past two decades, its use is not yet widespread, due to issues with accessibility and affordability (20, 29). Other barriers experienced with the uptake of technological devices include physical discomfort, body image concerns, and interfering alarms (20). SH thus remains common among young people with T1D (30). A recent register-based population study in a Danish paediatric cohort including 2715 children and adolescents with T1D with a mean age of 13.7 years showed an overall incidence of SH of 7.6 per 100 person-years (31). This is comparable with the findings of a systematic review that indicated SH rates ranged from 3.3 to 7.1 per 100-person years in children and adolescents with T1D (26).

While studies in adults with T1D often distinguish between SH and self-treated hypoglycaemia (also sometimes referred to as "non-severe" hypoglycaemia), this distinction cannot be translated fully to children and adolescents with T1D, as they often need help with treatment of hypoglycaemia regardless of the severity (32). Consequently, various studies employ different definitions of “non-severe” hypoglycaemia, sometimes also referred to as “mild” or “moderate” hypoglycaemia. This makes it difficult to accurately estimate the frequency of both severe and non-severe hypoglycaemia. Studies have reported rates of non-severe hypoglycaemia ranging from 2 per week to 5 per month (9, 33). This is likely to be an underestimation of the problem of hypoglycaemia in everyday life, as non-severe hypoglycaemia is often significantly under-reported in retrospective studies.

Another important concern is the frequency of nocturnal hypoglycemia, which often remains undetected (34). In an earlier large population-based study in children and adolescents with T1D, 75% of SH episodes occurred during the night (35). A more recent study reported that hypoglycaemia occurred on 25% of the nights in children and adolescents with T1D (36). Additionally, the continuous glucose monitoring study of the Juvenile Diabetes Research Foundation indicated that the duration of nocturnal hypoglycaemia was longer in children and adolescents below 25 years old, compared to adults.

Repeated episodes of (severe) hypoglycemia place an individual at risk for impaired awareness of hypoglycemia (IAH), characterized by a loss of warning symptoms to recognize hypoglycaemia (37). Depending on the assessment method, IAH occurs in about 22-41% of children and adolescents with T1D (38, 39). A recent population-based study, however, showed a reduction in IAH among adolescents with T1D from 33% in 2002 to 21% in 2015 (40). Although this reduction is promising, IAH remains a significant risk factor for SH (38-40).

It is no surprise that (the threat of) hypoglycaemia can induce distress, worries and fear (41, 42). These worries can be adaptive and enable the person with diabetes (or their parent/caregiver) to take appropriate actions and treatment. However, when these worries become disproportionate, they can develop into a more severe, hypoglycaemia-specific form of anxiety, which is often referred to as fear of hypoglycaemia (FoH) (41). Though hypoglycaemia history is recognized as one of the most common predictors of FoH, one can also develop FoH regardless of a history of hypoglycaemia (43, 44). In addition, other factors, such as female gender or trait anxiety are also linked to FoH (45, 46). Although some diabetes technologies can potentially reduce FoH (47), there is ambiguous evidence on the impact of technology on fear levels (41, 43).

FoH can have negative consequences for diabetes management and/or QoL (41, 43, 48). The child/adolescent with T1D (or the person responsible for their daily diabetes management) might engage in avoidance or compensation strategies to avoid hypoglycaemia, such as deliberately maintain high blood glucose levels or reducing insulin intake (41, 48). In addition, FoH can lead to disruptions in sleep and avoidance of social and leisure activities which can impair QoL (41).

Although hypoglycaemia can be a burden for all people with diabetes and their family members (49, 50), different age groups have different experiences, risks, and needs in relation to hypoglycaemia that should be considered. Children and adolescents with T1D represent a unique group of people with diabetes, as developmental challenges (physiological, cognitive, psychological, social) can interact with diabetes self-management (29).

Children are not just small adults

For the purpose of this thesis, three developmental phases will be distinguished: early childhood, middle childhood, and adolescence (12). In the following section, specific issues and challenges in relation to diabetes management and hypoglycaemia in each of these phases will be described.

In early childhood, typically defined as 0-5 years, parents are often fully responsible for their child's diabetes management and care strategies are mainly focused on supporting parents (12, 51). In addition, young children tend to have unpredictable eating, sleeping and activity patterns, which can make it difficult to regulate their diabetes and make them more vulnerable to hypoglycaemia (29). As young children are not always able to recognize hypoglycaemia symptoms or to communicate their needs, their parents bear responsibility in recognizing and treating hypoglycaemia (12, 52). Since children experience more non-specific hypoglycaemia warning symptoms, such as behavioural symptoms, compared to adults with diabetes, it might be more complex for parents to timely recognize and treat hypoglycaemia in their child (9-11). In addition, some evidence suggests that SH events, especially if they occur before the age of 6, can have a negative impact on neurocognitive functioning and development (53, 54), although it is unclear whether this is solely the consequence of SH, or whether it is the result of variability in glucose levels in general (53, 55, 56).

During middle childhood, typically defined as 6-11 years, there is a rapid development of various skills, including cognitive, social, physical, and emotional skills (29, 57). Children start to focus more on their peers than their family and to gain autonomy (57). Parents often remain heavily involved in diabetes management, while at the same time children get increasingly involved in management decisions and start to learn self-care skills, such as injecting insulin, counting carbohydrates and recognizing or treating hypoglycaemia (12, 29). Diabetes care strategies are often focused on enabling satisfactory diabetes management in settings outside the home, such as school (29). Parents might sometimes allow their child to maintain glucose levels above target to avoid hypoglycaemia when the child is participating in activities when the parent is not around (58).

Adolescence, typically defined as 12-18 years, is characterized by many physical and psychological changes, and developmental tasks for adolescents include gaining independence from their parents and a need to belong with their peers (57, 59). Many adolescents experience difficulties with maintaining their glucose levels within optimal range, as illustrated by a registry study (comprising 13.000 adolescents with T1D) in which it was found that approximately four in five had HbA_{1c} levels outside the recommended target range (60, 61). This can be attributed to various factors (62). First, physiological changes in hormonal levels can lead to decreased insulin sensitivity, which can contribute to a deterioration in HbA_{1c}. Second, diabetes self-management responsibilities are often transferred from parent to child during adolescence (12). This is a complex and individual process, as transferring both too little or too much responsibility to the child can have negative consequences for diabetes management and/or quality of life (63). Furthermore, the increased burden of diabetes self-management tasks can conflict with other developmental tasks which can be stressful for adolescents with T1D (63). Consequently, adolescents might sometimes compromise their diabetes management because they want to feel ‘normal’ and not be different from their peers (64). Thirdly, adolescence is a time of engagement in risk-taking behaviours, such as alcohol consumption and experimenting with drugs, which can adversely impact on their glucose levels (65, 66). Finally, concerns about physical appearance and body image are common in this age group, which can contribute to disordered eating behaviours, such as insulin omission to lose weight (67, 68).

The unique challenges experienced during each developmental phase can affect the experienced impact of hypoglycaemia on QoL in children and adolescents with T1D, compared to the impact in adults with T1D. Therefore, their experiences should be investigated separately. Furthermore, the challenges associated with managing T1D in daily life can put young people with T1D at risk of psychosocial problems, including diabetes distress (i.e., negative emotions related to living with and managing diabetes (69)), symptoms of depression and/or anxiety, fear of hypoglycaemia, disordered eating behaviours, and lower QoL (70-72). All these issues are associated with suboptimal engagement in diabetes self-care activities and less optimal diabetes outcomes (72-74).

Quality of life

While the main focus of diabetes management used to be on optimizing glycemic levels, international diabetes guidelines now recognize achieving optimal QoL as an equally important goal of diabetes care (75). This is well reflected in the ISPAD guidelines that recommend routine monitoring of psychological wellbeing and QoL in clinical care (75).

Although definitions of QoL vary widely, it is generally recognized as a multidimensional, subjective, and dynamic construct (76). The multidimensional part refers to there being multiple aspects of QoL, such as psychological, physical, and social. It is therefore important to measure these various aspects when referring to QoL; if only health is measured for example, this is only one aspect of QoL (76). The subjective part considers that what matters for one person’s QoL may be different to what matters for another person’s QoL; thus, there is no better way to assess QoL than to ask a person about the aspects of life that are important for their QoL (76, 77). Finally, the dynamic part refers to the fact that QoL changes over time. During different developmental phases in life, people find different things important for their QoL (76, 78); it could be that a younger adolescent finds blending in with peers very important, but as they grow older they may find starting a career becomes more important for their QoL.

Several generic and diabetes-specific QoL have been developed to measure QoL (79). Generic measures are especially useful in assessing a broad spectrum of aspects of life and can be used for comparisons between different populations, whereas diabetes-specific QoL measures aim to assess perceptions of how diabetes or specific aspects of diabetes-management impact on various aspects of life (80). There are several instruments available that aim to assess generic and diabetes-specific QoL in children and adolescents with T1D (81-84). A review on the utility of instruments that measure QoL in this group indicated that the Paediatric Quality of Life (PedsQL) generic and diabetes-specific modules and the KINDL-R appeared to be most suitable for measuring QoL in children and adolescents with T1D (81). However, this review was conducted in 2007 and several other tools have been developed since, for example the Mind-Youth questionnaire (MY-Q) (84) and the Type 1 Diabetes and Life (T1DAL) measures (83).

A systematic review indicated that although the generic QoL of young people with T1D seems to be similar to that of their peers without diabetes, diabetes impacts negatively on their social relationships and daily functioning, and young people with diabetes are worried about the potential consequences of the condition, such as passing out (85). In addition, previous studies have identified that lower QoL is associated with several sociodemographic and clinical factors, including but not limited to being female (86, 87), older age (88, 89), and less optimal glycemic levels (88, 90, 91).

Another factor that might affect the QoL of young people with T1D is hypoglycaemia. While the physical consequences of hypoglycaemia are well documented (42), there is limited evidence regarding the impact of hypoglycaemia on QoL in children and adolescents with T1D, including its impact on daily activities and social and emotional domains.

What we do not know yet

Most research on the impact of hypoglycaemia in this group has focused on FoH, by assessing worries about hypoglycaemia and avoidance behaviours related to hypoglycaemia (41, 48). However, the impact of hypoglycaemia on QoL goes beyond worries and fear only and can impact on different aspects of life (92), such as relationships with friends or school/studies. However, these impacts are not captured when only assessing FoH. In addition, hypoglycaemia was described as one of the three main challenges of living with T1D from the perspective of children and adolescents aged 6-18 years (96). Although preliminary evidence suggests that the experience of hypoglycaemia can affect QoL (42, 92), studies that investigated this relationship in children and adolescents with T1D are conflicting. While some studies have found that a history of SH is associated with lower QoL (89, 93), other studies have found no such association (94, 95).

Currently, there is a lack of studies that have captured the full impact of hypoglycaemia on QoL. Most studies investigating the impact of hypoglycaemia solely focus on the impact of SH (88, 91, 96). Although non-severe hypoglycaemia occurs more frequently than SH, studies that investigate this relationship are scarce. Moreover, the impact of hypoglycaemia on QoL is broader than the impact of just its occurrence and also encompasses the impact of subjective experiences with hypoglycaemia, living with the risk of hypoglycaemia and worries or fear about it.

To date, hypoglycaemia remains a major threat and burden for young people with T1D, yet there is limited understanding of how hypoglycaemia affects the QoL of children and adolescents with T1D. Since QoL is an important goal of diabetes care (75) and more optimal diabetes-specific QoL has been associated with favourable diabetes outcomes (73), it is essential to investigate this relationship. Furthermore, it has yet to be explored what methods can best be used to investigate this relationship.

Aims and objectives of this thesis

The aim of the present thesis is to examine the impact of hypoglycaemia on QoL in children and adolescents with T1D. This is done using a mixed-method approach that addresses this research question in three different studies. In **Study 1**, different aspects of hypoglycaemia (frequency, perceived severity, and fear of hypoglycaemia) are simultaneously investigated to examine their independent associations with QoL in adolescents with T1D. **In Study 2,** previous studies that examined the association between hypoglycaemia and QoL and related outcomes in children and adolescents with T1D are systematically reviewed and evaluated, including a critical examination of the instruments that have been used to assess QoL when examining this association. Based on these findings, **Study 3** explores the impact of hypoglycaemia on QoL using a novel approach to assess QoL in adolescents with T1D.

Throughout this thesis, these studies will be referred to as: **Study 1**: a cross-sectional quantitative study on the associations between hypoglycaemia, perceived severity of hypoglycaemia, FoH and QoL in adolescents with T1D; **Study 2**: a systematic review on the association between hypoglycaemia and QoL and related outcomes in children and adolescents with T1D; and **Study 3**: a qualitative web-based study exploring the impact of hypoglycaemia on QoL in adolescents with T1D.

Chapter 2
Methods

Methods

The following section provides an overview of the various methods used in the three studies included in this thesis. As the studies significantly differed in their design, the methods for each study will be described separately. For a full overview of the methods specific to each study, please refer to the full papers as included in the appendices, short descriptions are given below.

Sources of data

The data for Study 1 were collected in The Netherlands as part of the multimethod project "Whose Diabetes is it Anyway". These data were already collected in the Netherlands (March-October 2018) prior to the start of the current PhD programme of research, without the involvement of MC. Studies 2 and 3 were conducted as part of the large European Union funded Hypo-RESOLVE program (97). This program involves an international consortium of 23 academic, industry, and patient collaborators from ten countries, with the collective aim of reducing the burden of hypoglycemia and its consequences among people living with diabetes (97). The program consists of eight Work Packages, including Work Package 6 (WP6), which aims to understand the psychological impact of hypoglycaemia on people with diabetes (i.e., children/adolescents and adults with T1D; and adults with type 2 diabetes) and their family members (in particular, parents and partners) (97). Studies 2 and 3 of the present thesis were conducted as part of WP6, in close collaboration with other members of Hypo-RESOLVE. For studies 2 and 3, MC was responsible for the study design, data collection, management, analysis, and interpretation for the specific population of children and adolescents with T1D. In addition, data collection for Study 2 (i.e., the systematic literature searches and screening) resulted from a collaboration between WP6 and the Information Resources Group at the University of Sheffield's ScHARR (School of Health and Related Research), UK.

Participants

Research with children and adolescents requires several considerations. First, there are developmental differences between children and adolescents that require appropriate research designs and methods that are tailored to the needs and skills of different age groups. The online nature of Study 3 in combination with the abstract nature of the method used to assess QoL in this study ("Wheel of Life" activity, see p. 23-24) required a level of reflection and (cognitive) skills to articulate thoughts, feelings, and experiences in writing. As these cognitive skills might not yet be fully developed in younger children (57), this method might be more suitable for adolescents. In addition, when it comes to studying children and adolescents with T1D, the differences in terms of responsibilities for their diabetes management and its associated burden should be considered. Younger children often have less responsibility for diabetes self-care tasks which might affect the experienced impact of hypoglycaemia on QoL (12). Therefore, it was determined that the two empirical studies only included adolescents with T1D aged 12-18 years old. The same considerations were not required for the systematic review, thus this study focused on the full developmental life span (i.e., 0-18 years old), in order to provide a complete overview of the research field.

Another important consideration of doing research with adolescents can be the difficulty with engaging them in research projects. Adolescents with a chronic condition are often focused on 'being normal' and do not always want to be reminded of their condition, which can be a barrier to study participation (98). Several steps were taken to improve response rates in the studies. Participants were offered incentives for their participation. In addition, including adolescents in different stages of the research project can help to enhance relevance and quality of the research (98). Therefore, in the third study, six adolescents with T1D were interviewed about the importance, appropriateness, and relevance of the survey, which resulted in some improvements to the survey.

The data for Study 1 came from the "Whose diabetes is it anyway" study, which was carried out in four diabetes clinics and paediatric hospitals in the Netherlands. Families were eligible if they had a child with T1D aged 6-18 years old who had a diabetes duration of more than six months, had no intellectual disabilities or severe physical or mental comorbidities, and were able to complete questionnaires in Dutch. Study 1 was based on a subset of these data and included adolescents between 12-18 years old. Study 2 was a systematic review and studies were eligible for inclusion if participants were children and/or adolescents with T1D below 18 years old. Study 3 included adolescents with T1D aged 12-17 years from Denmark, Germany, The Netherlands, and the United Kingdom who were able to complete the questionnaire in Danish, German, Dutch or English.

Protocol

For Study 1, families who were eligible were invited to participate via post. If they wanted to participate, they could complete questionnaires either on paper or online. Adolescents received a €7.50 gift card after participation.

For Study 2*,* first, a protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020154023). Systematic searches for this review were conducted in November 2019 (and updated in September 2021), in four different databases: Medline, PsycINFO, CINAHL and Cochrane Library. Search terms included 'T1D', 'children and adolescents', 'hypoglycaemia', 'QoL and related outcomes', separated by the Boolean operator "and". The full search string can be found in the full paper as included in the appendices.

After the searches were conducted, title and abstract screening was conducted by three reviewers, followed by full text screening conducted by MC. When all eligible studies were identified, reference checking and citation searching of these studies were done to search for additional relevant papers. A pilot data extraction form was developed iteratively. When agreed on the final extraction form, relevant data such as participant details, assessment of outcomes and results on the association between hypoglycaemia and QoL or related outcomes were extracted from the included studies by MC. Each of the steps was conducted (partially or fully) by two people; 10% of the abstracts and full text records were being double screened by a third independent reviewer, full-text screening was conducted with input from a third reviewer and extracted data was checked by two independent reviewers. Discrepancies were discussed until consensus was reached. In addition, quality assessment of the included studies was conducted by MC.

Study 3 was a web-based qualitative survey conducted in Denmark, Germany, the Netherlands and the United Kingdom between September and December 2020. The survey was originally developed in English, and was translated Danish, Dutch and German following the principles of translation for patient reported outcome measures (99). Advertisements to the study were posted online on social media channels or websites/newsletters of diabetes associations, and in waiting rooms of diabetes clinics. The survey was accessible via an open link. Participants had a chance to win a €50 gift voucher after completing the survey.

Measures

For Study 1, demographic and clinical information such as gender, diabetes onset, HbA_{1c} levels and treatment modality were extracted from the adolescents' medical records. Other factors, including education level, nationality, glucose monitoring modality, frequency of blood glucose monitoring and comorbidities were collected via self-reported questionnaires. Frequency hypoglycaemia was assessed by self-report. SH was defined as 'the number of hypoglycaemic episodes when blood glucose was so low that you were unable to recognize symptoms, ask for help, or treat yourself due to mental confusion or unconsciousness' in the past 12 months. Self-treated hypoglycaemia was defined as 'the number of hypoglycaemic episodes when blood glucose was so low that it interfered with what you were doing, and you had to wait a while to recover', in the past six months. Perceived severity of hypoglycaemia was assessed by asking adolescents how upsetting their worst episodes of self-treated or SH were in in the past 6 to 12 months. FoH was assessed using the worry scale of the Hypoglycaemia-Fear Survey Child version (HFS-C) (48). This subscale consists of 15 items and adolescents rated how often they had concerns about hypoglycaemia: e.g., "*No one being around to help me during a low"* on a 5-point Likert scale from never (0) to almost always (4). Higher scores indicate higher FoH. Internal consistency in this study was good (α=0.87). Diabetes-specific QoL was assessed with the PedsQL-Diabetes Module (PedsQL-DM) (82). This is a validated questionnaire consisting of 33 items (32 items for adolescents aged 12 years old) that assesses various problems related to diabetes and its treatment. Adolescents indicated the frequency of these problems in the past month, ranging from never (0) to almost always (4). There are two subscales: '*diabetes symptoms*' and '*diabetes management*' (82). Higher scores indicate better QoL. Internal consistency in the current study was good-excellent (α=0.93 for total scale, α=0.88 for 'diabetes symptoms' and α=0.90 for 'diabetes management').

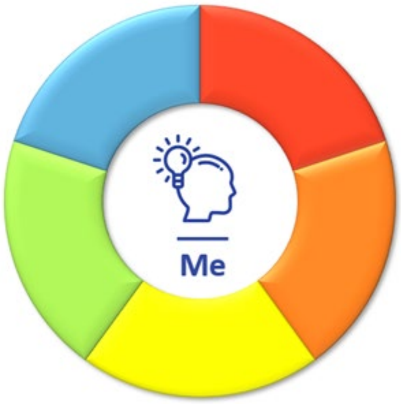
In Study 2, the measures to assess QoL or related outcomes are the measures that are being used in the respective included studies. In addition, quality assessment was conducted with the use of the Johanna Briggs Institute (JBI) tool for cross-sectional studies (100). The JBI critical appraisal tool consists of eight criteria on study design, data collection and analysis, and reliability and validity of exposure and outcome. Each item is rated as yes, no, unclear or not/applicable. There is no total/cumulative quality rating produced.

In Study 3*,* data were collected via self-reported questionnaires. Sociodemographic and clinical information included age, gender, nationality, diabetes duration, HbA_{1c} level, type of insulin treatment and comorbidities. Frequency of hypoglycaemia over the past 12 months was assessed with the Hypoglycemia Awareness Questionnaire (HypoA-Q) (101). SH was categorized into SH requiring help: *"How often did you need help to treat hypoglycaemia, because you were conscious but unable to recognize symptoms, ask for help or treat yourself because you were confused?"*; or SH requiring medical care: *"How often were you taken to the emergency department, hospital or had to stay overnight in the hospital due to hypoglycaemia?"*. Hypoglycaemia awareness was assessed by the subscale of the HypoA-Q and the Gold score (102). FoH was assessed with the Hypoglycaemia Fear Survey-Short Form (HFS-SF) (103). Both the HFS-SF and the HypoA-Q do not have adolescent specific versions, so adaptations were made in consultation with the original instrument developers to ensure suitability for adolescents with T1D.

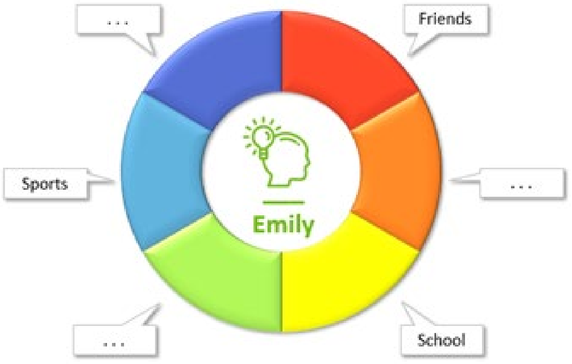
QoL was assessed with the novel '*Wheel of Life'* method (104-106) (Figure 1). In this method, adolescents are presented with a wheel and asked to imagine that this wheel represents their QoL. This wheel was divided into sections that represented different domains of life. First, adolescents were asked to choose domains of life that are important to them from a list of domains. Although there was initially no pre-defined list of domains included in the "Wheel of Life" activity, this was added as the adolescents in the interviews during the development of the survey indicated difficulties with nominating domains without prompts. They also had the opportunity to specify another domain if an important domain was not listed. After this, they were asked to describe in a free text field if and how hypoglycaemia affects these domains that are important to them.

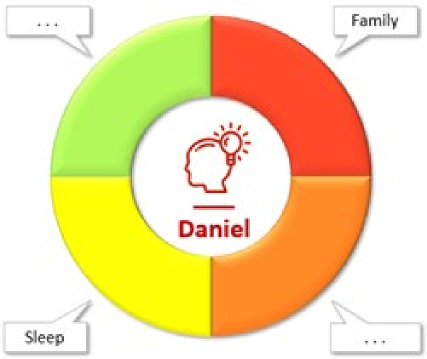
Figure 1. Wheel of life activity with instructions as shown in the survey

The next few questions are about hypoglycaemia and your quality of life. We would like you to imagine this wheel as your quality of life. The sections are areas of your life that are important to you right now.



What is important to you might not be important to your friends or parents. Here are some examples of what other people your age care about and find important in their lives.





- From the dropdown boxes, we would like you to choose the areas of life that are most important to you right now.
- We would then like you to tell us if/how hypoglycaemia affects each of these things.
  - Most people can think of at least 5 areas of life that are important to them.
  - It is important that you try to answer the questions in as much detail as you can. There are no right or wrong answers, and you don't need to worry about your spelling or grammar.
  - To make sure that no-one can identify you from your responses, make sure that you do not include details such as your name, address or school.

Analyses

Data for Study 1 were already transferred into SPSS and cleaned when the data file was provided. Prior to analysis, assumptions of linearity, normality, homoscedasticity, and (no) multicollinearity were checked and met. Correlations between all the independent variables and QoL were assessed using Pearson correlations.

To test for independent associations between hypoglycaemia, perceived severity of hypoglycaemia, FoH and QoL, hierarchical regression analyses were conducted. In the first step, covariates including age, gender and HbA_{1c} were entered into the analysis. In the second step, frequencies of self-treated and SH were entered, in the third step, perceived severity of hypoglycaemia of both self-treated and SH were added, and in the last step, FoH was added. The dependent variable was the PedsQL-DM total score. Additionally, analyses were conducted for the different subscales of the PedsQL-DM ('*diabetes management*' and '*diabetes symptoms*') as dependent variables. Analyses were conducted in SPSS v24 (Chicago, IL, USA)

In Study 2, analysis included narrative synthesis of the study findings and quality assessment of the included studies. Due to heterogeneity in outcomes, definitions and recall periods of hypoglycemia, and age groups across the included studies, meta-analysis was not possible. Within the narrative synthesis, studies were grouped based on outcome measures, using a conceptual framework of QoL based on the scope and the attribution of the measure (107). For each outcome, findings were discussed separately for SH and non-severe hypoglycaemia. The following aspects were considered when interpreting the evidence, to avoid vote counting based on statistical significance (108); 1) assessment of hypoglycaemia; 2) assessment of outcomes; 3) age of the participants; 4) in/exclusion criteria of the studies; and 5) effect sizes.

The survey described in Study 3 was conducted in the online survey platform 'REDCap', and data were transferred into Excel / SPSS after the end date of the study. Since this study was conducted in four different countries, and answers were given in four different languages, responses were first translated into English, to facilitate analysis within an international research team. After this, researchers familiarized themselves with the data by repeatedly reading the responses to the open-ended items. Data was coded by MC and 50% of the data was independently coded by a second reviewer. Data was coded using NVivo 12. Reflexive thematic analysis following the guidelines by Braun and Clarke was used to analyse the data (109). Coding was done inductively, and themes were generated from the data. After the initial coding framework was developed, several members from the research team met and discussed the framework. Changes were made iteratively until the final framework was accepted by the whole research team. During the analysis it was checked if themes differed between different countries, ages, and genders.

The quantitative data were cleaned before analysis commenced. Analyses were conducted in SPSS v24 (Chicago, IL, USA) and included comparisons between countries, performed with Kruskal-Wallis tests or Fisher's Exact test.

Ethics and data management

Given that two of the three studies involved participation of adolescents aged 12-18 years old, ethical approval was sought for these studies and are further detailed below.

Since data that was used for Study 1 was collected prior to the current PhD programme of research, MC was not involved in applying for ethics for this study. Ethical approval was obtained from the Psychological Ethics Committee of Tilburg University (EC-2017.85). Both adolescent and parental consent were sought before participation.

The data file has been pseudonymized and study IDs were assigned, of which only the coordinating researcher has the key file that can link study IDs to families. Moreover, personal, and identifiable information such as names, addresses, telephone numbers, and personal numbers, were deleted from the data file.

Given that Study 2 was a systematic review, no ethical approval or data management plans were needed for this study.

Study 3 was conducted in four different countries, and ethical approval was sought in all countries (Table 1). MC was involved in all the ethics approvals, with help from the partnering institutions in the respective countries.

A specific issue with regards to conducting research in adolescents in Study 3 was obtaining parental consent in an online study. As consent in an online study is given by ticking a box (i.e., it is not witnessed by the researcher), parents were asked to provide their email addresses, to avoid adolescents consenting on their parents' behalf. These email addresses were not further used. Although it cannot be assumed that all respondents actually sought parental consent, the implications of this were considered minimal, given the anonymous and non-sensitive nature of the survey. Adolescents were only asked about their QoL and not about psychiatric disorder or risk of suicide. Moreover, this was balanced against the risk of 'losing' participants along the way due to a lengthy parental consent procedure. This is in line with recommendations from the ethics guidelines for internet mediated research (110). Online consent and information procedures should be designed so they enable participants who would like to participate to proceed easily, while carefully weighing the harmful effects should someone who does not meet the eligibility criteria (e.g., because of age) access the survey and participate (110).

It was acknowledged that some of the questions asked adolescents to reflect upon difficult experiences or emotional difficulties, which could possibly lead to mild discomfort. However, this risk was perceived as low since hypoglycaemia is a common experience for adolescents with T1D. In case the survey resulted in discomfort, participants were encouraged to discuss these feelings with other people or with their national diabetes associations, for whom contact details were provided in the survey. In addition, one of the ethics committees raised concerns about asking young people about whether they were living alone, given that there was no opportunity to follow up on this. It was therefore decided to remove this option.

With regard to data storage, no identifiable information such as name, date of birth or ID numbers were collected in the survey. E-mail addresses of parents were collected at the stage of giving consent but were not further used or linked to participant responses. At the end of the survey, participants could participate in a prize draw by entering their email addresses. These email addresses were stored in a different database and not linked to responses and deleted after the end of the study. After data collection ended, the data were kept in a secure folder in SharePoint. All participants were given a unique identifier number.

Table 1. Overview of ethical approvals for Study 3

Country	Committee	Approval number
Denmark	Research Ethics Committee University of Southern Denmark	19/78420
Germany	Research Ethics Committee German Society for Psychology	HermannsNorbert2020-05-12VA
The Netherlands	Ethics Committee Radboud University Medical Centre	2020-6587
United Kingdom	UK Health and Social Care Research Ethics Committee	20-NI-0054

Chapter 3
Results

Results

In this chapter, a brief overview of the results from the three studies included in this thesis is given. Further detail can be found in the full papers (see Appendices).

Study 1- Quantitative study

The total sample for Study 1 included 96 adolescents, aged 12-18 years old (mean age (SD) 15.2 (1.6)). There was an equal representation of males and females in the sample. Of the 96 adolescents, 81% (n=78) were using insulin pump therapy, and 33% (n=31) were using a sensor to monitor their glucose levels. The most important descriptive and clinical characteristics are presented in Table 2.

Table 2. Sociodemographic and clinical characteristics of the 96 participating adolescents

	Number of valid cases	% (n)	Mean (SD)	Range
Age (years)	96		15.2 (1.6)	12-18
Gender, male	96	48 (46)		
Adolescent education	95			
Diabetes duration (years)	96		7.0 (4.3)	
Insulin administration	96			
Insulin pump		81 (78)		
Multiple daily injections		19 (18)		
Glucose monitoring modality	95			
Real-time CGM		19 (18)		
Flash glucose monitoring		14 (13)		
Fingerpicks only		67 (64)		
Hypoglycaemia				
Frequency of severe hypoglycaemic episodes past 12 months			0.7 (2.4)	0-20
Frequency of self-treated hypoglycaemic episodes past 6 months			17.4 (29.9)	0-200
Perceived severity of hypoglycaemia (HFS-C; range 0-4)[1]				0-4
Worst episode of severe hypoglycaemia past 12 months			1.3 (1.5)	
Worst episode of self-treated hypoglycaemia past 6 months			2.0 (1.2)	
Fear of Hypoglycaemia (HFS-C worry scale; range 0-60)[1]	96		12.8 (8.3)	0-41
Diabetes-specific QoL (PedsQL-DM; range 0-100)[2]	96			
Total score			74.0 (13.3)	17.4-99.2
Diabetes Symptoms subscale score			64.3 (14.9)	15.0–98.3
Diabetes Management subscale score			81.5 (15.0)	16.7–100

Adapted from Coolen et al. 2021 (Diabetic Medicine), in Appendices (paper 1)

CGM, Continuous glucose monitoring; HFS-C, Hypoglycaemia Fear Survey-Child Version; PedsQL-DM, Paediatric Quality of Life Inventory-Diabetes Module

[1] Higher scores indicate higher perceived severity/fear of hypoglycaemia

[2] Higher scores indicate better quality of life

The final step of the model of the hierarchical regression analysis with the PedsQL-DM total score as the dependent variable showed that FoH was a significant independent predictor of QoL, after controlling for age, gender, HbA_{1c}, frequency of hypoglycaemia and perceived severity of hypoglycaemia. Even though frequency of SH and severity of self-treated and severe hypoglycaemia were significant predictors in earlier steps of the model, these effects were negated by the addition of FoH to the model. The analyses yielded similar results when repeated for 'diabetes symptoms' and 'diabetes management' as dependent variables. Results of the last step of the regression model for the analyses with the PedsQL-DM total score and subscale scores are presented in Table 3.

Table 3. Fully adjusted hierarchical regression analyses examining associations of demographic and clinical characteristics, frequency of hypoglycaemia, severity of hypoglycaemia and fear of hypoglycaemia with total and subscale scores of diabetes-specific QoL (PedsQL-DM)

PedsQL DM	**Total score**		**Diabetes symptoms**		**Diabetes management**	
	β		***β***		***β***	
1. Demographic and clinical information						
Age (years)	-.11		-.08		-.13	
Gender, male	.10		.09		.11	
HbA_{1c}	-.13		-.05		-.15	
2. Frequency of Hypoglycaemia						
Severe hypoglycaemia (past 12 months)	-.03		-.06		-.003	
Self-treated hypoglycaemia (past 6 months)	-.04		-.03		-.03	
3. Perceived severity of hypoglycaemia^1						
Severe hypoglycaemia (past 12 months)	-.06		-.16		.02	
Self-treated hypoglycaemia (past 6 months)	-.09		-.11		-.03	
4. Fear of hypoglycaemia^1						
Fear of hypoglycaemia	-.60	**	-.51	**	-.58	**
Adjusted R^2	.52	**	.45	**	.41	**
R^2 change	.24	**	.17	**	.23	**

Adapted from Coolen et al. 2021 (Diabetic Medicine), in Appendices (paper 1)
PedsQL-DM, Paediatric Quality of Life Inventory-Diabetes Module
Gender is binary coded, 1=male, 0=female
^{1}: higher scores indicate higher perceived severity/fear
**p*<0.05, ***p*<0.01

Study 2 – Systematic review

The searches identified 1165 references. After title and abstract screening, 217 studies were screened at full-text stage; 17 studies met inclusion criteria. Ten additional studies were found through forward and backward chaining. In total, 27 studies were included. A flow chart of this process can be found in the full paper, as included in the appendices.

The 27 studies included *N*=141,530 participants; sample sizes ranged from *N*=39 to *N*=75,258 and were conducted in 18 different countries. One of the studies was conducted in multiple countries in Europe, Japan, and USA. The age of the participants in the studies ranged from 5-25 years old. Across the studies, 19 different instruments were used to assess QoL or related outcomes. See Table 4 for the classification of the QoL and related outcomes.

Quality of the included studies

The most important limitations identified in the studies were related to the definition of the exposure (hypoglycaemia) and outcome (QoL). First, only 52% of the studies used a definition that aligned with those recommended by the ISPAD guidelines. Second, while 70% of the studies used measures that were validated in adolescents with T1D to assess QoL, 19% used non-validated measures. The remaining 11% used both validated and non-validated measures. Finally, although many studies identified confounding factors, 33% of these studies did not adjust for confounding factors in analyses.

Synthesis of the results

An important finding was that none of the studies used a hypoglycaemia-specific QoL measure to assess the relationship between hypoglycaemia and QoL. Studies assessed generic QoL (n=5), various domains of generic QoL (n=6) and diabetes-specific QoL (n=4). In addition, studies assessed related outcomes including diabetes distress (n=11), FoH (n=7), anxiety (n=3), depression (n=4), posttraumatic stress (n=1), and disordered eating (n=1).

Synthesis of the results indicated that there was insufficient evidence for an association between SH and generic and diabetes-specific QoL. There appeared to be no association between non-severe hypoglycaemia and generic QoL, but there was not enough evidence to draw conclusions about the association between non-severe hypoglycaemia and diabetes-specific QoL.

With regards to the related outcomes, the results indicated that SH in the past 12 months was associated with greater worries about hypoglycaemia, but the evidence for FoH-related behaviours and total FoH, diabetes distress, anxiety, depression, disordered eating and post-traumatic stress was too limited to draw firm conclusions. For non-severe hypoglycaemia, the evidence suggested no association with diabetes distress, while for the other outcomes (FoH and anxiety) there was insufficient evidence to draw conclusions.

In addition, there was some evidence suggesting that more recent (i.e., past 1-3 months), more severe (i.e., involving convulsions, loss of consciousness or coma), more frequent episodes of hypoglycaemia, or hypoglycaemia in a social context were more likely to be associated with negative outcomes.

Although the evidence is largely inconclusive, the review clearly highlighted the gaps in the current evidence base that need to be addressed by future studies, to better understand the impact of hypoglycaemia on QoL. These include: 1) adopting hypoglycaemia definitions as recommended by guidelines to increase comparability between studies; 2) assessing hypoglycaemia using methods that are less prone to recall bias; 3) developing hypoglycaemia-specific QoL measures that include domains that are important to young people with diabetes; and 4) conducting analysis for children and adolescents separately.

Table 4. Overview of quality of life and related outcome measures in the included studies, by breadth and attribution

Quality of Life (QoL) and related outcomes		**Generic**	**Diabetes-specific**	**Hypoglycaemia-specific**
		(no attribution)	**(attribution to diabetes)**	**(attribution to hypoglycaemia)**
Global QoL		• KINDL-R Total score • PedsQL total score	• DISABKIDS DCGM-12 • DQOLY total score • DQOLY impact scale • DQOLY Diabetes life satisfaction scale • DQOLY Short Form total score	None
Broad domains of QOL	*Physical functioning*	• KIDSCREEN 27: physical wellbeing • KINDL R: physical • PedsQL: physical functioning • EQ5D VAS scale	None	None
	Social functioning	• PedsQL: social functioning • PedsQL: psychosocial functioning	None	None
	Psychological functioning	• KIDSCREEN 27: psychological well-being • KINDL R: emotional wellbeing • PedsQL: emotional functioning • KIDSCREEN-10 index	None	None
Specific domains of QoL	*Family*	• KINDL R: family • KIDSCREEN 27: Autonomy and relationships with parents	None	None
	Friends	• KINDL R: friends • KIDSCREEN 27: Relationships with friends or peers	None	None
	School / Studies	• PedsQL: school functioning • KINDL R: school • KIDSCREEN 27: school	None	None
	Self-esteem	• KINDL R: self-esteem	None	None
	Sleep	• Adolescent Sleep/Wake scale	None	None

Quality of Life (QoL) and related outcomes	**Generic**	**Diabetes-specific**	**Hypoglycaemia-specific**
	(no attribution)	**(attribution to diabetes)**	**(attribution to hypoglycaemia)**
Related psychological outcomes	• Screen for Child Anxiety-Related Disorders • ICD-10 anxiety disorder diagnosis • State-Trait Anxiety Inventory for Children, Trait Subscale • Center for Epidemiological Studies-Depression Scale • Children's Depression Inventory, Short version • Adolescents – IV (DSM IV depression diagnosis)	• DQOLY: Worries about diabetes • KINDL-R chronic illness scale • PedsQL-DM: diabetes distress • PedsQL-DM: ‘diabetes symptoms’ • PedsQL-DM: ‘diabetes management’ • DISABKIDS impact scale • Diabetes Eating Problem Survey-Revised	• Hypoglycaemia Fear Survey – child version (HFS-C) total scale • HFS-C ‘worries about hypoglycaemia’ subscale • HFS-C ‘fear of hypoglycaemia related behaviors’ • Child Posttraumatic Stress Reaction Index (hypoglycaemia is referred to as the traumatic event) • Child Hypoglycaemia Index-2

Adapted from Coolen et al. 2021 (Under Review), in Appendices (paper 2)

DQOLY, Diabetes Quality of Life-Youth; EQ5D-VAS, EuroQoL 5 Dimensions- Visual Analog Scale; HFS-C, Hypoglycaemia Fear Survey – Child version; ICD International Classification of Diseases; PedsQL, Pediatric Quality of life Inventory; PedsQL-DM, Paediatric Quality of Life inventory-Diabetes Module; QoL, Quality of Life

Study 3 – Web-based qualitative study

The sample in Study 3 was comprised of 75 adolescents: 14 from Denmark, 16 from Germany, 21 from the Netherlands and 24 from the United Kingdom. The mean (SD) age of the participants was 15(2) years. The majority of the adolescents were female (73%). Sixty-one percent used insulin pump treatment and 81% used a sensor to monitor their glucose levels. An overview of the most important demographic and clinical characteristics divided by country are given in Table 5.

Table 5. Sociodemographic and clinical characteristics of 75 participating adolescents

	Valid cases	**Total N=75**	**Denmark n=14**	**Germany n=16**	**The Netherlands n=21**	**United Kingdom n=24**	**P value**
Age (years)	74	14.9 (1.7)	13.8 (1.1)	14.2 (2.0)	15.9 (1.2)	15.1 (1.6)	.001[1]
Gender: female	75	73% (55)	43% (6)	69% (11)	91% (19)	80% (19)	.015[1]
Diabetes duration (years)	72	5.5 (4.4) R 0-16	6.4 (4.4) R 0-13	6.5 (4.6) R 1-12	5.2 (4.6) R1-15	4.6 (4.3) R 0-16	.465
Insulin administration	69						.021[2]
Multiple daily injections		31% (23)	7% (1)	19% (3)	52% (11)	33% (8)	
Insulin pump		61% (46)	93% (13)	75% (12)	48% (10)	46% (11)	
Glucose monitoring modality	62						.852
Finger prick		4% (3)	7% (1)	0% (0)	5% (1)	20% (1)	
Sensor (CGM or Flash)		81% (61)	50% (7)	88% (100)	95% (20)	83% (20)	
Open-source APS/ artificial pancreas use	73	12% (9)	14% (2)	19% (3)	0% (0)	17% (4)	.230
Hypoglycaemia							
Any type in past week: frequency	69	4.9 (6.4) R 0-50	4.1 (2.9) R 1-10	5.6 (4.1) R 0-15	4.2 (2.9) R 0-11	5.5 (10.1) R 0-50	.526
≥1 SH (needed help t treat hypoglycaemia) in past 12 months[6]	75	48% (36)	57% (8)	19% (3)	52% (11)	58% (14)	.070
≥1 SH requiring medical care in past 12 months[7]	75	20% (15)	14% (2)	13% (2)	29% (6)	21% (5)	.645
Fear of hypoglycaemia (HFS-SF)	75	10.9 (5.8) R 1-24	8.1 (3.4) R 3-14	8.9 (5.3) R 1-16	6.4 (2.3) R 2-18	15.5 (5.6) R 1-24	<.001[3,4,5]

Adapted from Coolen et al. 2021 (Submitted), in Appendices (paper 3)

Data are mean(SD), range (R) for continuous variables and %(n) for categorical variables

APS, Artificial Pancreas System; CGM, Continuous Glucose Monitoring; HFS-SF, Hypoglycaemia Fear Survey-Short Form; SH, Severe Hypoglycaemia

[1] Significant difference between Denmark and the Netherlands

[2] Post hoc test revealed no significant differences between countries

[3] Significant difference between United Kingdom and the Netherlands

[4] Significant difference between United Kingdom and Denmark

[5] Significant difference between United Kingdom and Germany

[6] SH: needed help to treat a hypo (you were conscious but unable to recognize symptoms, ask for help or treat yourself because you were confused)

[7] SH requiring medical care includes passing out due to hypoglycaemia, taken to emergency department after hypoglycaemia and stayed overnight in hospital due to hypoglycaemia

Adolescents nominated 17 different domains as important for their QoL (Table 6). Most adolescents (61%) nominated five domains as important for their QoL, with a range from 2-7 domains. The five most nominated domains were ‘school’, ‘friends’, ‘family’, ‘sleep’, and ‘sports’. Interestingly, ‘diabetes’ was only nominated by 12% and ‘physical health’ was only nominated by 5% of the adolescents as important for their QoL. The five most nominated domains were similar between the four countries, except for the UK, where ‘mood’ was the 3rd most nominated domain. There were some additional small differences observed between the countries. A complete overview of the domains divided by country can be found in the full paper as included in the appendices.

Table 6. Domains of life nominated by adolescents with T1D as important for their quality of life in descending frequency

Area of life	% (n)
School	68% (51)
Friends	63% (47)
Family	61% (46)
Sleep	59% (44)
Sports	52% (39)
Mood	43% (32)
Hobbies or leisure activities	21% (16)
Parties / going out	16% (12)
Self-confidence	16% (12)
Eating and drinking	15% (11)
Diabetes	12% (9)
Traveling	11% (8)
Pets	7% (5)
Physical health	5% (4)
Work	4% (3)
Sex / relationships	4% (3)
Physical appearance	4% (3)

Adapted from Coolen et al. 2021 (Submitted), in Appendices (paper 3)

Adolescents described that all these domains were impacted by hypoglycaemia. Most of the participants described a negative impact on multiple domains of their QoL, although eight participants described that hypoglycaemia did not impact on one or two of the domains important for their QoL. Although most of the participants described that hypoglycaemia impacted their lives negatively, three adolescents described that hypoglycaemia had a positive impact on one of the domains of their life, via a better relationship with their friends or via an increase in self-confidence when they successfully treated hypoglycaemia.

Thematic analysis of the responses to the open-ended questions generated eight main themes. Five themes were related to the impact of hypoglycaemia episodes: physical impact, emotional impact, social impact, behavioural impact, and cognitive impact. Three themes related to the impact of living with the risk of hypoglycaemia: worries, reduced freedom, and suboptimal glucose management. An overview of the themes and descriptions is given in Table 7. Example quotes can be found in the full paper as included in the appendices.

Table 7. Themes and codes related to the impact of hypoglycaemia on QoL

Impact	Theme	Description
Impact of hypoglycaemia episodes	Physical impact	• Sleep problems (poor sleep, loss of sleep) • Tiredness and depleted energy • Feeling unhealthy • Experiencing unwanted weight gain • Increased risk of hypoglycaemia unawareness
	Emotional impact	• Feelings of frustrations and annoyance • Reduced enjoyment • Negative impact on mood and self-confidence • Feeling embarrassed and different from their peers • Feeling a burden and worried about other people's judgement
	Social impact	• Impact on relationships • Help and support perceived as supportive • Help and support perceived as unwanted and resulting in arguments • Lack of understanding • Direct impact on others
	Cognitive impact	• Concentration difficulties
	Behavioural impact	• Interruptions of activities • Participation with hypoglycaemia at the cost of quality or performance • Unable to participate in different activities
		•
Impact of risk of hypoglycaemia	Worries	• Worries about having hypoglycaemia and its consequences
	Reduced freedom	• Being preoccupied and having to plan everything to avoid hypoglycaemia • Not able to do the things in the way they would like to do them
	Suboptimal glucose management	• Keeping blood glucose levels above target to avoid hypoglycaemia or because of fear of hypoglycaemia

Adapted from Coolen et al. 2021 (Submitted), in Appendices (paper 3)

Chapter 4
Discussion

Discussion

Although the increased availability of structured diabetes education programmes and diabetes technologies over the last two decades has had some beneficial effects in relation to the prevention and management of hypoglycaemia, it remains an important issue affecting children and adolescents with T1D (9, 111). However, the impact of hypoglycaemia on QoL is still unclear, as previous studies that investigated this relationship yielded conflicting findings, and a clear overview of the evidence of the relationship between hypoglycaemia and QoL was lacking. Therefore, the aim of the present thesis was to examine the impact of hypoglycaemia on QoL in children and adolescents with T1D. This was examined with a mixed-method approach that shed light on various aspects of this question. The following chapter provides an overall integration of the main findings of these studies, followed by strengths and limitations, clinical implications, suggestions for future research, and concluding remarks.

Integration of main findings

Broad impact of hypoglycaemia

While the findings of Studies 1 and 2 indicate no clear association between hypoglycaemia and QoL, the findings of Study 3 indicate that hypoglycaemia episodes had physical, social, emotional, cognitive, and behavioural consequences that impacted on various domains of adolescents' QoL. A possible explanation for these discordant findings is that the impact of hypoglycaemia is often only studied by examining the cross-sectional association between the frequency of hypoglycaemia and QoL. This might mask the full impact of hypoglycaemia, as the findings of Study 1 suggest that only investigating the frequency of hypoglycaemia may provide limited insight into whether someone's QoL is impacted by hypoglycaemia, but that other aspects, such as the subjective experiences or worries and fears about it might play an important role in determining its impact. In line with this, findings of Study 3 indicated that not only the episodes of hypoglycaemia, but also living with the risk of hypoglycaemia, efforts taken to prevent hypoglycaemia, and thoughts and worries about hypoglycaemia impacted on multiple domains of QoL that were identified as important by adolescents with T1D.

These findings highlight the importance of investigating the full and broad impact of hypoglycaemia on QoL in children and adolescents with T1D. Although these studies are the first to address this in children and adolescents with T1D, the importance of looking at subjective and broad experiences with hypoglycaemia has been observed in other populations including parents of children with T1D (45, 112) and adults with T1D (106). For example, frequency of problematic hypoglycaemia according to the parents' subjective definition (112) or the belief whether their child carried glucose were indicators of parental FoH (45), while the history of hypoglycaemia according to a biomedical definition was not (45, 112). In addition, a recent study among adults with T1D indicated that even though hypoglycaemia impacted different domains of QoL, its impact on QoL goes beyond the impact of hypoglycaemia episodes only (106).

Conceptualization and assessment of QoL

To gain an overview of the evidence base for an association between hypoglycaemia and QoL, a systematic review was conducted to critically examine the evidence regarding the association between hypoglycaemia and QoL or related outcomes in Study 2. Although the evidence for a relationship between hypoglycaemia and QoL was inconclusive, it is important to note that absence of evidence is not evidence of absence. More specifically, there was considerable heterogeneity in how the studies assessed both hypoglycaemia and QoL. This impeded the ability to draw the evidence together and make strong conclusions. Importantly, none of the studies used a measure that was designed to assess hypoglycaemia-specific QoL. Consequently, studies used measures of generic or diabetes-specific QoL to assess the impact of hypoglycaemia on QoL. When such measures are being used to assess the impact of hypoglycaemia, the ratings might be influenced by other aspects of living with diabetes (beyond hypoglycaemia) and obscure the true impact of hypoglycaemia on QoL. Moreover, while some studies aimed to measure QoL they often used instruments that assessed diabetes distress (87, 88, 91, 93, 94, 113-115) or only a single domain of QoL (116). In addition, quantitative questionnaires that measure psychological outcomes such as depression often assess the average of such outcomes over several weeks (e.g., depressive symptoms over the past two weeks). These measures might not be sensitive enough to capture the day-to-day impact of hypoglycaemia on these outcomes.

Therefore, Study 3 used an individualized, novel assessment of QoL (i.e., the “Wheel of Life”) to specifically investigate the impact of hypoglycaemia on QoL, thereby highlighting the unique impacts of hypoglycaemia on QoL. While some of the impacts of hypoglycaemia observed in Study 3 are in line with the impacts of diabetes more generally, including ‘not wanting to be different from their peers’ (117, 118), diabetes impacting on their social life (85), and self-management tasks affecting other activities (117, 118), the findings of this study also add insight into unique impacts of hypoglycemia on QoL. These unique impacts include intentionally keeping glucose levels above recommended target levels, having to interrupt activities when glucose levels are low, feeling embarrassed when experiencing hypoglycaemia, having to eat when not wanting to, experiencing a lack of understanding with regards to being able and/or allowed to treat hypoglycaemia (e.g., for example at school, or while travelling), and waking up during the night to monitor glucose levels or treat hypoglycaemia.

Individual impact

While the quantitative studies (i.e., Study 1 and studies included in the review) that have investigated the impact of hypoglycaemia at a population level seem conflicting, the qualitative findings of Study 3 indeed show that hypoglycaemia can have an individual impact on the QoL of adolescents with T1D. The distribution of SH episodes is often skewed, with a subset experiencing the majority of the episodes (119). It is likely that the association between hypoglycaemia and QoL is individual and multifaceted and can be affected by various factors. In addition, though it is recognized that QoL is a subjective construct (76), only the third study included personal preferences in relation to QoL.

It could be that the impact of hypoglycaemia differs for different (groups of) adolescents with T1D, but these differences are overlooked when inferences are made based on group studies. The importance of identifying subgroups has also been highlighted in a previous study that stratified adults with T1D into subgroups based on their risk of SH and their level of FoH (120). In this study, the different subgroups showed different relationships with adverse psychological outcomes such as symptoms of depression and anxiety (120). This has important implications for interventions, as subgroups might benefit from different interventions.

Non-severe hypoglycaemia

The findings of Study 2 indicated that there seems to be no association between non-severe hypoglycaemia and (domains of) generic or diabetes-specific QoL, although this was only examined in four of the 27 included studies (95, 116, 121, 122). In contrast, the findings of Study 3 suggest that hypoglycaemia impacts on QoL, regardless of the severity of the episode. This indicates that the impact of hypoglycaemia does not solely result from severe episodes, which has also been reported in adults with T1D (106).

The different methods used to examine the association between hypoglycaemia and QoL might have contributed to a disparity in findings, especially since the studies included in the systematic review examined the association between non-severe hypoglycaemia and QoL using generic and/or diabetes-specific QoL questionnaires. These measures might be less sensitive to the impact of non-severe hypoglycaemia than hypoglycaemia-specific QoL measures and therefore should be interpreted with caution.

Strengths and limitations

Strengths

This thesis had several key strengths. First, the use of various research methods to investigate the relationship between hypoglycaemia and QoL (i.e., systematic review, quantitative research methods, and qualitative research methods) enabled a critical examination of the research question and provided a more rich and in-depth understanding of the research question than could be obtained from just one research method alone (i.e., either quantitative or qualitative). In this thesis, the use of mixed-methods has provided more insight in contradicting findings between the quantitative and qualitative studies. This also highlighted the methodological problems in quantitative studies that examined the association between hypoglycaemia and QoL and provided suggestions for future research.

Second, the conceptual model of QoL used in Study 2 enabled to include and evaluate a diverse body of literature and to identify the gaps in QoL research. For example, by identifying the domains of QoL with a lack of evidence and those with most evidence for an impact of hypoglycaemia. In addition, this study shows that the research on the impact of QoL is often measured by assessing related psychological outcomes. The novel methods used in the third study to assess not only the impact of hypoglycaemia but also the domains of life important for the participants' QoL directly addressed the limitations of previous studies and key gaps identified by Study 2. As a result, this study was the first to highlight the unique impact of hypoglycaemia on QoL, in addition to the impact of diabetes on QoL that is documented in previous studies. Furthermore, this added insight into important aspects of the assessment of QoL, such as the consideration of personal preferences, and into what adolescents with T1D consider as important for their QoL. These insights have important implications for both research and clinical care, as optimizing QoL is an important goal of paediatric diabetes care. Therefore, QoL needs to be appropriately measured, for example when used to evaluate effectiveness of interventions.

Third, the Hypo-RESOLVE consortium included a broad range of expertise in the area of hypoglycaemia, including researchers, clinicians, industry partners, diabetologists, psychologists and people with diabetes. This multidisciplinary input into the design and execution of the studies strengthened the research by including these different perspectives that helped to improve relevance and transferability of the research findings to clinical care settings.

Limitations of study designs

Study 1 and the studies identified in the systematic review (Study 2) had a cross-sectional design, limiting the ability to draw causal relationships between hypoglycaemia and QoL. While it is likely that hypoglycaemia impacts on QoL, this relationship could also be bidirectional: adolescents with a lower QoL might engage in less optimal self-management behaviours, which may make them more vulnerable to hypoglycaemia. However, in Study 3, adolescents were specifically asked to describe how hypoglycaemia impacted on different domains of their QoL. The results of this study support the notion that hypoglycaemia impacts on QoL.

The two empirical studies had relatively small sample sizes and were conducted in high income countries with good access to medical care. This might limit the generalisability to the broader population of adolescents with T1D, as it could be that the impact of hypoglycaemia differs in countries with different health care settings that have for example less access to diabetes technologies. However, response rates in Study 1 were similar to those reported in other studies conducted in adolescents with T1D (123, 124) and the sample size in Study 3 was relatively large given the qualitative nature of the study. In addition, the aim of qualitative studies is not to achieve generalisable results, but rather to gain a rich and in-depth understanding of the phenomena being investigated from the individual's perspective (125, 126). More specifically, in this study, the goal was not to establish the prevalence of the impact of hypoglycaemia on QoL, but to gain an understanding of the lived experiences of adolescents with T1D experiencing hypoglycaemia. Future studies with larger and more diverse samples are needed to investigate if the current findings can be transferred to the broader population of adolescents with T1D.

Limitation of self-reported hypoglycaemia

The empirical studies (i.e., Studies 1 and 3) and most of the studies included in the systematic review (Study 2) were based on self-report of hypoglycaemia which is, by definition, subjective, and potentially prone to recall and/or social desirability bias. Especially for non-severe hypoglycaemia, which occurs more frequently than severe hypoglycaemia, it can be difficult to accurately recall episodes longer than a week ago (127). Although self-report of hypoglycaemia has its limitations, there is no 'golden standard' when it comes to the assessment of hypoglycaemia, as biochemical measures of hypoglycaemia also have their limitations. First, there is no consensus on a numerical definition of hypoglycaemia for children with diabetes and biochemical measures are not necessarily directly related to the experience of a hypoglycemic event (9). In addition, if for example glucose levels measures by a CGM were used, it is unclear if an impact stems from a direct effect from the symptoms of hypoglycaemia on QoL or is it an indirect effect from the CGM readings and/or the fact that (information about the) hypoglycemic episode interferes with their daily activities. Additionally, results from Study 3 indicated that adolescents still experience an impact of hypoglycaemia on their lives even after glucose levels have returned to target range. For example, they reported to feel bad because some physical symptoms lasted after hypoglycaemia was treated, difficulties to focus on what they were doing after hypoglycaemia and that hypoglycaemia during the night impacted on their energy levels and mood the next day. To date, no studies in children or adolescents with T1D have compared the self-reported rates of hypoglycaemia with objective biochemical measures of hypoglycaemia; this would be an important avenue for future research.

Studies that use ecological momentary assessment (EMA) to repeatedly measure experiences or behaviours in real world context at different intervals (i.e., when an event occurs or at prespecified times) could minimize this bias and maximize ecological validity (128). Though the feasibility and acceptability of such methods for adolescents with T1D needs to be further investigated, they could contribute to a deeper understanding of the daily impact of hypoglycaemia on various aspects of QoL and provide insight in how this impact might differ in various settings or at various times.

Limitations of QoL assessment

As mentioned earlier, QoL is often used as an umbrella term that refers to many different constructs, resulting in great variety in how it is operationalized across studies. Within this thesis, different conceptualizations of QoL have been used across studies. While the PedsQL DM has been used to assess diabetes-specific QoL in the first study recent insights from the Study 2 suggested that this instrument might not be the most optimal to assess diabetes-specific QoL but is instead assessing diabetes distress. The majority of the items in this questionnaire are reflective of (emotional) aspects to specific aspects of living with and managing diabetes, as opposed to the extent to which important aspects of QoL (e.g., social relationships or leisure activities) are impaired by living with and managing diabetes. However, as results of the Study 2 also show, there are currently no hypoglycaemia-specific measures available. To address these limitations, Study 3 used a personalized approach to measure QoL that provided the adolescents the opportunity to indicate what is important for their QoL and then assessed how hypoglycaemia impacted on these domains.

Limitation of participant age

While the aim of this thesis was to examine the impact of hypoglycaemia on QoL in children and adolescents with T1D, only Study 2 included children and adolescents across the whole developmental lifespan. The other two studies only focused on adolescents aged 12-18. The conclusions that can be drawn from this thesis are thus somewhat limited to this age group. However, findings of Study 2 highlighted that one of the limitations of previous studies investigating the impact of hypoglycaemia was the pooling of children and adolescents together in analyses. Given the differences in responsibilities for diabetes-management and its associated burden in children and adolescents with T1D (29), the impact of hypoglycaemia might differ between these age groups and should thus be investigated separately.

Investigating this relationship in younger children poses some additional challenges however, as their capability to self-report QoL is limited compared to older children (129). In these cases, parents are often reporting on their child's QoL, although this has important limitations (130). Given that QoL is a highly subjective construct, this should be assessed from the individual's perspective whenever possible (76, 130). In addition, studies have indicated that parental proxy and self-report often differ and parental variables, such as their own mental health, might influence their ratings of their child's QoL (130, 131). Future studies should explore what methods can be used to examine the impact of hypoglycaemia on QoL in this age group specifically.

Implications for clinical practice

The aim of this research was to examine the impact of hypoglycaemia on QoL of young people with T1D. These findings have to be seen in the light of the ultimate goal of improving the QoL of young people with T1D. With this goal in mind, these findings have several implications for clinical practice.

It is more than just a low glucose level

First and foremost, the findings of this thesis suggest that hypoglycaemia can have an impact on the QoL of young people with T1D in various ways. It thus seems relevant for healthcare professionals to address and acknowledge the full experiences with hypoglycaemia and the impact of these full experiences in clinical care. It is important to not only discuss whether or how often children and adolescents with T1D experience hypoglycaemia, but also discuss the broad impact it can have, as fears or worries about hypoglycaemia can independently impact on QoL, for example through compensatory or avoidance strategies (43, 115).

Even though overall levels of FoH were relatively low in the samples that were investigated in this thesis, the results still show a clear impact of FoH on QoL. More importantly, this impact was observed despite the high availability and uptake of technological devices such as CSII or CGM. Although these devices might help to reduce FoH for some young people with T1D, it is not a 'one size fits all' solution, reflected by the conflicting findings in the literature (41, 43). This illustrates that there might be a large group of adolescents who struggle with hypoglycaemia and have unmet needs. This suggest that there is a need for additional support regarding the impact of hypoglycaemia that does not only target adolescents with elevated levels of fear or with a history of hypoglycaemia. Instead, this needs to become more integrated in regular care strategies. For adults with T1D, several psycho-education programmes are available that target the impact of hypoglycemia by reducing fear, improving awareness of hypoglycemia, and reducing fear (92). However, programmes that target the impact of hypoglycaemia are not available for children and adolescents with T1D (92). Given the impact of hypoglycemia on QoL for adolescents with T1D, as highlighted in the present thesis, such programs are warranted. These should be tailored to specific experiences with hypoglycaemia within this age group. When more persistent FoH is detected in clinical care, the adolescents and healthcare professional could discuss whether a referral to the psychologist within the diabetes-team could be beneficial for more intensive treatment or support.

There is no single truth about experiencing hypoglycaemia

While healthcare professionals often tend to focus on the medical or physical aspects of diabetes, only a few adolescents nominated 'health' or 'diabetes' as important aspects of their QoL. This is in line with findings from previous studies, which indicated that adolescents found 'diabetes' or 'health' less important for their QoL than other domains such as 'friends' or 'school' and that diabetes-nurses had difficulties identifying what aspects of QoL were important to adolescents with T1D (77, 132). Consequently, adolescents might sometimes prioritize other things for their QoL which can be less optimal for their diabetes management. It thus seems important for clinicians to discuss with adolescents what is important for them, and how hypoglycaemia (or diabetes) interferes with these things, to offer more tailored care. The 'Wheel of Life' method used in Study 3 could potentially be used as a "talk-facilitating tool" or "conversation starter" to help health care professionals to engage in such discussions. For example, some of the adolescents in study 3 nominated 'sports' as important for their QoL and described they sometimes deliberately kept their glucose levels above recommended targets when exercising. Health care professionals could discuss with adolescents how they, for example, could still do sports without engaging in this compensatory strategy and how that could benefit their sports performances. This could help to improve both diabetes outcomes and QoL.

Expanding the care model

While healthcare professionals could play an important role in addressing the impact of hypoglycaemia, adolescents spend most of their time outside the healthcare setting in other, social, contexts with their peers, family, or at school. Findings of Study 3 suggested that social functioning was an important determinant of adolescents' QoL. Some adolescents described their social relationships as a source of emotional and practical support in relation to hypoglycaemia, while others described this as an additional stressor, as they did not always feel understood or felt embarrassed or judged when having or treating hypoglycaemia. In addition, findings of Study 2 indicated that the context in which hypoglycaemia takes place can have consequences for its impact. This underscores the importance of expanding the care model to other settings.

As adolescents are focused on “fitting in” with their peers (59) they are sometimes inclined to compromise their diabetes management (e.g., monitoring of glucose levels, administering insulin) to avoid being different from their peers (133). Furthermore, previous studies in combination with the findings from Study 3 show that adolescents sometimes tend to hide their diabetes due to experiencing stigma at school. As a result, they might not engage in optimal self-management behaviours (e.g., taking appropriate actions when their glucose levels are low) which could in turn increase their risk of hypoglycaemia. Moreover, this prevents teachers and peers from providing adequate help in case of hypoglycaemia (134).

Given the key role of peers during adolescence, it is important to promote peer support for adolescents with T1D. A peer group intervention that included adolescents with T1D and their friends led to increased knowledge in friends and increased social support (135). A systematic review suggested that promoting specific forms of support might be most effective in relation to improving diabetes self-management skills (136). Peer support interventions should focus on promoting hypoglycaemia-specific support, such as providing adequate treatment for hypoglycaemia or helping teens to ‘feel good’ about themselves despite having hypoglycaemia. This might help to alleviate the social and emotional impacts of hypoglycaemia. In addition, adolescents with T1D expressed an interest in peer mentoring interventions where they could share diabetes-related experiences with a peer mentor with T1D (137). Such interventions could potentially be used to share hypoglycaemia related experiences and improve coping with (social) barriers to hypoglycaemia prevention and management. Lastly, increasing awareness for diabetes and hypoglycaemia at schools might help to create a safe environment that allows young people to engage in adequate self-management behaviours and equip teachers and peers with knowledge about recognizing and treating hypoglycaemia (138). This might reduce feelings of stigma and promote diabetes and QoL outcomes.

The use of e-health interventions is increasing, and such interventions have been successful in promoting self-management and improving problem-solving skills (139, 140). This could be a potential way to offer support to a broad population of young people with T1D and their friends and families. Though the feasibility and efficacy in reducing the burden of hypoglycaemia of such interventions should be further investigated, these could for example include online psychoeducational modules about the impact of hypoglycaemia, or social media platforms where adolescents with diabetes can connect with their peers with diabetes and share experiences.

While the above-mentioned support strategies might be beneficial for some adolescents, they should be tailored to individual needs. Given the disparity in adolescents experiences with support reflected in the findings of Study 3, it seems important to discuss with the adolescent whether support in other context or involvement of family and friends in clinical care is appreciated.

Words are powerful, so choose wisely

Across all settings, it is important to be attentive to the language used when discussing hypoglycaemia and its impact. Adolescents reported feeling judged, ashamed, or blamed when they experienced hypoglycaemia, consistent with the findings of a previous qualitative study focused on how adolescents, parents and health professionals interact regarding 'uncontrolled diabetes' (141). As adolescents with T1D do not have full control over all the factors that influence their glucose levels, it is important to avoid using judgmental language such as "poor control" or "bad numbers", but rather use neutral language and talk about actual glucose levels or optimizing glucose levels when talking about hypoglycaemia, as also recommended by a current position statement on language use in people with diabetes (142). Even more importantly, children and adolescents with T1D should not be defined by their 'numbers' or glucose levels. It is important to also focus on issues other than glucose levels or diabetes, such as their hobbies (142).

Suggestions for future research

In addition to suggestions for future research as described in the full papers in the appendices, there are several potential directions for future research that result from this thesis.

If the only tool you have is a hammer, you tend to see every problem as a nail - Abraham Maslow

Maintaining QoL is an important goal of diabetes management (75). Moreover, more optimal diabetes-specific QoL has been associated with favourable diabetes outcomes (73). Therefore, it is of great importance to assess QoL in a valid and reliable way in both research and clinical care. Yet, there is still substantial variation in how QoL is conceptualized and assessed. As a result, several questionnaires that aim to assess generic or diabetes-specific QoL have been used across studies.

The results of Study 2 have added some insight into the conceptualization and assessment of QoL. As highlighted in these findings, the PedsQL-DM, one of the most widely used instruments to assess QoL in children and adolescents with T1D, might be measuring diabetes distress rather than QoL. While diabetes distress refers to the negative emotions related to living with and managing diabetes, ones QoL includes a broad range of aspects in addition to health and emotional well-being, such as career, social relationships, and leisure activities (76). As these are distinct constructs, it is important for future studies to use the right tools to measure the respective constructs. There are diabetes-specific tools that assess the impact of diabetes on various domains of life, while allowing for personal preferences, such as the Audit of Diabetes Dependent Quality of Life Teen (ADDQoL-Teen) (143). In this questionnaire, adolescents with T1D can not only indicate whether or not diabetes impacts on different domains of their life, but also how much these impacts matter to them (143). However, this is a diabetes-specific QoL measure that includes many aspects of diabetes, in addition to hypoglycaemia.

There is currently no hypoglycaemia-specific QoL tool for children and adolescents with T1D available. Although there are methods, such as the 'Wheel of Life', that could be used to investigate the impact of hypoglycaemia on QoL in research and clinical care, this method might not be suitable for all study designs. Therefore, the most important gap that needs to be addressed is the development of a measure of hypoglycaemia-specific QoL that is age appropriate and considers personal preferences where possible. Such tools should be developed following available guidelines, including the FDA (Food and Drug Administration) guidelines and the COSMIN (Consensus based Standards for the selection of Health Measurement) guidelines (144, 145).

Risk management

As highlighted by our findings, the relationship between hypoglycaemia and QoL is individual and complex. Future studies could focus on identifying whether there are subgroups of children and adolescents with T1D that might be especially vulnerable to impaired QoL due to hypoglycaemia. For example, family structure (i.e., one parent household) is associated with a higher risk of hypoglycaemia in young people with T1D (146). In another study, there was a significant interaction between a history of SH and single parent household; only those living with one parent reported a significant impact of SH on their lives, but this was not observed in those with a two-parent household (113).

Investigating such patterns could be done by combining different research methods that might do more justice to this individual impact (147). First, qualitative research methods could be used to explore and identify factors that can affect the association between hypoglycaemia and QoL. Then, quantitative methods that apply statistical techniques such as latent class analysis might help to examine whether such factors can help to identify subgroups of children/adolescents with different impacts of hypoglycaemia T1D when examining this association in larger population-based studies.

Understanding underlying mechanisms

The association between a history of hypoglycaemia and higher FoH is well established (41, 43). It may well be the case that for some adolescents with T1D the impact of hypoglycaemia on QoL is mediated by FoH. In addition, as levels of FoH were relatively low in these samples, future studies could also explore the potential moderating effect of FoH and investigate whether the impact of hypoglycaemia on QoL is different for adolescents with higher levels of fear.

Some adolescents in Study 3 reported different forms of stigma in relation to hypoglycaemia, including non-disclosure, feelings of blame and guilt, and feeling excluded from peers. It could be possible that for these adolescents, stigma mediates the association between hypoglycaemia and QoL. Though this is only speculative, future studies could further explore these mechanisms.

Need for interventions with impact

The current findings, in combination with findings from existing literature, confirm the association between

FoH and QoL and/ or glucose management (41, 43). This indicates that, despite the need to address this in regular care strategies, there is a need for evidence-based interventions aimed at reducing FoH. Such interventions have been developed for parents of young children with T1D (148) or for young adults with T1D (149) and include principles from cognitive behavioural therapy and exposure therapy to target dysfunctional cognitions about hypoglycaemia and to gradually expose one to situations that are being avoided due to fear (e.g., being home alone). These programs often also promote coping strategies such as relaxation techniques or seeking support (148, 149).

In addition, the recently developed Hypoglycaemia Awareness Restoration Programme for People with Type 1 Diabetes and Problematic Hypoglycaemia Persisting Despite Optimised Self-care HARPdoc trial explores and targets dysfunctional cognitions in relation to the risk of hypoglycaemia with the aim of reducing hypoglycaemia and improving QoL (150). This novel intervention addresses so called ‘thinking traps’ using visual examples and metaphors, such as ‘the soldier’, to discuss the belief that one should go on despite having hypoglycaemia (150). Although this intervention is focused on adults with IAH, some of these techniques could also be used in interventions for young people with T1D.

However, there are currently no such interventions available for adolescents with T1D and these need to be developed. Although some of the abovementioned techniques could be used in adolescents with T1D, there might be age-specific contributors to this fear such as the fear of negative social consequences (44). These interventions should thus be tailored to age-specific needs.

Concluding remarks

To date, 100 years after the discovery of insulin, and despite numerous technological developments that have improved diabetes care particularly in the past quarter century, hypoglycaemia remains a significant problem within paediatric diabetes that can adversely impact QoL of children and adolescents with T1D. The findings of the present thesis suggest that the impact of hypoglycaemia is not just related to the objective occurrence or severity of hypoglycaemia per se, but that the subjective experiences, worries, and fears about hypoglycaemia are as, if not, even more, important in relation to QoL. This needs to be recognized in both future research studies and in clinical care. Moreover, the impact of hypoglycaemia on QoL needs to be addressed in clinical care. Future studies need to further investigate whether interventions to reduce the impact of hypoglycaemia can improve QoL for children and adolescents with T1D. Suitable measures of hypoglycaemia-specific QoL are needed to enable appropriate evaluation of such interventions.

Overview of key findings resulting from this thesis

Key findings
• This thesis is the first to show the unique and profound impacts of hypoglycaemia on various aspects of quality of life in children and adolescents with type 1 diabetes. • This impact is broad and goes beyond the impact of severe episodes only. The impact of hypoglycaemia encompasses the impact of hypoglycaemia episodes (regardless of their severity), thoughts, worries and fears about hypoglycaemia, and efforts taken to prevent or minimize hypoglycaemia. • Quality of life is a highly subjective construct and personal preferences should be considered when assessing quality of life in children and adolescents with type 1 diabetes. Hypoglycaemia-specific quality of life tools need to be developed that consider personal preferences and age specific needs of children and adolescents with T1D to further investigate the impact of hypoglycaemia on quality of life. • The impact of hypoglycaemia should be acknowledged and addressed in routine clinical care. There is a need for interventions targeted at reducing the impact of hypoglycaemia for children and adolescents with type 1 diabetes.

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Appendices

Paper 1

Hypoglycaemia and diabetes-specific quality of life in adolescents with type 1 diabetes

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What is new?

- Increasing evidence suggests that hypoglycaemia is associated with reduced quality of life.
- This is the first study that examines independent relationships of frequency, perceived severity and fear of hypoglycaemia with diabetes-specific quality of life in adolescents with type 1 diabetes.
- Fear of hypoglycaemia was the only factor independently associated with lower diabetes-specific quality of life and this was consistent across domains of diabetes-specific quality of life.
- These findings highlight the importance of awareness and assessment of fear of hypoglycaemia in clinical care, and the need for further development of interventions aimed at reducing fear of hypoglycaemia.

Abstract

Aims: To examine whether frequency, perceived severity and fear of hypoglycaemia are independently associated with diabetes-specific quality of life in adolescents with type 1 diabetes.

Methods: Cross-sectional self-reported data on demographics, frequency and perceived severity of both self-treated and severe hypoglycaemia, fear of hypoglycaemia (Hypoglycaemia Fear Survey- Child version), and diabetes-specific quality of life (Paediatric Quality of Life Diabetes Module; PedsQL-DM) were obtained from the project 'Whose diabetes is it anyway?'. Hierarchical regression analyses were performed for the total scale and recommended summary scores of the PedsQL-DM as dependent variables; independent variables were entered in the following steps: 1) age, gender, HbA_{1c}, 2) frequency of hypoglycaemia; 3) perceived severity of hypoglycaemia and 4) fear of hypoglycaemia.

Results: 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.

Conclusions: 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.

Keywords: hypoglycaemia, quality of life, fear of hypoglycaemia, adolescents

Introduction

Despite the recent improvements in diabetes care and greater access to technological devices assisting in insulin administration and glucose monitoring, hypoglycaemia remains a significant problem for young people with diabetes (1). Hypoglycaemia can range from unpleasant symptoms hampering daily functioning that can be self-treated, to severe events requiring assistance from others to recover (2). Hypoglycaemia is especially complex in adolescents with type 1 diabetes, both due to physiological changes in hormonal levels and developmental changes (e.g., becoming independent from parents, gaining peer acceptance and alcohol use) that can lead to increased risk of hypoglycaemia (3, 4). Supporting families to find an optimal balance between diabetes management and quality of life (QoL) is a major goal in paediatric diabetes care (5). QoL is a complex construct to measure, due to its dynamic, subjective, and multi-dimensional nature. Both generic and disease-specific measures can be used to assess QoL (6) Generic measures are especially useful to measure a broad spectrum of aspects of life and are not attributed to a specific situation (i.e., "how is your quality of life?") and can be used for comparison of outcomes between different populations. Diabetes-specific QoL instruments attribute QoL to diabetes specifically (i.e., "how does diabetes impact on your quality of life?") and are focused on how issues specifically related to diabetes and its management can impair QoL (7). Ideally, the impact of hypoglycaemia on QoL would be assessed with a "hypoglycaemia-specific QoL" measure, that attributes the assessment of QoL directly to the experience with hypoglycaemia (i.e., "how does hypoglycaemia affect your quality of life?"). However, there are currently none of these measures available; therefore, we opted for a diabetes-specific QoL measure in this study.

Although in some studies the frequency of hypoglycaemia resulting in comas or requiring assistance from others was unrelated to QoL (8, 9), other studies showed that children with more frequent hypoglycaemia where assistance from others was required (10) or severe hypoglycaemia (not further defined) (11) reported lower QoL. In addition to objective severity, the personal experience and perception of hypoglycaemia can also impact QoL (e.g., a hypoglycaemic event at home when parents are around could be perceived as less impactful than at school). A longitudinal study among adults with type 2 diabetes (both insulin and non-insulin users) showed that perceiving hypoglycaemia as burdensome was independently related to decreases in QoL, above and beyond the frequency of hypoglycaemia (12). Other studies have indeed found that hypoglycaemic events can be traumatic, and have a long-lasting emotional impact (13, 14). However, the role of the perception and experience of hypoglycaemia in relation to diabetes-specific QoL in adolescents with type 1 diabetes is less clear.

Additionally, people with diabetes could develop fear of hypoglycaemia. Although being concerned about hypoglycaemia is adaptive, extreme worries (referred to as fear of hypoglycaemia) could lead to the maintenance of higher blood glucose levels or hypoglycaemia avoidance behaviours that could compromise optimal diabetes management and/or quality of life. (15) A review about fear of hypoglycaemia in youth with type 1 diabetes reported that fear of hypoglycaemia is associated with impaired QoL (16). This fear could stem from previous severe hypoglycemic events or thoughts about future events, as well as from self-treated (also referred to as “mild” or “moderate”) hypoglycemia that hinders people in daily functioning.

A systematic review showed that general QoL did not differ between young people with diabetes and their peers without diabetes, although diabetes negatively impacted their QoL (i.e., negative impact of diabetes on QoL and worries about diabetes) (17). Therefore, it is important to identify factors that can affect diabetes-specific QoL in this population, such as hypoglycaemia (i.e., the occurrence, experiences, thoughts and fears about it (8, 17). Previous studies in adolescents with type 1 diabetes have predominantly focused on severe hypoglycaemia and did not explore associations between the frequency, perceived severity, and fear of hypoglycaemia on diabetes-specific QoL simultaneously.

Therefore, the aim of this study was to examine whether perceived severity of severe and self-treated hypoglycaemia, and fear of hypoglycaemia have additional value over frequency of hypoglycaemia in explaining (domains of) diabetes-specific QoL in adolescents with type 1 diabetes. Furthermore, it was hypothesized that associations between perceived severity and fear of hypoglycaemia with diabetes-specific QoL would be stronger for adolescents who had experienced more episodes of hypoglycaemia.

Participants and methods

Data were extracted from the quantitative part of the multi-method research project “Whose diabetes is it anyway?”. This project focuses on the division and transfer of diabetes care responsibilities among children and adolescents with type 1 diabetes and their parents. Families were recruited from four Dutch specialist diabetes centers and paediatric departments of general hospitals between March and October 2018. Inclusion criteria were a diabetes duration of more than six months, no intellectual disabilities, and sufficient knowledge of the Dutch language. Eligible families were invited via post to complete questionnaires; reminders were sent after two weeks. For study participation, adolescent and parental consent were sought. After completion of the questionnaires, adolescents received a €7.50 gift card.

Of the 262 adolescents who were invited, 116 agreed to participate (response rate=44%). Responders had a significantly lower HbA_{1c} (7.6%) and were more often insulin pump users (79%), compared to non-responders, who did not consent to participate, but gave permission for comparison of data extracted from their medical record (HbA_{1c}=8.4%; insulin pump use=57%), $p<0.05$. There were no differences in gender, age and diabetes duration (p’s>0.05). For the current study, 96 adolescents completed all relevant measures. The project received ethics approval from the Psychological Ethics Committee of Tilburg University (EC-2017.85).

Measures

Socio-demographic and clinical information

Socio-demographic (i.e., date of birth, gender) and clinical data (i.e., date of diagnosis, $HbA_{1c,}$ and insulin treatment modality) were retrieved from medical records. Age, and diabetes duration were subsequently calculated. Additional demographic information (i.e., ethnic background, educational level), and clinical characteristics (i.e., comorbidities, glucose measurement modality, average number of blood glucose readings per day) were self-reported.

Frequency and perceived severity of self-treated and severe hypoglycaemia

Frequencies of self-treated and severe hypoglycaemia were assessed with items of the Hypoglycaemia Fear Survey – Children version (HFS-C part 2) (18). A forward-backward translation method was used to translate the items into Dutch. Severe hypoglycaemia was defined as the number of 'hypoglycaemic episodes when your blood glucose was so low that you were unable to recognize symptoms, ask for help, or treat yourself due to mental confusion or unconsciousness' in the previous 12 months. Self-treated hypoglycaemia was defined as the number of 'hypoglycaemic episodes when your blood glucose was so low that it interfered with what you were doing, and you had to wait a while to recover', in the previous 6 months. Additionally, perceived severity was assessed by asking the adolescents to rate how upsetting the worst episode of severe hypoglycaemia was (in the past twelve months) as well as how upsetting the worst episode of self-treated hypoglycaemia was (in the past six months), on a 5-point Likert scale ranging from 0 (not at all upsetting) to 4 (extremely upsetting). The response option 'not applicable' was recoded into 0, as these adolescents did not experience an upsetting hypoglycaemic episode.

Fear of hypoglycaemia

Fear of hypoglycaemia was assessed with the 15-item worry subscale of the Hypoglycaemia Fear Survey – Children version (HFS-C) (18). For each item, adolescents indicated their level of concerns related to hypoglycaemia (e.g., "Not recognizing that my blood glucose is low") on a 5-point Likert scale, ranging from 0 (never) to 4 (often). Items were summed to generate total scores (range 0-60), with higher scores indicating higher levels of fear. Following the manual, missing values were substituted with within - person mean values if less than 25% was missing (n=5). Satisfactory psychometric properties have been demonstrated for the HFS-C worry scale (18); in the current study internal consistency was good (α=0.87).

Diabetes-specific QoL

Diabetes-specific QoL was measured using the Dutch version of the Pediatric Quality of Life Diabetes Module 3.2 (PedsQL-DM 3.2) (19). This is a 33-item multidimensional questionnaire for children ≥12 years (32 items for adolescents aged 12 years old). Recent guidance recommends using two summary scores assessing the frequency of diabetes symptoms (15 items) and problems with diabetes management (18 items) in the past month. To enable the readers to compare our study with previous findings and to follow these recommendations, we have included all three scores as outcomes in our analysis**.** Each item was scored on a 5-point Likert scale, ranging from 0 (never) to 4 (almost always). All items were linearly converted to a 0-100 scale, with higher scores indicating more optimal diabetes-specific QoL. Mean scores were computed if <50% of the items were missing (n=6). The PedsQL-DM is considered a reliable and valid measure of diabetes-specific QoL in adolescents with type 1 diabetes (19); reliability of the overall scale in the present study was excellent (α=0.93). Reliability of the summary scores were good (symptoms α=0.88;management α=0.90)).

Statistical analyses

Spearman correlation analysis was used to assess correlations between frequencies of hypoglycaemia and fear of hypoglycaemia. A hierarchical regression analysis was performed to examine whether frequency of hypoglycaemia, perceived severity of hypoglycaemia and fear of hypoglycaemia were independently related to diabetes-specific QoL (total score). Independent variables were entered in the following steps: 1) covariates (i.e., age, gender, HbA_{1c}, based on their relationship with diabetes-specific QoL in previous studies (10, 20, 21), 2) frequency of severe and self-treated hypoglycaemia; 3) perceived severity of severe and self-treated hypoglycaemia, 4) fear of hypoglycaemia and 5) interactions of centred values (frequency*severity of hypoglycemia, frequency*fear of hypoglycemia). The analysis was repeated for each of the two separate summary scores of the PedsQL-DM as the dependent variable. To determine statistical significance, α was set at 0.05.

In all regression models examining associations of frequency, perceived severity and fear of hypoglycaemia with diabetes-specific QoL, assumptions of linearity and homoscedasticity were met. Although moderate correlations were observed between hypoglycaemia variables, and between gender and hypoglycaemia variables, the assumption of multicollinearity was not violated. A breach of normality (skewness=-0.13, kurtosis=2.65, Shapiro Wilks test *p*=0.004) was noted in the main analysis (total score of PedsQL-DM), which appeared to be due to a single outlier. Removing this case from the analysis resulted in a normal distribution of standardized residuals (skewness=0.51, kurtosis=0.97, Shapiro Wilks test *p*=0.10), but did not affect the results of the regression analysis. Therefore, the current analysis was based on the data of all respondents (n=96). All statistical analyses were performed using SPSS v24 (Chicago, IL, USA).

Results

Of the total sample (n=96), the majority had diabetes for >1 year (99%) and mean HbA_{1c} was 58 (SD=9.8) mmol/mol (7.5%, SD=0.9) (22). Approximately 20% of the adolescents reported they had experienced at least one episode of severe hypoglycaemia within the past 12 months (range 0-20, median=0, interquartile range=0-0). In total, 87% of the adolescents reported at least one episode of self-treated hypoglycaemia in the past 6 months (range 0-200, median=6, interquartile range=2-20). The frequency of severe hypoglycemia and self-treated hypoglycemia were not associated (r=0.16, *p*=0.11).The correlations between frequency of severe hypoglycaemia and self-treated hypoglycaemia were 0.16 (*p*>0.05) and between frequency of severe and self-treated hypoglycaemia and fear of hypoglycaemia were 0.32 (*p*<0.01) and 0.17 (*p*>0.05), respectively. Socio-demographic information and clinical characteristics of the participants can be found in Table 1.

Factors related to diabetes-specific QoL (PedsQL-DM total score)

Results of the hierarchical regression analysis are presented in Table 2. The first model, including gender, age, and HbA_{1c}, significantly explained 14% of the variance in diabetes-specific QoL (*Pp*=0.001). Female adolescents (*Pp*=0.001) and participants with higher HbA_{1c} level (*p* =0.031) reported significantly lower diabetes-specific QoL. In the second step, the total model did not significantly improve by adding the frequency of severe and self-treated hypoglycaemia (*p*=0.053). In addition to gender and HbA_{1c}, a higher frequency of severe hypoglycaemia was significantly associated with lower diabetes-specific QoL (*p*=0.035), while frequency of self-treated hypoglycaemia was not. In the third step, the addition of perceived severity of severe and self-treated hypoglycaemia resulted in a significant improvement of the model (*p*=0.003); 26% of the variance in diabetes-specific QoL was explained. Adolescents who reported severe hypoglycaemia (*p*=0.047) and self-treated hypoglycaemia as upsetting (*p*=0.007) reported lower diabetes-specific QoL. In this step, the associations between HbA_{1c} and the frequency of severe hypoglycaemia with diabetes-specific QoL were no longer significant. Adding fear of hypoglycaemia in the final step further improved the model (*p* <0.001); 52% of the variance in diabetes-specific QoL was explained. In this step, only higher fear of hypoglycaemia was significantly associated with lower diabetes-specific QoL scores (*p* <0.001). The previous significant associations of gender and perceived severity of self-treated hypoglycaemia with diabetes-specific QoL were negated.

When the analysis was repeated with the interaction terms in the fifth step, this did not significantly improve the model (*p*'s>0.05; data not shown). This analysis was also repeated with frequency of severe hypoglycaemia as a categorical instead of a continuous variable, but this yielded similar results (data not shown).

Factors related to Diabetes Symptoms and Diabetes Management summary scores of diabetes-specific QoL

Hierarchical regression analyses with the different summary scores of the PedsQL-DM as dependent variables (Table 3) resulted into similar conclusions compared to the analysis with total score of PedsQL-DM.

Discussion

In this study among 96 adolescents with type 1 diabetes, demographic variables, HbA_{1c}, and frequency, perceived severity and fear of hypoglycaemia together explained 52% of the variance in diabetes-specific QoL. However, only greater fear of hypoglycaemia was independently associated with lower diabetes-specific QoL.

In line with previous literature (8, 16), fear of hypoglycaemia is a considerable burden for adolescents with diabetes, though the levels of fear were relatively low in this sample (23). Greater fear of hypoglycaemia was consistently related to reduced diabetes-specific QoL, across the different summary scores, suggesting that the observed association for overall diabetes-specific QoL is not driven by one individual summary score.

Before adding fear of hypoglycaemia in the regression, our results were in line with other studies reporting an association between a higher frequency of severe hypoglycaemia and lower diabetes-specific QoL (10, 11), while inconsistent with others (8, 9). However, fear of hypoglycaemia negated this association. The definitions of severe hypoglycaemia differed greatly across studies, which could possibly explain conflicting findings. The less strict definition used in this study could also explain the relatively high frequency of severe hypoglycaemia, compared to rates reported by the International Society of Pediatric and Adolescent Diabetes (4).

Contrary to previous QoL studies amongst adults with diabetes (12, 24), the frequency of self-treated hypoglycaemia and diabetes-specific QoL were unrelated in youth. However, the rate of self-treated events in this study (average of 17 events in the past six months) was relatively low compared to an average of two events per week among children and adolescents reported elsewhere (4). As self-treated hypoglycaemia is common for adolescents with diabetes, it is possible that a potential negative impact of self-treated hypoglycaemia only occurs in adolescents who experience more frequent self-treated events. The six-months recall period might have led to an underreport of self-treated hypoglycaemia in this study. Furthermore, self-report of hypoglycaemia might be less reliable in this group, as there were some discrepancies observed between the self-reported frequency and perceived severity of these events (i.e., some adolescents reported that they did not experience a hypoglycaemic episode, but also reported their worst hypoglycaemic episode in the past 12 or 6 months as upsetting). Future studies using (blinded) continuous glucose monitoring in addition to self-report, and ideally combined with ecological momentary assessments of outcome measures, might provide more insight into the relationship between hypoglycaemia and diabetes-specific QoL.

Although frequency of self-treated hypoglycaemia was not significantly associated with diabetes-specific QoL, there was an association between perceived severity of self-treated events and diabetes-specific QoL, that was negated by fear of hypoglycaemia. The experience and perception of hypoglycaemia could contribute to fear of future hypoglycaemia (25). Since greater fear of hypoglycaemia was associated with reduced diabetes-specific QoL in this study, the impact of self-treated events should not be overlooked, as they can indirectly affect diabetes-specific QoL. In contrast to a previous study, we did not observe an interaction effect between frequency and perceived severity of hypoglycaemia, although this was based on a sample of adults with type 2 diabetes (12).

This study has several limitations. First, the overall sample was relatively small and adolescents using a pump and with lower HbA_{1c} levels were more likely to participate in this study, which might limit the generalizability of our findings. Second, the cross-sectional design of the study does not allow examination of causal interpretations. Third, to preserve sufficient power, only covariates that were most consistently associated with QoL in previous studies were included in the current analyses. It is recognized that the exclusion of other covariates (e.g., type of insulin administration, diabetes duration), may have affected the results (10, 21, 26-29). Fourth, based on new insights on QoL, it can be argued that the PedsQL-DM might not be the most optimal assessment of diabetes-specific QoL (30). Since "hypoglycaemia-specific" QoL measures are not currently available, the full understanding of the impact of hypoglycaemia on QoL remains elusive. Future studies that focus on the development of these measures can help to improve our understanding of the true impact of hypoglycaemia on QoL in people with diabetes. Notwithstanding these limitations, this is the first study that simultaneously examined different aspects (i.e., frequency, perceived severity and fear) of both self-treated and severe hypoglycaemia in relation to diabetes-specific QoL, allowing for the exploration of independent associations. Furthermore, the multidimensional evaluation of QoL provides a more detailed understanding of the association between hypoglycaemia and diabetes-specific QoL in adolescents with type 1 diabetes and adds insight into the way that frequency, perceived severity and fear of hypoglycaemia are interrelated.

Clinical implications

Despite limitations, the results highlight the need to be aware and assess of fear of hypoglycaemia in clinical care, as only fear of hypoglycaemia was independently related to diabetes QoL. Fear of hypoglycaemia is related to hypoglycaemia history (18), both recent and traumatic events that happened years ago might still affect emotions and behaviours in the present (13, 14). Fear of hypoglycaemia can also be an anticipatory anxiety about future events (18) and might also occur when reading or hearing about severe events, irrespective of one's own experiences. Adolescents who report higher levels of fear of hypoglycaemia and are thus more worried about hypoglycaemia and its consequences, may be more likely to engage in hypoglycaemia avoidance behaviours (i.e., avoiding social or physical activities), that can impair their QoL (16). This suggests that fear of hypoglycaemia, and not solely recent events and experiences with hypoglycaemia, should be measured in clinical care, as this fear is a potentially modifiable factor that can strongly contribute to reduced diabetes-specific QoL. Future (longitudinal) studies should explore the underlying mechanisms of the relationship between fear of hypoglycaemia and diabetes-specific QoL, as it is possible that these can be influenced by personality traits such as neuroticism or trait anxiety (23). For example, an association between fear of hypoglycaemia and reduced QoL on the diabetes management domain could be the result of adolescents who are more worried in general as they might experience both higher fear of hypoglycaemia and difficulties in engaging in self-management behaviours (31, 32).

For adults with diabetes and parents of young children with diabetes, there are interventions available to reduce fear of hypoglycaemia (33, 34). Interventions for adolescents with diabetes may ideally focus on reducing fear of hypoglycaemia accompanied by self-management strategies that reduce hypoglycaemia risk. Although fear of hypoglycaemia in adults and adolescents with diabetes showed similar underlying factors, there are also notable differences. As adolescent development is characterized by the desire to not feel different from peers, the concern about potential negative social evaluations because of hypoglycaemia might be more pronounced in this group (35). Future studies on interventions to manage fear of hypoglycaemia in youth with type 1 diabetes should incorporate these age specific needs.

Conclusion

In conclusion, this study showed that greater fear of hypoglycaemia is associated with lower diabetes-specific QoL in adolescents with type 1 diabetes, over and above frequency and severity of hypoglycemia. This has important implications for clinical practice; future studies are needed to identify if reduction of fear of hypoglycaemia is associated with an improvement of diabetes-specific QoL in adolescents with type 1 diabetes.

Table 1. Socio-demographic information and clinical characteristics of the 96 participating adolescents (aged 12-18 years) with type 1 diabetes

	Number of valid cases	% (n)	Mean (SD)	Range
Age (years)	96		15.2 (1.6)	12-18
Gender, male	96	48 (46)		
Adolescent education	95			
Elementary school		3 (3)		
High school		85 (82)		
Further education		10 (10)		
Ethnicity	95			
Dutch		95 (91)		
Double (one is Dutch)		3 (3)		
Non-Dutch		1 (1)		
Somatic comorbid conditions[1]	96			
None		62 (67)		
≥1		34 (33)		
Psychological comorbid conditions[2]				
None		70 (75)		
≥1		26 (25)		
Diabetes duration (years)	96		7.0 (4.3)	
Insulin administration	96			
Insulin pump		81 (78)		
Multiple daily injections		19 (18)		
Glucose monitoring modality	95			
Real-time CGM		19 (18)		
Flash glucose monitoring		14 (13)		
Fingerpicks only		67 (64)		
Frequency of glucose monitoring per day[3]	77			
Real-time CGM	16		14.1 (6.9)	5-25
Flash glucose monitoring	13		13.7 (8.7)	3-30
Fingerpicks only	48		5.3 (1.7)	3-10
HbA$_{1c}$ (mmol/L)[4]	96		58 (9.8)	34-90
HbA$_{1c}$ (%)[4]	96		7.5 (.9)	5.3-10.4
Hypoglycaemia				
Frequency of severe hypoglycaemic episodes past 12 months			0.7 (2.4)	0-20
Frequency of self-treated hypoglycaemic episodes past 6 months			17.4 (29.9)	0-200
Perceived severity: worst episode of severe hypoglycaemia past 12 months (HFS-C; range 0-4)[5]			1.3 (1.5)	0-4
Perceived severity: worst episode of self-treated hypoglycaemia past 6 months (HFS-C; range 0-4)[5]			2.0 (1.2)	0-4
Fear of hypoglycaemia (HFS-C worry scale; range 0-60)[6]	96		12.6 (8.3)	0-41
Diabetes-specific QoL Total score (PedsQL-DM; range 0-100)[7]	96		74.0 (13.3)	17.4-99.2
Symptoms summary score (range 0-100)			64.3 (14.9)	15.0-98.3
Management summary score (range 0-100)			81.5 (15.0)	16.7-100

HFS-C, Hypoglycaemia Fear Survey – Child version; PedsQL- DM, Paediatric Quality of Life Inventory-Diabetes Module

[1] Somatic comorbid conditions included eczema, asthma, celiac disease, allergy, hypothyroidism, cataract, juvenile rheumatoid arthritis, and other conditions (erb's palsy and vitiligo).

[2] Psychological comorbid conditions included ADHD, autism, anxiety disorder, dyslexia and dyscalculia.

[3] For sensor; frequency of checking sensor was used, for Flash Glucose Monitoring; frequency of flashings was used, for no sensor; frequency of finger pricking was used.

[4] Most recent HbA_{1c} between 2 months before and 2 months after study participation (Mean=28.1 days, SD=18.4)

[5] Higher scores indicate higher perceived severity

[6] Higher scores indicate higher fear of hypoglycaemia

[7] Higher scores indicate higher diabetes-specific QoL

Table 2. Hierarchical linear regression analysis examining the association between diabetes-specific QoL (PedsQL) and demographics, HbA1c, frequency of hypoglycaemia, severity of hypoglycaemia and fear of hypoglycaemia in adolescents with type 1 diabetes (n=96)

PedsQL DM	**Model 1**	**Model 2**	**Model 3**	**Model 4**
	β	***β***	***β***	***β***
1. Demographic and clinical information				
Age (years)	-.05	-.07	-.12	-.11
Gender, male	.35 **	.31 **	.23 *	.10
HbA$_{1c}$	-.21 *	-.20 *	-.16	-.13
2. Frequency of Hypoglycaemia				
Severe hypoglycaemia (past 12 months)		-.20 *	-.14	-.03
Self-treated hypoglycaemia (past 6 months)		-.09	-.06	-.04
3. Perceived severity of hypoglycaemia[1]				
Severe hypoglycaemia (past 12 months)			-.20 *	-.06
Self-treated hypoglycaemia (past 6 months)			-.26 **	-.09
4. Fear of hypoglycaemia[1]				
Fear of hypoglycaemia				-.60 **
Adjusted R^2	.14 **	.18 **	.26 **	.52 **
R^2 change	.17	.05	.10 *	.24 **

[1] higher scores indicate higher perceived severity/fear

*p<0.05, **p<0.01

Gender is binary coded, 1=male, 0=female

Table 3. Fully adjusted linear regression analyses examining associations of demographics, HbA_{1c}, frequency of hypoglycaemia, severity of hypoglycaemia and fear of hypoglycaemia with diabetes symptoms summary score and diabetes management summary scores of diabetes-specific QoL (PedsQL) in adolescents with type 1 diabetes (n=96)

PedsQL DM-summary scores	**Diabetes Symptoms**		**Diabetes Management**	
	β		***β***	
1. Demographic and clinical information				
Age (years)	-.08		-.13	
Gender, male	.09		.11	
HbA_{1c}	-.05		-.15	
2. Frequency of Hypoglycaemia				
Severe hypoglycaemia (past 12 months)	-.06		-.003	
Self-treated hypoglycaemia (past 6 months)	-.03		-.03	
3. Perceived severity of hypoglycaemia[1]				
Severe hypoglycaemia (past 12 months)	-.16		.02	
Self-treated hypoglycaemia (past 6 months)	-.11		-.03	
4. Fear of hypoglycaemia[1]				
Fear of hypoglycaemia	-.51	**	-.58	**
Adjusted R2	.45	**	.41	**
R2 change	.17	**	.23	**

[1] higher scores indicate higher perceived severity/fear.

*p<0.05, **p<0.01.

Gender is binary coded, 1=male, 0=female

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Authors’ contribution

J.A., F.P., E.H. and G.N. designed and obtained funding for the “Whose diabetes is it anyway?” project. J.A. coordinated data collection. H.J.A. assisted in data collection and provided administrative support. M.C., J.A., M.B., G.N. and F.P drafted the manuscript. M.C. analysed the data. All authors have reviewed the manuscript for important intellectual content and have approved the final version of the manuscript.

Disclosure statement

The authors report no conflicts of interest related to this manuscript.

Ethical approval

Ethical approval was obtained from the Psychological Ethics Committee of Tilburg University (EC-2017.85).

Paper 2

The impact of hypoglycemia on quality of life and related outcomes in children and adolescents with type 1 diabetes: a systematic review

Under review, PLOS ONE

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Abstract

Objective: To conduct a systematic review to examine associations between hypoglycaemia and quality of life (QoL) in children and adolescents with type 1 diabetes.

Methods: Four databases (Medline, Cochrane Library, CINAHL, PsycINFO) were searched systematically in November 2019 and searches were updated in September 2021. Studies were eligible if they included children and/or adolescents with type 1 diabetes, reported on the association between hypoglycaemia and QoL (or related outcomes), had a quantitative design, and were published in a peer-reviewed journal after 2000. A protocol was registered the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020154023). Studies were evaluated using the Joanna Briggs Institute's critical appraisal tool. A narrative synthesis was conducted by outcome and hypoglycaemia severity.

Results: In total, 27 studies met inclusion criteria. No hypoglycaemia-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 hypoglycaemia and outcomes across studies. SH was associated with greater worry about hypoglycaemia, 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 hypoglycaemia may be associated with adverse outcomes and that the context in which hypoglycaemia takes places might be important in relation to its impact.

Conclusions: There is insufficient evidence regarding the impact of hypoglycaemia on QoL in children and adolescents with type 1 diabetes at this stage. There is a need for further research to examine this relationship, ideally using hypoglycaemia-specific QoL measures.

Key words: hypoglycaemia, type 1 diabetes, quality of life, patient-reported outcomes, children and adolescent

Introduction

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) (1, 2). The goal of diabetes management is to achieve and maintain recommended glycemic levels to prevent/delay acute and long-term complications (1). However, treatment with insulin can lead to hypoglycaemia (low blood glucose level) (3). Hypoglycaemia 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 hypoglycaemia (SH) have been associated with neurocognitive impairments, especially in young children (4).

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) (5-7), a recent systematic review still reported an incidence of 1.21–30 events per 100 person-years in young people with type 1 diabetes (8). Hypoglycaemia 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 (9). Among adolescents, both hormonal changes leading to insulin resistance (10) 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 hypoglycaemia (11).

Another important goal of paediatric diabetes management is to achieve and maintain optimal quality of life (QoL) (12). While some studies have shown that hypoglycaemia is negatively associated with QoL (13, 14), other studies have not found such an association (15, 16). Although QoL is defined and assessed in many different ways across studies, it is recognized that QoL is a multidimensional, dynamic and subjective construct (17). 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 (18, 19). 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, and which are measuring related outcomes (such as diabetes-specific emotional distress or health status) rather than QoL (18). Synthesis of the current evidence base is needed to determine the relationship between hypoglycaemia and QoL-related outcomes.

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

Methods

Search strategy

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (20) and was registered on the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020154023) database. A systematic search of Medline, Cochrane Library, CINAHL and PsycINFO databases was conducted in November 2019 and updated in September 2021, as part of a larger search strategy for five related systematic reviews examining the impact of hypoglycaemia in various populations. 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) hypoglycaemia and (4) QoL and related outcomes. There were no limits applied to date or language at the search stage. The search string is provided in the supporting information.

Inclusion & exclusion criteria

Studies were eligible if they: (1) included children and/or adolescents with type 1 diabetes, majority aged ≤18 years (or mean age <18 years old), (2) assessed the history of hypoglycaemia, (3) included outcomes of generic, diabetes-specific or hypoglycaemia-specific QoL (or domains of QoL) or related outcomes (e.g., fear of hypoglycaemia, depression, diabetes distress), (4) examined the association between hypoglycaemia and QoL or related outcomes, (5) had a quantitative design, (6) were published in a peer-reviewed journal with full text available in English, (7) were published after 2000. The focus was limited to publications in the past two decades, as diabetes management strategies and rates of hypoglycaemia have changed considerably in recent decades (5-7). Studies were excluded if they: (1) focused on cognitive functioning (21) or neurodevelopmental disorders (22), or (2) only included proxy-report (e.g., by parents) of outcomes (23).

Screening, article selection, and data extraction

Abstract screening was completed by three reviewers, with 10% of the abstracts being double screened (AS, AC and MCL). MC completed full text-screening (with input from a second reviewer (MB) where queries arose), and 10% of the full-text records were independently screened by a third reviewer (KM). In case of disagreement, reviewers discussed until consensus was reached. Additionally, forward chaining (i.e., citation searching of included studies in Google Scholar) and backward chaining (i.e., reference list checking of all included studies) was undertaken to identify additional eligible papers. Data extraction was performed by MC and KS; extracted data included reference details, study details, participant characteristics, analysis, results and discussion points. Extracted data were checked by two independent reviewers (HC, MB) and consensus was reached in case of discrepancies.

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) (24). 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 synthesis

Narrative synthesis was structured primarily by a conceptual framework of QoL (Table 1), wherein outcomes were grouped based on two dimensions (18): 1) the scope of the measure (global, broad, specific): i.e. whether a questionnaire assesses global QoL (e.g., 'overall QoL'), a broad domain of QoL (e.g., social functioning) or a specific domain of QoL (e.g., friends); and 2) the attribution of the measure (generic, diabetes- or hypoglycaemia-specific): generic QoL measures ask people to rate areas of their life overall. These ratings can be affected by many factors including but also unrelated to diabetes, whereas diabetes-specific [or hypoglycaemia-specific] QoL measures seek to attribute any impact to the condition, specifically asking: 'how does diabetes [or hypoglycaemia] impact on your QoL?'

If a measure did not assess QoL but assessed a concept closely related to QoL (such as depressive symptoms, diabetes distress, FoH), it was classified as a related outcome. Diabetes distress refers to the negative emotions related to living with diabetes (25). These related outcomes were grouped by the attribution of the measure (generic, diabetes- or hypoglycaemia-specific outcome). Within each outcome group, study findings were summarized separately for SH and non-severe hypoglycaemia (NSH) according to the authors' definitions, and where possible by outcome type/questionnaire.

To enhance consistency and transparency in the narrative synthesis and to avoid vote counting based on statistical significance (26), the following considerations were taken into account to interpret the evidence per outcome: 1) whether definitions and recall periods of hypoglycaemia varied between studies; 2) whether there was a valid assessment of QoL and/or related outcomes; 3) whether analyses were conducted for children and adolescents separately or together; 4) whether there were exclusion criteria that directly related to hypoglycaemia or QoL outcomes; and 5) whether effect sizes were available: small ($r \geq 0.10$ and <0.30), moderate ($r \geq 0.30$ and <0.50), and large $r \geq 0.50$) (27).

It was determined that there was insufficient evidence to draw a conclusion for an outcome if: a) there were less than three studies examining the association, or b) there was considerable heterogeneity in definitions of hypoglycaemia and sample characteristics across studies.

Results

Included studies

The searches yielded 1165 results. Title and abstract screening resulted in 217 potential includes. After full-text screening, 17 studies were included. Forward and backward chaining yielded 10 extra includes. In total, 27 studies were included for data extraction and synthesis. Figure 1 provides an overview of the screening and selection process.

Study characteristics

The 27 studies included a total of *N*=141,530 participants, with sample sizes ranging from *N*=39 to *N*=2,602, with the exception of two large-scale studies (*N*=53,986 and *N*=75,258*)*. The studies were conducted in 18 countries, the majority conducted in USA (*n*=6) and Germany (n=4). One study included multiple countries in Europe, North America and Japan (37). The age of participants ranged from 5-25 years. Most studies included participants between 8-18 years, although eight studies also included participants above 18 years, and four studies also included participants aged 5-7 years. One study included children aged 6-12 years and five studies included adolescents aged 12-18 years. Study characteristics are detailed in Table 2.

All studies had a cross-sectional design. Assessment of hypoglycaemia relied mostly on retrospective self-report (*n*=19, 70%), with recall periods ranging from the past month (*n*=4) to the past three (*n*=5), six (*n*=5) or 12 months (*n*=7), to period since diagnosis (*n*=1). Hypoglycaemia was reported by the child or adolescent with diabetes (*n*=10, 34%), their parent(s) (*n*=7, 24%), or both (*n*=1, 4%); or based on a combination of self-report and glucose meter data (*n*=2, 8%). Six studies (22%) focused on hypoglycaemia that involved coma or seizures, assessed via medical records. Two studies (7%) did not specify how hypoglycaemia data were derived.

Twenty-one studies (78%) examined SH, defined as episodes: 1) where assistance of others was needed (*n*=4); 2) resulting in confusion or seizures/coma (*n*=7), or 3) characterized by a combination of these definitions (*n*=8). Four studies did not specify a definition of SH. Ten studies (37%) examined "moderate" hypoglycaemia, which will be referred to as "non-severe" hypoglycaemia (NSH) throughout this review. Although it is recognized that NSH is usually referred to as "self-treated" hypoglycaemia (51), that is not appropriate when describing hypoglycaemia in (younger) children, as their parents often need to help regardless of the severity of the episode. Twelve studies (44%) used a continuous measurement of hypoglycaemia (e.g., frequency of SH in the past 6 months), and fifteen (55%) reported on categorical measurement of hypoglycaemia (e.g., absence or presence of SH).

The studies included 19 instruments to assess QoL and related outcomes (Table 1). The most commonly used were the Hypoglycaemia Fear Survey Child Version (HFS-C) (*n*=6) and the Pediatric Quality of Life Inventory (PedsQL) Generic (*n*=4) and Diabetes (*n*=6) modules. An overview of all scales being used in the studies can be found in Table S1.

Risk of bias assessment

Of the 27 studies, 93% included participants with a medically-verified diagnosis of type 1 diabetes. Most provided adequate details of their inclusion and exclusion criteria (89%) and participants and settings (74%). In 52% of the studies, hypoglycaemia was defined in accordance with the current

International Society for Pediatric and Adolescent Diabetes (ISPAD) definition; namely, SH as an event with severe cognitive impairment (including coma and seizures) requiring assistance by others, and NSH as events with a blood glucose value ≤3.9 mmol/L (70 mg/dL) (52). Most studies (81%) used statistical analyses appropriate to their data and, while all studies identified confounding factors, 67% adjusted analyses accordingly. Most studies (70%) used psychosocial outcome measures that were psychometrically valid and reliable instruments for use with children and adolescents with type 1 diabetes. In 11% of the studies, both validated and non-validated measures (13, 28, 36) were used, while 19% included measures that were not validated in adolescents with type 1 diabetes (14, 34, 35, 43, 47). A full overview of the risk of bias assessment is presented in Table S2.

Narrative synthesis

Table 3 provides a summary of the main findings of each study.

Global QoL

Table 1 shows that both generic measures and diabetes-specific measures of global QoL were used. One study used a non-validated questionnaire (13). The age of the participants in these studies ranged from 11-21 years, and one study conducted analysis for children and adolescents separately (30).

Severe hypoglycaemia

Three studies examined the relationship between SH and generic QoL using the KINDL-R (13) or the PedsQL (30, 31). One study showed that those with SH (not further defined) in the past month reported significantly lower QoL than those without SH, but this was not observed for SH in the past year (13). Two studies found no significant differences in generic QoL between groups with and without SH (not further defined (30) or episodes requiring assistance from others (31)) in the past 6 (31) to 12 months (30).

Three studies explored the association between SH and diabetes-specific QoL using the DISABKIDS DCGM-12 (13, 28) or the DQOL-Y (33). In two studies, SH (not defined (13) or episodes requiring assistance (28)) in the past 12 months was not associated with diabetes-specific QoL after adjustment for covariates (e.g., age, gender, HbA_{1c}). However, one of these studies indicated that those who experienced SH (not further defined) in the past month reported significantly lower diabetes-specific QoL than those who had not (13). The third study found that SH with coma since diagnosis was significantly associated with lower diabetes-specific QoL (33).

Non-severe hypoglycaemia

One study found no significant differences diabetes-specific QoL scores on the DQOL-Y, between those who experienced NSH (glucose levels below 70 mg/dl) in the past three months and those who did not (32).

Two studies reported no significant association between frequency of NSH (glucose levels below 60 or 70 mg/dl) in the past month and generic QoL (PedsQL) after adjusting for covariates such as gender, hyperglycaemia and age of onset of diabetes (16, 29).

Broad and specific domains of QoL

Table 1 shows that studies examined three broad domains of QoL (psychological, physical, or social functioning), and/or the following specific domains of QoL: school, family, friends, self-esteem and sleep. Three studies used non-validated QoL questionnaires (13, 14, 34). The participants' age range was 8-21 years, one study only included adolescents aged 12-18 (35).

Severe hypoglycaemia

Four studies examined the relationship between SH (not further defined (13), or inability to self-treat due to neurological dysfunction (14, 34) or requiring assistance from others (31)) and broad domains (physical, psychological, social), or specific domains (self-esteem, family, friends or school) of QoL.

Three studies found no significant relationship between SH in the past 1-12 month(s) and physical functioning, (13, 14, 34). In contrast, one study indicated that those with two or more episodes of SH in the past six months reported significantly lower physical functioning than those without SH, but not for those who only had one SH (31).

Three studies found no significant relationship between SH in the past six (31) to 12 months and psychological functioning (13, 31, 34). However, one study examined various recall periods and found that SH in the past month was significantly associated with lower psychological functioning (13). The fourth study reported that those with SH in the past three months reported significantly lower psychological functioning than those without (14). Two studies examined the association between in the past 1-12 months and self-esteem and found no significant results (13, 34).

One study reported no significant associations between SH in the past six months and social functioning (31). Three studies reported no significant associations between SH in the past 1-12 months and relationships with family (13, 14, 34). None of the studies reported a significant association between SH in the past 3-12 months and school (13, 14, 31, 34), although one study indicated that SH in the past month was significantly associated with lower school functioning (13). Three studies examined the association between SH and quality of friendship (13, 14, 34). One found that SH in the past year was significantly associated with lower quality of friendship, but this was not observed for SH in the past month (13). Two studies found no significant association between SH and quality of friendship in the past 3-12 months (14, 34).

Non-severe hypoglycaemia

Two studies examined associations of NSH and domains of QoL using the PedsQL (16) or the ASWS (35). The first study found no significant associations between NSH (glucose levels below 70 mg/dl) in the past month and physical functioning or psychosocial functioning (16). The second study found no association between nocturnal hypoglycaemia (glucose levels below 70 mg/dl or symptomatic hypoglycaemia) in the past month and adolescents' sleep quality (35).

Related outcomes - hypoglycaemia-specific

Table 1 shows that although hypoglycaemia-specific QoL was not assessed, related outcomes were assessed, including fear of hypoglycaemia (FoH), and hypoglycaemia-specific post-traumatic stress symptoms. One study used a non-validated questionnaire (47). The participants' age range was 6-20 years. Three studies specifically focused on adolescents aged 12-18 (36, 38, 42) and one on children aged 6-12 (39).

Severe hypoglycaemia

Seven studies examined the association between SH and FoH measured with the HFS-C (15, 36, 38, 39, 41, 42) or the CHI-2 (44).

Four studies examined relationships between SH and worries about hypoglycaemia (36, 38, 41, 42) Three of these studies reported significant, small-to-medium, positive correlations between frequency of SH (not further defined (41) or inability to self-treat due to mental disorientation or seizures (38, 42)) in the past 12 months and greater worries about hypoglycaemia. However, in one study, this only remained statistically significant for female adolescents after controlling for gender (38). The fourth study found no significant difference in worries about hypoglycaemia between adolescents who never lost consciousness and those who ever lost consciousness due to SH, after controlling for covariates such as age gender and other types of hypoglycaemia (36).

Three of the studies also explored associations between SH and FoH related behaviours (36, 38, 41). One study reported no significant association between frequencies of SH episodes (inability to self-treat due to mental disorientation or seizures) and FoH related behaviours (38). The second study indicated that those who had passed out due to hypoglycaemia significantly reported more hypoglycaemia related avoidance behaviours compared to those who had never passed out (36). In contrast, the third study reported that those who needed medical attention due to SH reported significantly less hypoglycaemia related avoidance behaviours than those who did not (41).

Three of the eight studies examined associations between SH (inability to treat due to mental confusion or unconsciousness in the past three months (39) or SH resulting in seizures or coma (15, 44)) and overall FoH, but found no significant associations (15, 39, 44).

An additional study found that frequency of SH (loss of consciousness or requirement of glucagon) in the past month was a significant predictor of self-reported post-traumatic stress (PTSD) assessed with the CPTS-RI after adjustment for age and family history of diabetes (47).

Non-severe hypoglycaemia

Four studies explored the relationship between NSH and HFS-C subscale scores (36, 38, 41, 42). Three of these studies reported no significant associations between frequency of NSH (glucose values below 70 mg/dl (41) or interfering with ability to function (38, 42)) and FoH. The fourth study found that frequency of NSH and 'hypoglycaemia while at school', 'awake' or 'asleep' were significantly associated with at least one of the HFS-C scales, after adjustment for clinical factors and other types of hypoglycaemia (e.g., passing out because of hypoglycaemia). This was not observed for 'hypoglycaemia in front of friends' (36).

Related outcomes - diabetes-specific

Table 1 shows that studies assessed the relationship between hypoglycaemia worries attributed to diabetes, diabetes-related disordered eating, and diabetes distress. One study used a non-validated questionnaire (34). The participants' age range was 5-21 years. Two studies focused on adolescents aged 12-18 (30, 42) and one study conducted analysis for children and adolescents separately (28).

Severe hypoglycaemia

Eight studies investigated the association between SH and diabetes distress (13, 15, 28, 30, 34, 37, 42, 45). Four of these studies used the PedsQL DM (15, 30, 42, 45). One of these reported that SH (not further specified) in the past 12 months was significantly associated with higher diabetes distress, compared to those without SH, with a small effect size (30). This was confirmed for those who experienced two or more SH episodes (requiring assistance from others) in the past six months, but not for only one SH (45). In contrast the other two studies reported no significant association between SH (inability to self-treat due to mental confusion) in the past 12 months) (42) or SH (resulting in seizure or coma) since diagnosis (15) and diabetes distress.

Two of the studies using the DISABKIDS Diabetes Module found a significant association between SH (not further defined (13) or requiring assistance from others (28)) and greater diabetes distress if hypoglycaemia was experienced in the past month (13) but not in the past year (13, 28). One study reported no significant association between SH (inability to self-treat due to neurological dysfunction) and illness-related distress using the KINDL-R (34).

An additional study (using the DQOL-Y) reported that those who had SH involving seizures or coma in the past three months reported significantly more worries about diabetes than those without (37).

In addition, in one study frequency of SH (requiring assistance from others) in the past 6 months did not significantly differ between those with and without disordered eating measured with the DEPS-R (50).

Non-severe hypoglycaemia

Four studies examined the association between NSH (glucose concentrations below 60 or 70 mg/dl (29, 32, 46) or interfering with ability to function (42)) in the past 1-6 months and diabetes distress using the PedsQL DM (29, 42, 46) or the DQOL-Y (32). None of these studies reported a significant association between NSH and diabetes distress.

Related outcomes - generic

Table 1 shows that generic outcomes including anxiety or depression symptoms, or diagnosis were examined in the studies. Some of the studies used measures that are not validated in young people with diabetes (36, 38, 43, 44). The participants' age range was 0-25 years.

Severe hypoglycaemia

Three studies reported no significant association between SH and depressive symptoms; the first explored the association between SH in the past 6 months (not further defined) and CDI-S scores (48) and the other two explored the association between SH resulting in coma or seizure and CES-D scores (43, 44). In contrast, another study reported a significant positive relationship between SH (requiring assistance from others and unconsciousness or application of glucagon) in the past year and a DSM-IV depression diagnosis (49).

Two studies investigated the associations between SH and anxiety symptoms assessed by the SCARED (36) or an ICD-10 anxiety disorder diagnosis (40). The first study reported that a history of passing out due to SH was significantly associated with greater symptoms of separation anxiety and school avoidance, but not with panic disorder, generalized anxiety or social anxiety (36). The second study reported no significant associations between SH (loss of consciousness) and diagnosis of anxiety disorders (40).

Non-severe hypoglycaemia

Two studies examining associations between hypoglycaemia in different situations and various anxiety types (using the SCARED (36) or STAIC (38)) found that having 'hypoglycaemia while at school', 'in front of strangers', 'while awake' or 'asleep' (36) was significantly associated with greater symptoms anxiety, for example social anxiety or separation anxiety (36) and that hypoglycaemia in social situations was significantly associated with higher trait anxiety, with a moderate effect size (38).

Discussion

To our knowledge, this is the first systematic review that critically examines evidence on the relationship between hypoglycaemia and QoL and related outcomes among children and adolescents with type 1 diabetes. 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 hypoglycaemia-specific QoL measures to explore the association between hypoglycaemia and QoL. In addition, there was some evidence suggesting an association between SH in the past 12 months and greater worries about hypoglycaemia, and no association between NSH and diabetes distress. There was insufficient evidence to draw conclusions regarding the relationship between hypoglycaemia and diabetes distress (for SH), FoH worries (for NSH), FoH-related behaviors and total FoH, anxiety, depression, disordered eating and PTSD.

A possible explanation for inconsistent findings is the heterogeneity in definitions of and recall periods for hypoglycaemia and measures used to assess QoL across studies. This variation limits the ability to compare studies and draw conclusions. 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 hypoglycaemia, and the self-report of hypoglycaemia over several months or even back to diagnosis, which might have led to recall bias. The key recommendation for future studies is to use a definition of hypoglycaemia 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 hypoglycaemia that does not rely on recall of episodes, to determine the direct, day-to-day impact of hypoglycaemia on various domains of QoL in children and adolescents with type 1 diabetes.

Although the current evidence suggests no clear association between hypoglycaemia and some outcomes, it is important to note that studies were more likely to show statistically significant associations between hypoglycaemia and outcomes when SH was experienced recently (in the past 1-3 months), more frequently, or when it involved convulsions, unconsciousness, or coma. In addition, some studies suggested that the context in which hypoglycaemia takes places (e.g., in social situations) might have implications for its impact. However, this was only based on a few studies, some of which have methodological limitations. Thus, more evidence is needed to confirm these associations.

Although emerging evidence shows the importance of self-treated hypoglycaemia in relation to QoL and related outcomes in adults with diabetes (50, 51), current evidence on this relationship in youth with type 1 diabetes suggested no association between NSH and QoL. However, this should be interpreted with caution, as these studies are limited by the use of generic and diabetes-specific QoL questionnaires, while hypoglycaemia-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 hypoglycaemia while asleep and sleep quality (28). This highlights the need for more studies that investigate such relationships.

Although QoL has been considered as a key outcome in paediatric diabetes care (12), only two studies had a primary aim to examine the impact of hypoglycaemia on QoL (15, 42). Fifteen of the 27 studies aimed to explore QoL, however, only seven of these studies included measures that actually assess QoL, whereas the others focused on particular domains of QoL or measured related outcomes such as diabetes distress (13, 15, 28, 30, 34, 37, 42, 45) or health status (14), rather than QoL. Even though other studies included in this review have focused on identifying sociodemographic and clinical factors that are associated with QoL, it is difficult to identify the impact of hypoglycaemia specifically in these studies (13, 14, 16, 28, 30-34, 37, 45, 46). Importantly, some of the studies that explored the impact of hypoglycaemia on QoL as a secondary aim had very low rates of hypoglycaemia in their samples. To truly understand the impact of hypoglycaemia on QoL, a questionnaire that assesses how hypoglycaemia affects domains of life that are important to the individual should be used (18). Given that there are currently no hypoglycaemia-specific QoL measures that are designed to assess the impact of hypoglycaemia on QoL in children and adolescents with type 1 diabetes, these need to be developed and would need to be age appropriate and to incorporate specific domains that are important to young people with diabetes. There might be other domains of importance to young people's QoL, such as leisure activities, that were not included in questionnaires used in current studies.

Finally, the majority of studies included in this review pooled children and adolescents together when examining the link between hypoglycaemia and QoL or related outcomes. Although these studies usually included age-appropriate assessments of outcomes, the impact of hypoglycaemia 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 (53, 54). During this challenging process of transferring responsibilities, the burden of self-management for the adolescents increases and can lead to increased hypoglycaemia, which can interfere with other demands and lead to family conflicts, reduced self-efficacy and increased FoH, all aspects that can compromise QoL in adolescents with diabetes (42, 55). Future studies should thus explore if the relationship between hypoglycaemia and QoL is different in different age groups. Additionally, adolescence is characterized by a strong desire to be accepted by peers (54). Episodes of hypoglycaemia in this age group could be experienced as embarrassing and mark out adolescents with diabetes as different. Hypoglycaemia has indeed previously been associated with higher stigma in young people with diabetes (56), which can lead to poorer psychosocial and medical outcomes (57). Future studies need to explore the role of stigma as a possible mechanism by which hypoglycaemia impacts on QoL.

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 hypoglycaemia 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 hypoglycaemia 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.

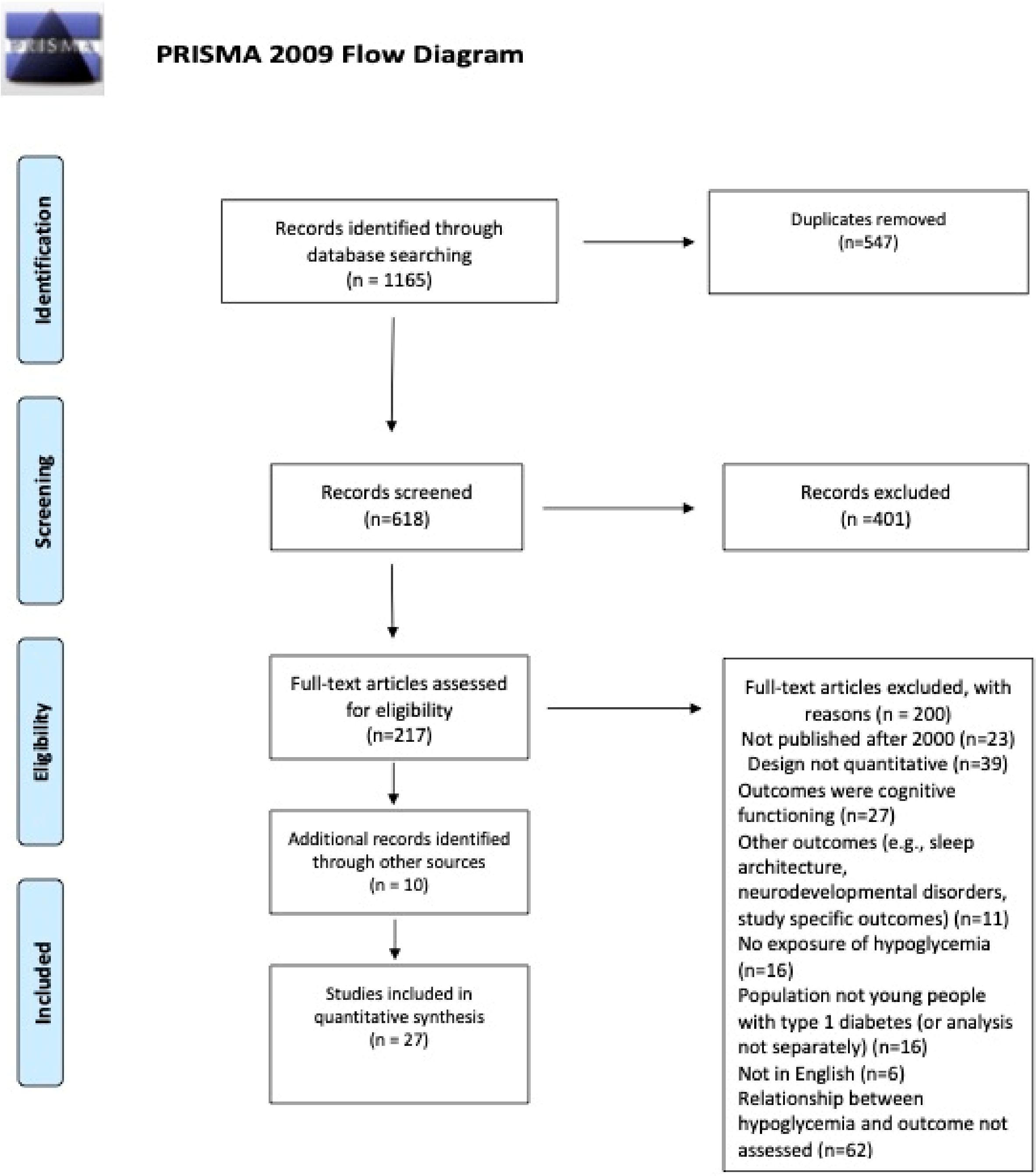
Implications for clinical practice

The implications for clinical practice that can be drawn from this review are limited due to the inconclusive and relatively small evidence-base. However, some evidence suggests that more recent episodes of hypoglycaemia might have an impact on various outcomes. This may be useful for clinicians, as they could ask specifically about hypoglycaemia and its impact in the weeks/months following episodes of SH.

Conclusion

This systematic review shows that there is insufficient evidence on the relationship between hypoglycaemia 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 hypoglycaemia on QoL. Additionally, there seems to be an association between SH and greater worry about hypoglycaemia, while the evidence is too limited for other related outcomes. Although limited, some evidence suggests that issues such as timing and context of hypoglycaemia might influence its impact. Future research should focus on the development of measures that can assess the impact of hypoglycaemia in children and adolescents with type 1 diabetes and use agreed definitions of hypoglycaemia that increase comparability between studies.

Figure 1. PRISMA Flowchart of the systematic search and screening, reasons for exclusions, and final number of included studies.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Table 1. Overview of quality of life and related outcome measures in the included studies, by breadth and attribution

Quality of Life (QoL) and related outcomes		**Generic**	**Diabetes-specific**	**Hypoglycaemia-specific**
		(no attribution)	**(attribution to diabetes)**	**(attribution to hypoglycaemia)**
Global QoL		• KINDL-R Total score (13) • PedsQL total score (16, 29-31)	• DISABKIDS DCGM-12 (13, 28) • DQOLY total score (32) • DQOLY impact scale (32) • DQOLY Diabetes life satisfaction scale (32) • DQOLY Short Form total score (33)	None
Broad domains of QOL	*Physical functioning*	• KIDSCREEN 27: physical wellbeing (14) • KINDL R: physical (13, 34) • PedsQL: physical functioning (16, 31) • EQ5D VAS scale (14)	None	None
	Social functioning	• PedsQL: social functioning (31) • PedsQL: psychosocial functioning (16, 31)	None	None
	Psychological functioning	• KIDSCREEN 27: psychological well-being (14) • KINDL R: emotional wellbeing (13, 34) • PedsQL: emotional functioning (31) • KIDSCREEN-10 index (14)	None	None
Specific domains of QoL	*Family*	• KINDL R: family (13, 34) • KIDSCREEN 27: Autonomy and relationships with parents (14)	None	None
	Friends	• KINDL R: friends (13, 34) • KIDSCREEN 27: Relationships with friends or peers (14)	None	None
	School / Studies	• PedsQL: school functioning (31) • KINDL R: school (13, 34) • KIDSCREEN 27: school (14)	None	None
	Self-esteem	• KINDL R: self-esteem (13, 34)	None	None
	Sleep	• Adolescent Sleep/Wake scale (35)	None	None

Quality of Life (QoL) and related outcomes	**Generic**	**Diabetes-specific**	**Hypoglycaemia-specific**
	(no attribution)	**(attribution to diabetes)**	**(attribution to hypoglycaemia)**
Related psychological outcomes	• Screen for Child Anxiety-Related Disorders (36) • ICD-10 anxiety disorder diagnosis (40) • State-Trait Anxiety Inventory for Children, Trait Subscale (38) • Center for Epidemiological Studies-Depression Scale (43, 44) • Children's Depression Inventory, Short version (48) • Adolescents – IV (DSM IV depression diagnosis) (49)	• DQOLY: Worries about diabetes (32, 37) • KINDL-R chronic illness scale (34) • PedsQL DM: diabetes distress (15, 29, 30, 42, 45, 46) • PedsQL DM: 'diabetes symptoms' (42) • PedsQL DM: 'diabetes management' (42) • DISABKIDS impact scale (13, 28) • Diabetes Eating Problem Survey-Revised (50)	• Hypoglycaemia Fear Survey – child version (HFS-C) total scale (15, 38, 39) • HFS-C 'worries about hypoglycaemia' subscale (36, 38, 41, 42) • HFS-C 'fear of hypoglycaemia related behaviors'(36, 38, 41) • Child Posttraumatic Stress • Reaction Index (hypoglycaemia is referred to as the traumatic event) (47) • Child Hypoglycaemia Index-2 (44)

DQOLY, Diabetes Quality of Life-Youth; EQ5D-VAS, EuroQoL 5 Dimensions Visual Analog Scale; HFS-C, Hypoglycaemia Fear Survey-Child version; ICD, International Classification of Diseases; PedsQL, Pediatric Quality of life Inventory; PedsQL-DM, Pediatric Quality of Life inventory Diabetes Module; QoL Quality of Life

Table 2 Sociodemographic and clinical information and inclusion and exclusion criteria of the included studies

Author, year. Country	**Study design; Sample size**	**Age in years Mean (SD), Range**	**Diabetes duration in years Mean (SD)**	**Diabetes management**	**Inclusion/Exclusion criteria**	**HbA_{1c} (DCCT unit) Mean (SD)**	**Hypoglycaemia assessments**
Adler et al. (2017) (35) Israel	Cross-sectional *N*=45	14.9 (1.7) R (12.2–17.9)	5.9 (3.6)	MDI: 28.9% CSII: 71.1% CGM 35.6%	Included: age 6-30 years, diabetes duration: ≥1 year Excluded: psychiatric / neurological comorbidities, psychotropic medication, night shifts in the last 3 months, language difficulties	7.96 (1.47)	No. of nocturnal H episodes last month: Less than once/week 48.9% 1-2 times/week 17.8% ≥3 times/week 6.7%
Al Hayek et al. (2014) (36) Saudi Arabia	Cross-sectional *N*=187	15.3 (1.6)	7.1 (5.2)	CSII 19.3% MDI 80.7%	Included: age 13-18 years, follow up for ≥12 months Excluded: psychopathological and medical instability, visual, hearing, or cognitive impairment	HbA_{1c} >7 81.8% HbA_{1c} ≤7 18.2%	Trouble with H past 12 months: 1-2 times: 7.5% 3-6 times: 34.9% 7-11 times: 16.6% ≥12 times: 41.8% Passed out due to H: 33.2% H episode while asleep: 82.9% H while awake but by themselves: 67.9% H in front of friends of strangers: 84% H when at school: 80.7%
Amiri et al. (2014) (39) Iran	Cross-sectional *N*=61	9.2 (2.0) R (6.0-12.7)	3.2 (2.0) R (0.5-10.5)	NR	Included: age 6-12 years, diabetes duration≥6 months Excluded: other diseases (e.g., thyroid, celiac)	NR	Mean number of SH (past 3 months): 1.4 SD 5.4, range 0-36

Table 2 Sociodemographic and clinical information and inclusion and exclusion criteria of the included studies

Author, year. Country	**Study design; Sample size**	**Age in years Mean (SD), Range**	**Diabetes duration in years Mean (SD)**	**Diabetes management**	**Inclusion/Exclusion criteria**	HbA$_{1c}$ **(DCCT unit) Mean (SD)**	**Hypoglycaemia assessments**
Caferoglu et al. (2016) (16) Turkey	Cross-sectional *N*=70	Median 13.0 R (11.00-15.00)	Median 3.5 R (2.0-6.0)	MDI 100%	Included: aged 8-18 years, diabetes duration ≥1 year, using MDI Excluded: mental retardation and/or other chronic diseases (coeliac disease, hypothyroidism etc.)	Median 7.80, R (7.10-9.03)	Median and (Q1-Q3) number of NSH episodes 2.50 (0.00-5.25)
Coolen et al. (2021)(42) The Netherlands	Cross-sectional *N=96*	15.2 (1.6) R 12–18	7.0 (4.3)	MDI:19% CSII: 81% CGM: 33%	Included: diabetes duration ≥ 6 months, no intellectual disabilities	7.5 (.9) R 5.3–10.4	No SH past 12 months: 80% SH past 12 months: 20% Mean number SH past 12 months: 0.7(2.4). Mean number of NSH past 6 months: 17.4 (29.9)
Dłużniak-Gołaska et al. (2019) (46) Poland	Cross-sectional *N*=197	13.9 (2.3) R (8-18)	<5 years: 45.7% ≥5 years: 54.3%	CSII 100% CGM 31%	Included: diabetes duration ≥1 year, CSII treatment Excluded: other chronic diseases (e.g., coeliac disease)	NR	No/several times a month: 131 Several times a week/every day: 66
Galler et al. (2021) (40) Germany, Austria, Switzerland, and Luxembourg	Observational *N= 75,258*	16.4 R 13.1-17.7	6.0 R 3.3-9.4	CSII: 41%	Included: diabetes duration ≥1 year from 431 participating centers between 1995 until June 2019	7.9 R 7.1-9.0	Rate of SH/patient year (95% CI): 12.8 (12.4; 13.3)
Gonder-Frederick et al. (2006) (38)	Cross-sectional *N*=39	15.4 (1.5)	7.0 (4.0)	CSII 36%	Included: age 12-17 years, diabetes duration ≥1 year	NR	Mean number NSH in past 12 months: 6.74, SD 5.03 Mean number SH past 12 months; 0.46, SD 2.11

Table 2 Sociodemographic and clinical information and inclusion and exclusion criteria of the included studies

Author, year. Country	**Study design; Sample size**	**Age in years Mean (SD), Range**	**Diabetes duration in years Mean (SD)**	**Diabetes management**	**Inclusion/Exclusion criteria**	HbA$_{1c}$ **(DCCT unit) Mean (SD)**	**Hypoglycaemia assessments**
USA					Excluded: significant comorbidity (e.g., cystic fibrosis) and cognitive or learning disabilities		
Hanberger et al. (2009) (28) Sweden	Cross-sectional *N*=93 children *N*=145 adolescents	13.2 (3.9) R (8–19.6)	5.1 (3.8) R (0.3–17.6)	CSII 17%	NR	7.1(1.2) R (4.0–10.7)	NR
Hassan et al. (2017) (33) Egypt	Cross-sectional *N*=150	12.3 (1.8) R (10-18)	<3 years: 46.7% 3–5 years: 34.7% >5 years: 18.6%	NR	Included: age 10-18 years, diabetes duration ≥1 year, completed diabetes education program	<7.5, 42.7% 7.5–9.0, 32% >9.0, 25.3%	SH with coma: 7% SH without coma: 93%
Hoey et al. (2001) (37) Multi country (17 countries in Europe, Japan and North America)	Cross-sectional *N*=2101	13.8 R (10-18)	5.2	NR	Included: age 10-18 years, born between 1980-1987	8.7 (1.7) R (4.8-17.4)	Incidence of SH =15.6 /100 patient years
Johnson et al. (2013) (15)	Cross-sectional	11.8 (3.7)	4.8 (3.5)	CSII 34.8%	Included: age 8-18 years old, diabetes duration ≥6 months, recent clinic attendance	8.0 (0.9)	SH: 18.8%

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Author, year. Country	**Study design; Sample size**	**Age in years Mean (SD), Range**	**Diabetes duration in years Mean (SD)**	**Diabetes management**	**Inclusion/Exclusion criteria**	HbA$_{1c}$ **(DCCT unit) Mean (SD)**	**Hypoglycaemia assessments**
Australia	*N*=196				Excluded: significant comorbid condition, parent unable to answer the questionnaire		
Jurgen et al. (2020) (44) USA	Cross-sectional *N=83*	13.87 (3.21)	NR	CSII: 45% MDI: 24% 2 daily injections: 31%	Included: age 8-20 years, diabetes duration ≥1 year Excluded: type 2 diabetes, under 18 without parent, no HbA$_{1c}$ measurement, no blood glucose meter	9.5 (1.8)	SH: 12.8%
Kalyva et al. (2011) (29) Greece	Cross-sectional *N*=117	10.9 (4.0) R (5-18)	NR	MDI 99% CSII 1%	Included: age 5-18 years, diabetes duration ≥1 year	8.05 (1.39) R (5.5–11.9)	Mean number of NSH episodes 5.82 SD 1.08, R 0–7
Lawrence et al. (2012) (45) USA	Cross-sectional *N*=2,602	13.6 (4.1)	5.2 (3.9)	MDI 50% CSII 22%	Included: age >5 years, diabetes duration ≥1 year Excluded: not taking insulin, no HbA$_{1c}$ measurements	Good glycemic control, n= 32.3% Intermediate glycemic control, 47.6 % Poor glycemic control = 20.1%	0 SH = 88.1% 1 SH = 6.6% ≥ 2 SH = 5.3%
Matziou et al. (2010) (32)	Cross-sectional	14.9 (2.4)	7.3 (4.0)	CSII 32.7%	Included: age 11–18 years diabetes duration ≥6 months	NR	NSH in past 3 months: 23.5%

Table 2 Sociodemographic and clinical information and inclusion and exclusion criteria of the included studies

Author, year. Country	Study design; Sample size	Age in years Mean (SD), Range	Diabetes duration in years Mean (SD)	Diabetes management	Inclusion/Exclusion criteria	HbA_{1c} (DCCT unit) Mean (SD)	Hypoglycaemia assessments
Greece	*N*=98				Excluded: psychiatric disorders		No NSH in past 3 months: 76.5%
Murillo et al. (2017) (14) Spain	Cross-sectional *N*=136	13.5 (2.9)	5.0 (3.7)	MDI 98.5% CSII 1.5%	Included: age 8-19 years, diabetes duration ≥6 months Excluded: cognitive problems	NR	SH in past 3 months: 2.2% No SH in past 3 months: 97.8%
Naughton et al. (2008) (31) USA	Cross-sectional *N*=2,188	14.6 (3.6)	6.2 (3.9)	Oral /no diabetes medications 0.6% MDI 76.9% CSII 22.5%	Included age≤20 years, resident in geographical center population, member of the participating health plan Excluded: diabetes as secondary to another condition	NR	0 SH in past 6 months: 88.1% 1 SH in past 6 months: 6.4% ≥2 SH in past 6 months: 5.5%
Nip et al. (2019) (50) USA	Cross-sectional *N*=2,156	17.7 (4.3) R (10-25)	NR	CSII 55% CGM 18.5%	Included: diabetes duration ≥5 years, diagnosed between 2002-2008 Excluded: type 2 diabetes not on insulin.	NR	NR
Plener et al. (2015) (49) Germany/Austria	Observational *N*=53,986	NR	5.77	NR	Included: Age <25 years	NR	Rate of SH/patient year (95% CI) - Depression: 0.56 (0.52-0.58), No depression: 0.20 (0.19-0.20) Rate of SH coma/patient year (95% CI) - Depression: 0.04 (0.03-0.05), No depression: 0.03 (0.03-0.03)

Table 2 Sociodemographic and clinical information and inclusion and exclusion criteria of the included studies

Author, year. Country	**Study design; Sample size**	**Age in years Mean (SD), Range**	**Diabetes duration in years Mean (SD)**	**Diabetes management**	**Inclusion/Exclusion criteria**	HbA$_{1c}$ **(DCCT unit) Mean (SD)**	**Hypoglycaemia assessments**
Riaz et al. (2017) (43) Pakistan	Cross-sectional *N*=104	15.8 (3.1)	5.1 (4.0)	NR	Included: age 12-20 years, diabetes duration ≥1-year, recent clinic attendance Excluded: comorbid mental disorders or receiving psychotherapy	10.3 (3.5)	SH in past six months = 20.2%
Serkel-Schrama et al. (2016) (30) The Netherlands	Cross-sectional online survey *N*=129	14.0(2.0) R (12-18)	6.0 (4.0) R (0–18)	CSII 71%	Included: age 12-18 years, self-reported type 1 diabetes, sufficient language skills	NR	No SH in last 12 months: 78% ≥1 SH last in 12 months: 12%
Shepard et al. (2014) (41) USA	Observational (validation study) *N*=259[1]	10.6 (3.3) R (6-18)	5.2 (3.3)	MDI 60% CSII 40%	Included: diabetes duration ≥1 year, 4 BG readings/day for 4 weeks Excluded: medical comorbidities (e.g., asthma, cystic fibrosis), cognitive or learning disabilities	8.01 (0.97)	NR
Sismanlar et al. (2012) (47) Italy	Cross-sectional *N*=42	M 13.67, SD 2.39	3.8 R (1-12)	NR	Included: age 8-18 years	7.9	SH: 28.6% H attacks in last month CTPS-RI<40: 7.11 (6.89), CPTS-RI ≥40: 13.57 (15.34)
Stahl-Pehe et al. (2013) (13) Germany	Cross-sectional *N*=840	M 16.3, SD 2.3 R (11.3–21.9)	M 13.3, SD 2.0, R (10.0–17.7)	CSII: 46.9 % MDI 53.1%	Included: age 11-21 years, age of onset <5 years, diagnosed between 1993-1999, diabetes duration ≥10 years	8.3 (1.4) R (5.6–15.4)	No SH in the last year: 41.7% SH in the last year (incl. last six months): 34.1% SH in last month (incl. last week): 24.3%

Table 2 Sociodemographic and clinical information and inclusion and exclusion criteria of the included studies

Author, year. Country	**Study design; Sample size**	**Age in years Mean (SD), Range**	**Diabetes duration in years Mean (SD)**	**Diabetes management**	**Inclusion/Exclusion criteria**	**HbA_{1c} (DCCT unit) Mean (SD)**	**Hypoglycaemia assessments**
Strudwick et al. (2005) (48) Australia	Cross-sectional *N*=84	10.1 R (6-15)	6.9	NR	Included: age of onset <6 years, treatment at the center Excluded: neurologic or significant health problems unrelated to diabetes, psychiatric condition, developmental delay	NR	SH with seizures: 48.8% Number of SH: M; 2.5, SD; 2.2
Wagner et al. (2005) (34) Germany	Cross-sectional *N*=68	8–12 years: 72% 13–16 years 28%	M 4.2, SD 2.8, R (0.42–11.33)	MDI 100%	Included: age 8-16 years, diabetes duration ≥5 months	NR	SH: 19.6/100 patient years

CGM, Continuous Glucose Monitoring; CSII, Continuous Subcutaneous Insulin Infusion; H, hypoglycaemia; MDI, Multiple Daily Injections; NR, not reported; SD, standard deviation; SH, severe hypoglycaemia

[1] Aggregation of five studies

Table 3 Hypoglycaemia definition, measurement and relationship with quality of life and related outcomes

Author, year (ref)	Hypoglycaemia definition	Hypoglycaemia measurement	Recall period (months)	QoL domain or related outcome	Instrument	Findings: Association between hypoglycaemia and QoL / related outcome
Adler et al. (2017) (35)	Nocturnal H: BG levels <70 mg/dL or symptomatic H	No. nocturnal H episodes; self or parent reported	1	Sleep quality	ASWS	N.S. for sleep quality (data NR)
Al Hayek et al. (2014) (36)	Frequency of trouble with H episodes Passed out due to H H episode while asleep H episode while you were awake but by yourself H in front of friends or strangers? H when you were at school?	Categorical (1-2, 3-6, 7-11, >11) and yes vs. no; self-reported	12 Ever	Worries about H; H related behavior; panic disorder; generalized anxiety disorder; separation anxiety disorder; social anxiety disorder; significant school avoidance	HFS -C SCARED	[1]Pass out due to H associated with H related behaviors (β=0.502***), separation (β= 0.189**) and school anxiety (β=-0.271***) H while asleep associated with worries about H (β=-0,508**) GAD (β=-0.253, p**) and separation anxiety (β=-0.274**) H while awake associated with H related behaviors (β=-0.300*), worries about H (β= -0.508**), panic disorder (β=-0.318***), GAD (β=-0.206**) and social anxiety (β=-0.388***) H in front of friends associated with panic disorder (β=0.595***), GAD (β=0.537***), separation anxiety (β=0.321**), social anxiety (β=0.362**) and school anxiety (β=0.303***). H at school associated with H related behaviors (β=-0.312*), panic disorder (β=-0.284***), GAD (β=-0.177*), separation anxiety (β=-0.232**) and social anxiety (β=-0.367***)

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Author, year (ref)	Hypoglycaemia definition	Hypoglycaemia measurement	Recall period (months)	QoL domain or related outcome	Instrument	Findings: Association between hypoglycaemia and QoL / related outcome
						All other associations are N.S. Covariates: age, gender, education, exercise, treatment type, duration of T1D, HbA_{1c}, passing out due to H, H as a big problem, H in front of friends and strangers and H at school
Amiri et al. (2014) (39)	SH: H with unconsciousness or consciousness but needing parent's help for treatment due to mental confusion and disorientation	No. of SH episodes; parent-reported	3	FoH Worries about H H related behaviors	HFS-C	N.S. for FoH (data NR)
Caferoglu et al. (2016) (16)	NSH: BG levels < 70 mg/dL, without seizures or coma	No. of NSH episodes; collected in interviews and checked with records from glucometers	1	Physical functioning; psychosocial functioning; general QoL	PedsQL	N.S. for psychosocial functioning, physical functioning and general QoL ($p>0.05$)
Coolen et al. (2021) (42)	SH: H when your blood glucose was so low that you were unable to recognize symptoms, ask for help, or treat yourself due to mental confusion or unconsciousness NSH: H when your blood glucose was so low that it interfered with what you were doing, and you had to wait a while to recover	No. of SH and NSH episodes; Self-reported	SH: 12 NSH: 6	Worries about H DD Diabetes symptoms Diabetes management	HFS-C PedsQL DM	↑ SH associated with ↑ worries about H** ($r=0.32$) N.S. for NSH and worries about H ($r=0.17$, $p>0.05$) N.S. for SH and NSH and diabetes distress, diabetes symptoms, or diabetes management ($p>.05$). Covariates include age, gender, HbA_{1c}, frequencies of H, perceived severity of H, fear of hypoglycaemia

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Author, year (ref)	Hypoglycaemia definition	Hypoglycaemia measurement	Recall period (months)	QoL domain or related outcome	Instrument	Findings: Association between hypoglycaemia and QoL / related outcome
Dłużniak-Gołaska et al. (2019) (46)	NSH: BG levels < 70 mg/dL	No/several times a month vs. Several times a week/every day; self-reported	NR	DD	PedsQL- DM	N.S. for DD (p>0.05) Covariates: method of controlling glycemia, daily insulin dose, hyperglycemia, carbohydrate exchanges (CE) calculation and infections
Galler et al. (2021) (40)	SH: loss of consciousness or seizure or requiring assistance from another person to actively administer carbohydrates, glucagon, or intravenous glucose)	No. of SH episodes	NR	Anxiety disorders	ICD-10 German Modification	N.S. for rates of hypoglycaemia per 100 patient years between those with and without anxiety disorders (p>0.05) Covariates: age, sex, diabetes duration, migratory background, type of insulin therapy, and treatment year and depression
Gonder-Frederick et al. (2006) (38)	NSH: BG so low that it interfered with the adolescent's ability to function, but 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 H in situations where the parent was not present (e.g.,	No. of H episodes (severe and moderate); parent-reported	12	FoH Worries about H H related behaviors Trait Anxiety	HFS C STAIC	SH with unconsciousness ↑ FoH vs. no SH with unconsciousness* ↑ SH associated with ↑ worries about H** and FoH** Only for girls after adjustment for gender (Total: r=.59*; Worries: r=.55*) ↑ H episodes in social situations associated with ↑ trait anxiety (r=0.37*) ↑ SH associated with ↑ FoH and ↑ worries about H** N.S. for SH and H related behaviors or trait anxiety (data NR) N.S. for H and FoH, worries about H, H

Table 3 Hypoglycaemia definition, measurement and relationship with quality of life and related outcomes

Author, year (ref)	**Hypoglycaemia definition**	**Hypoglycaemia measurement**	**Recall period (months)**	**QoL domain or related outcome**	**Instrument**	**Findings: Association between hypoglycaemia and QoL / related outcome**
	while sleeping, alone, at school, and in social situations)					related behaviors and trait anxiety (data NR) Covariates: trait anxiety scores frequency of H over the past year frequency of H, SH, episodes in situations where the child was likely alone) and gender
Hanberger et al. (2009) (28)	SH: needing assistance from another person	No SH vs. SH; self-reported	12	Diabetes-specific QoL and DD	DISABKIDS - DCGM-12 DISABKIDS Diabetes Module	N.S. differences for diabetes-specific QoL and DD (data NR) Covariates: gender, age, duration, HbA_{1c}, frequency of BG tests, parents living together or not, mother's educational level, use of insulin pump and center SH only associated with ↓ diabetes-specific QoL in single parent families, for adolescents (B=-1.22*) and children (B=-0.92*)
Hassan et al. (2017) (33)	SH with or without coma	SH with coma vs. SH without coma); taken from the medical record	NR	Diabetes-specific QoL	DQOL-Y	SH with coma vs. without coma associated with ↓ diabetes-specific QoL*
Hoey et al. 2001(37)	SH: seizures or unconsciousness	No SH vs. ≥1 SH; self-reported	3	Worries about diabetes	DQOL-Y	≥1SH associated with ↑ worries about diabetes than no SH (B=4.2*)
Johnson et al.	SH: event resulting in a seizure or coma	No SH vs. ≥1 SH; taken from	NR	DD FoH	PedsQL-DM HFS-C	N.S. for DD or FoH (p>0.05)

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Author, year (ref)	Hypoglycaemia definition	Hypoglycaemia measurement	Recall period (months)	QoL domain or related outcome	Instrument	Findings: Association between hypoglycaemia and QoL / related outcome
(2013) (15)		Western Australia Childhood Diabetes Database				Covariates: age and diabetes duration
Jurgen et al. (2020) (44)	SH: seizure or loss of consciousness	Parent reported	NR	FoH Depression	CHI-2 CES-DC	N.S. for FoH and depressive symptoms (r <.15, p>.05)
Kalyva et al. (2011) (29)	NSH: BG levels < 60 mg/dL without seizures or coma	No. of NSH episodes; parent-reported	1	General QoL DD	PedsQL PedsQL-DM	N.S. for general QoL or DD (p>0.05) Covariates: gender, age of onset episodes, number of hyperglycemic episodes, and HbA_{1c}
Lawrence et al. (2012) (45)	SH: event requiring assistance of another person	No SH vs. 1 SH No SH vs. ≥ 2 SH; parent-reported	6	DD	PedsQL-DM	≥ 2SH vs. no SH associated with ↑ DD** N.S. difference in no SH vs. 1 SH and DD (p>0.05)
Matziou et al. (2010) (32)	NSH: BG values <3.9 mmol⁄L (70 mg⁄ dL)	No NSH vs. ≥1 H; self-reported	3	Life satisfaction; disease impact; disease related worries; diabetes-specific QoL	DQOLY	N.S. for diabetes life satisfaction, disease impact, disease related worries and diabetes-specific-QoL (p>0.05)
Murillo et al. (2017) (14)	SH: BG levels <60 mg/dl with decreased level of consciousness requiring glucagon or the help of others	No SH vs. SH; taken from medical record	3	General QoL, health status, physical wellbeing; psychological wellbeing; parents/autonomy peers; school	EQ5D VAS KIDSCREEN-10 index KIDSCREEN 27	SH vs. no SH associated with ↓ general QoL (ES 1.28*) N.S. for health status, physical wellbeing, psychological wellbeing, parents/autonomy, peers and school (p>0.05)

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Author, year (ref)	Hypoglycaemia definition	Hypoglycaemia measurement	Recall period (months)	QoL domain or related outcome	Instrument	Findings: Association between hypoglycaemia and QoL / related outcome
Naugthon et al. (2008) (31)	SH: event requiring assistance of another person	No SH vs. 1 SH No SH vs. ≥2 SH; self-reported	6	Overall generic QoL; psychosocial; social; school; physical health; emotional	PedsQL	≥ 2 SH vs. no SH associated with ↓ physical health (β=-4.00***) N.S. for physical health between those with 1 SH vs. no SH and between those with 1 or ≥2 SH vs. no SH on general-QoL, social functioning, school functioning, emotional functioning and psychosocial functioning ($p>0.05$) Covariates: sex, race/ethnicity, age, highest level of parent education, and type of health insurance, BMI z score, duration of diabetes, type of diabetes treatment, HbA_{1c} level, number of comorbid conditions, emergency department visits, and hospitalizations in the preceding 6 months
Nip et al. (2019) (50)	SH: event requiring assistance of another person	No. of SH; self-reported	6	Overall eating behavior	DEPS-R	N.S. difference in frequency of SH between those with DEB vs. without DEB (data NR)
Plener et al. (2015) (49)	SH with need of assistance of other persons, defined by unconsciousness, seizures, or application of glucagon or intravenous glucose	Rate of SH/patient year, rate of SH coma/patient year; taken from patient registries	H/patient year, recorded prospectively	Depression (diagnosis or symptoms)	ICD-10 and DSM-IV	SH /patient year ↑ in those with depression vs. without depression** N.S. for SH coma/patient year ($p>0.05$)
Riaz et al. (2017) (43)	SH and hospitalizations due to H	No SH vs. SH No hospitalization due to H vs.	6	Depression	CES-D	N.S. for SH or hospitalizations due to H ($p>0.05$)

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Author, year (ref)	Hypoglycaemia definition	Hypoglycaemia measurement	Recall period (months)	QoL domain or related outcome	Instrument	Findings: Association between hypoglycaemia and QoL / related outcome
		hospitalizations due to H				
Serkel-Schrama et al. (2016) (30)	N/A	No SH vs. SH; parent-reported	12	General QoL and DD	PedsQL PedsQL-DM	SH vs. NO SH associated with ↑ DD (r=-0.19*) N.S. for generic QoL (p>0.05)
Shepard et al. (2014) (41)	SH (N/A) SH episodes requiring medical attention and NSH : % of readings <70 mg/dl	No. of SH episodes; Parent-reported	12	Helplessness; avoidance; maintaining high BG; social consequences	HFS C	↑ SH associated with ↑ helplessness (r=0.19**) N.S. for SH and maintaining high BG, avoidance and worry about negative social consequences (data NR) Those who needed medical attention due to H vs. those without reported ↓ avoidance* N.S. for medical attention due to H and helplessness, maintain high BG and worry about negative social consequences (data NR) Children scoring in the highest tertile vs. the lowest tertile of maintain high BG had ↑ SH episodes* N.S. for SH episodes, medical treatment due to H and % of readings <70 mg/dl and avoidance (p>0.05) and for medical treatment due to H and % of readings

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Author, year (ref)	Hypoglycaemia definition	Hypoglycaemia measurement	Recall period (months)	QoL domain or related outcome	Instrument	Findings: Association between hypoglycaemia and QoL / related outcome
						<70 mg/dl and maintaining high BG (p>0.05)
Sismanlar et al. (2012) (47)	NSH: BG levels <60mg/dl SH: H plus one of the following: BG levels ≤30 mg/dl, loss of consciousness, requirement of glucagon injection parenteral treatment at hospital	No. of SH; taken from BG charts and patients' home notes	1	PTSD	CPTS-RI	↑ SH associated with ↑ PTSD (ß= 0.450*) N.S. for any SH and PTSD (data NR) N.S. difference in SH in last month or any SH between those with severe PTSD and those with mild/moderate PTSD (p>0.05)
Stahl-Pehe et al. (2013) (13)	N/A	No SH vs. SH in past 12 months No SH vs. SH in past month; self-reported	12	Physical wellbeing; emotional wellbeing; self-esteem; family; friends; school; general QoL; diabetes impact; diabetes treatment; overall diabetes specific QoL	KINDL-R DISABKIDS	SH past year vs. no SH associated with ↓ quality of relationship friends (β=-3.1*) SH past month vs. no SH associated with ↓ emotional wellbeing (β=-4.2**), ↓ school functioning (β=-4.1*), ↓ general QoL (β=-3.0**), ↓ diabetes-specific QoL(β=-4.5**) ↓ diabetes impact (β=-3.8*) and ↓ diabetes treatment (β=-6.6**) N.S. association for SH past year or month vs. no SH and physical wellbeing, self-esteem, relationship with family (p>0.05) N.S. for SH past year and school functioning, diabetes-specific QoL, diabetes impact and diabetes treatment,

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Author, year (ref)	**Hypoglycaemia definition**	**Hypoglycaemia measurement**	**Recall period (months)**	**QoL domain or related outcome**	**Instrument**	**Findings: Association between hypoglycaemia and QoL / related outcome**
						general QoL emotional wellbeing (p>0.05) N.S. for SH past month and relationship with friends (p>0.05) Covariates: sex, age group, socioeconomic status, family structure, HbA_{1c} level, insulin regimen, treatment satisfaction, weight status, and history of hospitalization
Strudwick et al. (2005) (48)	SH: resulting in seizure or coma	SH without seizure vs. SH with seizure; taken from medical record	Collected at clinics every 3 months	Depression	CDI -S	N.S. for depressive symptoms (data NR)
Wagner et al. (2005) (34)	SH: episodes with severe neurological dysfunction (e.g. seizures, loss of consciousness, disorientation, inability to arouse from sleep) that require intervention with glucagon or intravenous dextrose or milder forms of hypoglycaemia associated with neurological dysfunction that were not recognized or self-treated	No. of SH episodes	NR	Physical; psychological; wellbeing; self-esteem; family; friends; school, illness related distress	KINDL-R	N.S. for physical wellbeing, psychological wellbeing, self-esteem, family, friends, school and illness related distress (data NR) Covariates: age and gender

ASWS, Adolescent Sleep Wake Scale; CDI-S, Children's Depression Inventory, Short version; CES-D, Center for Epidemiological Studies-Depression Scale; CHI-2, Child Hypoglycaemia Index 2; CPTS-RI, Child Posttraumatic Stress Reaction Index, DEPS-R, Diabetes Eating Problem Survey-Revised; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; DQOLY, Diabetes Quality of Life for Youth scale; EQ-5D, EuroQoL 5 Dimensions; HFS-C, Hypoglycaemia Fear Survey-

Children version; ICD-10, International Classification of Diseases -10, PedsQL, Paediatric Quality of Life Inventory; PedsQL-DM, Paediatric Quality of Life Inventory-Diabetes Module; SCARED, Screen for Child Anxiety Related Emotional Disorders; STAIC, State-Trait Anxiety Inventory for Children

BG, blood glucose; DD, diabetes distress; FoH, fear of hypoglycaemia; H, hypoglycaemia; SH, severe hypoglycaemia; No., number; N.S., Not significant ($p>0.05$); PTSD, Post-Traumatic Stress Disorder; QoL, quality of life, sig., significantly
[1] Multivariate analysis are displayed only
*$p<0.05$, **$p<0.01$, ***$p<0.001$

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Supporting information

Full search strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to August 20, 2019>
Search Strategy:
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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
6 exp Diabetes Mellitus, Type 2/
7 ("non-insulin* depend*" or "noninsulin depend*").tw.
8 (("typ* 2" or "typ* II") adj2 diabet*).tw.
9 (NIDDM or T2DM or T2D).tw.
10 or/6-9
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]**
15 10 and 13 **[T2DM + 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/
28 (Case control or cohort analy$).tw.
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.
33 or/27-32 **[SIGN Observational study filter]**
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]**
36 (14 or 15) and 23 and 35
37 14 and 23 and 34 and 35 **[Rev 1: T1DM + hypo + children]**
38 (14 and 23 and 35) not 34 **[Rev 2: T1DM + hypo + adults]**
39 (15 and 23 and 35) not 34 **[Rev 3: T2DM + hypo + adults]**
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]**
42 ((14 or 15) and 23 and 35) not 34
43 (family or families or spous* or husband* or wife or wives or partner* or son or sons or daughter* or children).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]
44 42 and 43 **[Rev 5: families of adults with T1DM or T2DM]**
45 37 or 38 or 39 or 41 or 44 **[Total – all reviews]**

Table S1. Overview of scales being used across studies

Instrument name	Aim	Number of items	Subscales	Recall period	Validated for use in children/adolescents with type 1 diabetes
Adolescent Sleep/Wake scale	To measure overall subjective sleep quality	28	• Difficulty going to bed • Falling asleep • Maintaining sleep • Reinitiating sleep • Returning to wakefulness	1 month	No
Center for Epidemiological Studies-Depression Scale	To assess self-reported depressive symptomatology	20	• N/A	1 week	No
Child Posttraumatic Stress Reaction Index	To assess reactions after traumatic events	20	• N/A	N/A	No
Children's Depression Inventory- Short version	To screen for depression in medically ill children	10	• N/A	2 weeks	Yes
Children's Hypoglycemia Index	To measure fear of hypoglycemia in children	24	• Situation • General • Behavior	N/A	Yes
Diabetes Quality of Life for Youth	To assess diabetes-specific health related quality of life	52	• Impact scale • Life satisfaction scale • Worries about diabetes • Health perception	N/A	Yes
Diabetes Quality of Life for Youth Short Form	To assess diabetes-specific health related quality of life	22	• Impact of treatment • Symptom impact • Impact on activities • Parents • Worry • Satisfaction	N/A	Yes
DISABKIDS DCGM-12	To assess health related quality of life of children and adolescents with chronic medical conditions	12	• N/A	4 weeks	Yes
DISABKIDS Diabetes Module		10	• Impact	4 weeks	Yes

Instrument name	Aim	Number of items	Subscales	Recall period	Validated for use in children/adolescents with type 1 diabetes
	To assess diabetes-specific aspects of health-related quality of life		• Treatment		
Diabetes Eating Problem Survey-Revised	To assess diabetes-specific self-reported disordered eating behaviors	16	• N/A	N/A	Yes
European Quality of life - 5 Dimensions (EQ-5D) - VAS scale	To evaluate general health status	1	• N/A	N/A	Yes
Hypoglycemia Fear Survey – Child version	To assess the levels of fear related to hypoglycemia	25	• Worries about hypoglycaemia • Fear of hypoglycaemia related behaviors	N/A	Yes
KINDL-R	To assess health-related quality of life	24/30	• Physical wellbeing • Emotional wellbeing • Family • Friends • Self-esteem • Chronic illness scale	1 week	No
KIDSCREEN 10 index	To assess general health related quality of life	10/11	• Global QoL	1 week	No
KIDSCREEN 27	To measure subjective health and well-being	27	• Physical wellbeing • Psychological well-being • Autonomy and relationships with parents • School • Relationships with friends or peers	1 week	No
Pediatric Quality of Life Inventory- Diabetes Module	To assess diabetes-specific health related quality of life	32/33	• Diabetes symptoms • Diabetes management	1 month	Yes
Pediatric Quality of Life Inventory – Generic Module	To assess health-related quality of life	23	• Physical functioning • Emotional functioning • School functioning • Social functioning	1 month	Yes

Instrument name	Aim	Number of items	Subscales	Recall period	Validated for use in children/adolescents with type 1 diabetes
Screen for Child Anxiety-Related Disorders	To screen for signs of anxiety disorders in children	41	• Panic disorder / somatic symptoms • Generalized anxiety disorder • Separation anxiety disorder • Social anxiety disorder • Significant school avoidance	3 months	No
State-Trait Anxiety Inventory for Children	To assess state and trait anxiety for children	40	• Trait Subscale • State subscale	N/A	No

Table S2. Quality assessment of the included studies

Author, year	**Inclusion criteria**	**Subjects and setting**	**Exposure measured**	**Objective measure of condition**	**Confounders identified**	**Dealt with confounders**	**Outcomes measured valid**	**Appropriate analysis**
Adler et al. (2017) [34]	Yes	Yes	Yes	Yes	Yes	No	Unclear	Yes
Al Hayek et al. (2014) [35]	Yes	Yes	No	Yes	Yes	Yes	Unclear	Unclear
Amiri et al. (2014) [38]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Caferoğlu et al. (2016) [16]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Coolen et al. (2021)	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Dłużniak-Gołaska et al. (2019) [42]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Galler et al. (2021)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gonder- Frederick et al. (2006) [37]	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes
Hanberger et al. (2009) [27]	Unclear	Yes	No	Yes	Yes	Yes	Unclear	Yes
Hassan et al. (2017) [32]	Yes	Unclear	Unclear	Yes	Yes	No	Yes	No
Hoey et al. (2001) [36]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	No
Johnson et al. (2013) [15]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Jurgen et al. (2020)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Kalvya et al. (2011) [28]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Lawrence et al. (2012) [41]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Matziou et al. (2010) [31]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Murillo et al. (2017) [14]	Yes	Yes	Yes	Yes	Yes	No	Unclear	No
Naugthon et al. (2008) [30]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Nip et al. (2019) [46]	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Plener et al. (2015) [45]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Riaz et al. (2017) [40]	Yes	Unclear	No	Yes	Yes	Yes	Unclear	No
Serkel-Schrama et al. (2016) [29]	Yes	Unclear	No	No	Yes	No	Yes	Yes
Shepard et al. (2014) [39]	Yes	Yes	Unclear	No	Yes	No	Yes	Yes

Author, year	**Inclusion criteria**	**Subjects and setting**	**Exposure measured**	**Objective measure of condition**	**Confounders identified**	**Dealt with confounders**	**Outcomes measured valid**	**Appropriate analysis**
Sismanlar et al. (2012) [43]	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Stahl-Pehe et al. (2013) [13]	Yes	Yes	No	Yes	Yes	Yes	Unclear	Yes
Strudwick et al. (2005) [44]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Wagner et al. (2005) [33]	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes

The option “unclear” was also used in case of mixed results. The option “unclear” was also used in case of mixed results. To assess whether a paper measured the outcome in a valid and reliable way, it was only coded “yes” if the included measurements were validated among adolescents with diabetes

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Authors’ contribution

Conceptualization: MC, MB, BDG, SH, CH, JS, FP
Data curation: MC, MB, HC, MCL
Formal Analysis: MC, MB, HC, JS, FP
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Investigation: MC, MB, HC, MCL
Methodology: MC, MB, JS, FP
Project administration: MB, JS, FP
Resources: N/A
Supervision: MB, JS, FP
Validation: MC, MB, HC, MCL
Writing – original draft: MC
Writing – review & editing: MB, HC, CH, BDG, SH, MCL, JS, FP

Disclosure statement

The authors report no conflicts of interest related to this manuscript

Paper 3

‘I don't want to stand out and be different’. A multi-country, web-based qualitative study of the impact of hypoglycaemia on quality of life among adolescents with type 1 diabetes

Submitted for publication

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Abstract

Objective: To explore the impact of hypoglycaemia on quality of life (QoL) in adolescents with type 1 diabetes.

Methods: Adolescents (aged 12-17 years) with type 1 diabetes from Denmark, Germany, the Netherlands and the United Kingdom completed a qualitative online survey in which they nominated domains of life that were important for their overall QoL and described, in their own words, if and how hypoglycaemia impacted on these domains. Thematic analysis was used to analyze the responses.

Results: In total, 75 adolescents (mean±SD age, 15±2 years) completed the survey. The majority (61%) nominated five domains of life important to their QoL. The domains of life nominated most frequently as important for their QoL were school, friends, family relationships, sleep and sports. Notably, neither health nor diabetes were among the most frequently nominated domains. Five themes represent the impact of the experience of hypoglycaemic episodes on these domains: physical, emotional, social, cognitive, and behavioral. Three additional themes arose relating to living with the risk of hypoglycaemia: reduced freedom, worries, and suboptimal glucose management. Eight participants (10%) reported no impact on one or two domains of life important for their QoL, and three (4%) reported a positive impact of hypoglycaemia (on their friendships and their self-confidence (9th most frequently nominated domain).

Conclusions: Both experiencing and living with the risk of hypoglycaemia impact on a range of domains of life important for adolescents' QoL. These findings highlight the importance of exploring the impact of hypoglycaemia and addressing this in personalized, clinical care.

Keywords: adolescents, hypoglycaemia, quality of life

Introduction

Adolescents with type 1 diabetes need to engage in demanding and intensive diabetes self-management activities, including administering insulin and monitoring glucose levels multiple times per day, with the goal of keeping glucose levels within target range to prevent both acute complications (e.g. hypoglycaemia) and long-term micro- and macrovascular complications (1). Another main goal in diabetes care is to maintain or optimize quality of life (QoL) (1). This can be challenging for adolescents with type 1 diabetes, as the demanding requirements of diabetes self-management can interfere with daily activities and other developmental challenges, such as becoming independent from parents and not wanting to be different from peers (2).

Hypoglycaemia (low blood glucose) is a burdensome and important side effect of insulin treatment. On average, it occurs twice per week in adolescents with type 1 diabetes (3). Biomedical impacts range from unpleasant symptoms (e.g., shakiness), to impaired cognitive function, unconsciousness, and on very rare occasions, death (4). The experience of hypoglycaemia is also linked to adverse psychosocial outcomes, such as fear of hypoglycaemia (FoH) (5, 6), anxiety (7) and reduced QoL (8).

While various definitions of QoL are used across studies, there is consensus that QoL is a multidimensional, subjective and dynamic construct (9). Due to the subjective aspect, there is no ‘one size fits all’ approach to measuring QoL (9). Therefore, it has been suggested that the best way to capture the impact of diabetes on QoL is to ask people directly what is important for their QoL and to subsequently ask them whether and how this is affected by living with diabetes (10). Two studies that used an individualized interview method to investigate QoL in adolescents with diabetes found that: a) although family, friends and school were identified as the most important domains of QoL in general, there were also individual differences; b) these domains were more important to the adolescents for their QoL than diabetes or health; and c) what adolescents considered as important for their QoL differed from what their parents or clinicians considered important (10, 11). This highlights the need for individual assessments of QoL in adolescents with type 1 diabetes.

Hypoglycaemia can impair QoL, but quantitative studies examining this relationship have yielded conflicting results (8, 12-17), and sometimes assess constructs better described as health status or diabetes distress, rather than QoL (9, 13, 16), or assess only one domain of QoL, (e.g., sleep) (18). In addition, these studies have not necessarily measured domains of QoL that are important to adolescents with diabetes experiencing hypoglycaemia.

There is a clear gap in the current understanding of how hypoglycaemia affects various domains of life important to the QoL of adolescents with diabetes. Qualitative research is warranted, which enables in-depth exploration of these issues. This multi-country qualitative study therefore explores what domains of life are important for the QoL of adolescents with type 1 diabetes, and the impact of hypoglycaemia on those domains, by analyzing their written responses to open-ended questions.

Methods

A web-based qualitative survey design was chosen to enable recruitment of large samples across multiple countries. The study received ethical approval in all participating countries (University of Southern Denmark: 19/78420; UK Health and Social Care: 20-NI-0054; Radboud University Medical Centre; 2020-6587 and German Society for Psychology: HermannsNorbert2020-05-12VA).

Participants

Participants were eligible if they were: adolescents (aged 12-17 years); reported being diagnosed with type 1 diabetes; living in Denmark, Germany, the Netherlands, or the United Kingdom; and able to complete the qualitative survey online in either Danish, German, Dutch, or English.

Protocol

Participants were recruited between September and December 2020 through advertisements on social media, websites of national diabetes associations, or posters in diabetes clinics. They could access the survey via an open link on their smartphone, tablet, or computer. Participants indicated their eligibility before being directed to study information and consent pages. Eligible adolescents were encouraged to read the study information with one of their parents. Subsequently, both adolescents and their parents were required to indicate their informed consent on separate pages. Parents' email addresses were requested at this stage, to discourage adolescents from consenting on their parent's behalf, but these were not further used. Upon completion of the survey, adolescents were invited to enter their email address to participate in a prize draw to win a €50 gift voucher (one voucher per 50 participants). Email addresses were stored in a separate database and not linked to survey responses. Subsequently, parents' and adolescents' email addresses were deleted to maintain participants' anonymity.

Measures

The survey included: 1) multiple choice items to collect data about demographics, diabetes-related clinical characteristics, hypoglycaemia history, and FoH; and 2) open-ended questions exploring domains of life important for the adolescent's QoL and the impact of hypoglycaemia on those domains (see QoL assessment). Four additional open-ended questions asked about support needs for hypoglycaemia; these data are not presented in the current paper. The survey, developed in English, was translated into Danish, Dutch, and German, following best-practice guidelines (19). The survey questions were developed with input from a patient and public involvement (PPI) group that was created for this specific study, and interviews were conducted with six adolescents to examine relevance, comprehensibility, and acceptability of the survey, which resulted in improved wording and addition of visual examples.

At the beginning of the survey, written instructions explained that the survey contained questions about the adolescents' experiences, thoughts, and feelings about hypoglycaemia. Given the abstract nature of QoL, it was important to make the task tangible to adolescents. Therefore, example quotes were used to prompt adolescents to report the personal impact of hypoglycaemia rather than solely describing the physical symptoms. For example: Erik (14 years old) told us: "*When I'm with my friends, I'm sometimes afraid that I will have a hypo. And that's really embarrassing."*

Quality of life assessment

QoL was examined using the novel "Wheel of Life" method (20-22). Adolescents were asked to imagine the wheel to depict their QoL, with the various sections as domains of their lives that are important for their QoL. Two examples were given to demonstrate what was meant by "domains of life" and that the number and importance of domains could differ between people (Figure 1). Then, adolescents were invited to choose from a list of domains of life those that were most important to them. The domains were informed by literature (10, 11, 23-25) and consultation with researchers and clinicians. Although the "Wheel of Life" method did not originally include a pre-defined list of domains, this was added as the adolescents in the PPI interviews indicated that nominating domains without prompts was too difficult. In addition, survey participants were offered the option to add other domains that were not listed. After nominating domains, participants were asked to explain in as much detail in a free-text field (unlimited characters) if and/or how hypoglycaemia affected each of these domains.

Demographic, clinical and hypoglycaemia-specific measures

Participants self-reported demographic (age, gender, ethnicity, and living situation) and clinical information (age of diabetes onset, diabetes treatment and management, frequency of glucose monitoring, comorbid conditions and HbA_{1c} level). After completing the survey, adolescents were asked to evaluate their experiences with completing the survey (i.e., good/bad, easy/hard, boring/interesting), to check whether the format of the survey was suitable for this age group.

Hypoglycaemia, awareness, and fear of hypoglycaemia

The 15-item Hypoglycaemia Awareness Questionnaire (HypoA-Q) was used to assess hypoglycaemia frequency, severity and healthcare utilizations over the past 12 months (26). SH needing help to treat hypoglycaemia was defined as "being conscious but unable to recognize symptoms, ask for help or treat yourself because you were confused". SH requiring medical care was defined as "being unconscious, taken to the hospital or staying overnight in the hospital because of hypoglycaemia". Five items assessed impaired awareness of hypoglycaemia (e.g., "I have symptoms when my blood glucose is low"). This questionnaire was originally designed for adults, but adaptations were made for adolescents in consultation with the developer of the questionnaire. Hypoglycaemia awareness status was also assessed by the Gold score, to facilitate categorization into aware vs. impaired aware subgroups (27).

Worry about hypoglycaemia was assessed with the validated 6-item worry subscale of the Hypoglycaemia Fear Survey-Short Form (HFS-SF) (28). As there is no adolescent version of the HFS-SF, the adult version was adapted based on the original wording of the child version (HFS-C) and approved by the developer of the original survey. Adolescents indicated how often in the past 6 months they had hypoglycaemia-related concerns (e.g., passing out in public).

Data analysis

Qualitative analysis

First, non-English responses to the open-ended items were translated into English using Google Translate. These were checked by native speakers of the original language with knowledge about the survey (MC, MVJ, KFG), to make sure the English translation matched the original response, and changes were made if necessary.

The data were analysed following a reflexive thematic analysis approach described by Braun and Clarke (29). Responses were coded using NVivo 12. Researchers familiarized themselves with the data by reading through the free-text responses multiple times. Data were initially divided by country, but as no specific between-country differences were observed in the data, thematic analysis was performed across countries. Data were coded by MC, with 50% coded independently by a second reviewer JLA. Data were coded inductively. If a subset of the data generated more than one concept, multiple codes were assigned. The initial codes applied by the two reviewers independently were compared, and discussed with co-authors (MB, FP, JS) to reach consensus and the framework was further developed iteratively. Initially, themes were structured by domain of life, but due to many overlapping themes under each domain, these were restructured to go beyond the domains and thematic analysis was conducted across the entire dataset. Once the final list of codes was generated, similar codes were combined, and initial key themes were generated. Themes were developed in relation to the overall research question ("how does hypoglycaemia impact on QoL?"). This was presented to the research team (MB, CH, FP, JS), and redefined until agreement was reached on the final framework. Finally, the wider multidisciplinary research team, including diabetologists, psychologists, and senior researchers with experience in health psychology and qualitative research, reviewed and agreed upon the final themes. Themes were checked for age and gender differences during coding and described in the results if apparent.

Quantitative Analysis

For demographic and clinical data, descriptive statistics (Mean±SD or n(%)) were calculated. Between-country comparisons were examined using Kruskal-Wallis tests for continuous variables and Fisher's Exact tests for categorical variables. Post-hoc tests with Bonferroni correction (α=0.008) were conducted. All analyses were performed using SPSS v24 (Statistical Package for Social Sciences, Chicago, IL, USA).

Results

Participants

In total, 75 adolescents with type 1 diabetes (aged 15±2 years) completed the “Wheel of Life” activity. Participants’ demographic and clinical characteristics are presented in Table 1. Diabetes duration ranged from <1 to 16 years. In total, 81% were using were using continuous glucose monitoring (CGM), and 61% were using an insulin pump. The median number of hypoglycaemic episodes of any type experienced in the past week was four (interquartile range 2-6, range 0-50 episodes), and 20% had experienced at least one episode of SH requiring medical care in the past 12 months.

Most adolescents (73%) found out about the survey via online advertisement, 16% via advertisement in clinics. However, this varied from Denmark (43% online) to the United Kingdom (88% online). None of the adolescents evaluated completing the survey as bad, and 44% indicated they found it interesting. While 17% indicated it was hard to complete the survey, 23% found it easy.

Domains of life important for quality of life

Of the 18 domains of life presented to the adolescents, 17 were nominated by at least one participant (Table 2). None of the adolescents nominated ‘religion’ or added a new domain. The majority (61%, n=46) nominated five domains of life (range: 2-7) that were important to their QoL. The five domains of life most frequently selected (all by >50% of participants) as important for the adolescents’ QoL were: school, friends, family, sleep, and sports. Diabetes was indicated as an important domain for QoL by 12% (n=9) of respondents. Participants from Denmark were more likely to nominate friends, sports, and pets than those from the other three countries. Participants from the United Kingdom were more likely to nominate sleep and mood. Participants from the Netherlands were more likely to nominate diabetes, health and sex and relationships.

Impact of hypoglycaemia on quality of life

In total, participants provided 345 free-text responses, with a mean length of 25 words per response (range 1-140 words). Responses were excluded from the thematic analysis if they: 1) were not detailed enough to enable interpretation of the impact on their QoL, for example *“when I do sports I can get low”*; or 2) were considered insufficiently focused on the specific research question of how hypoglycaemia impacts their QoL, for example: *“Especially because of T1D, not just hypos, my condition and physical performance have deteriorated drastically since my diagnosis”.* In total, 20 (6%) responses were excluded from the analysis.

All participants reported an impact of hypoglycaemia on at least one of the domains of life important for their QoL. Seven participants reported that one domain important for their QoL was not impacted by hypoglycaemia, and one participant reported that two domains were not impacted. The domains that were not impacted for these participants were friends (n=3), family (n=3), sleep (n=1), diabetes (n=1) and self-confidence (n=1). None of these eight participants had experienced SH requiring medical care in the past 12 months, and two reported SH requiring help to treat in that time period.

Free-text responses related to the impact of the experience of hypoglycaemic episodes on domains of life, and to the broader impact of living with the risk of hypoglycaemia. Five themes were generated for the impact of hypoglycaemic episodes on QoL: 1) physical; 2) emotional; 3) social; 4) cognitive and 5) behavioural. Another three themes illustrated the impact of living with the risk of hypoglycaemia on QoL: 1) reduced freedom, 2) worries, and 3) sub-optimal glucose management. An overview of the themes, codes, and example quotes are given in Table 3.

Physical impact of hypoglycaemia on QoL

Respondents described various ways in which hypoglycaemia impacted them physically. Most common was the negative impact on their sleep, which included loss of sleep quality or quantity, because of waking up and having to treat hypoglycaemia. They reported feeling tired the next day, which affected several domains of life (e.g., sports, mood, school). Daytime tiredness was also reported as a direct result of having a hypoglycaemic episode during the day. Participants described that the symptoms of hypoglycaemia, such as dizziness and shakiness, affected how healthy and active they felt, how they reacted towards others and how well they could concentrate. In addition, participants reported that multiple episodes of hypoglycaemia led to impaired awareness of hypoglycaemia, both during the day and at night. Another important consequence was the impact on diet and weight. Participants reported that it was frustrating having to eat when they did not want to, to prevent or self-treat hypoglycaemia, and described this as interfering with a healthy diet and negatively affecting their weight.

Emotional impact of hypoglycaemia on QoL

Hypoglycaemia impacted on adolescents' emotional well-being in many ways. Older females were most likely to describe an emotional impact of hypoglycaemia. In general, they reported a direct impact of hypoglycaemia on mood, e.g., feeling upset, anxious, or stressed. The most frequently reported impact of hypoglycaemia on mood was feeling irritable, agitated, or annoyed. One participant described a negative impact of recurrent hypoglycaemia on their overall mental health. Some adolescents blamed themselves for having hypoglycaemia, which made them feel insecure. In contrast, two participants described a positive impact on their self-confidence after treating hypoglycaemia.

Some adolescents felt embarrassed when they had to treat hypoglycaemia in front of others; particularly, in front of friends and peers at school, but also in front of strangers (e.g., on public transport). Participants also felt embarrassed when they acted differently and made mistakes at school or work during hypoglycaemia. Others described they were feeling different because they had to take actions to treat their hypoglycaemia in front of others, felt self-conscious, or did not like it when other people asked about it. Some mentioned specifically that they were worried about other people's reactions when they had hypoglycaemia and were afraid that others would judge them. Others felt annoyed when they perceived their friends or family to be checking on them too much.

In addition, feelings of frustration and annoyance were commonly reported. These frustrations were especially around having to interrupt or stop what they were doing (e.g., sports, studying, being with friends/family) to treat hypoglycaemia, having to eat when they did not want to, waking up during the night because of hypoglycaemia and constantly paying attention to glucose levels. Apart from the interruption of activities that impacted their QoL, participants also described that hypoglycaemia reduced their enjoyment of activities that were important to them, such as doing sports, spending time with friends, going to parties or traveling.

Social impact of hypoglycaemia on QoL

Participants described that hypoglycaemia impacted on their social life in various ways. Many reported that they relied on other people, such as friends or family, and in some cases on diabetes warning dogs to be made aware of hypoglycaemia. In addition, participants described that their family and friends helped with treating hypoglycaemia (e.g., by bringing sugary drinks or food with them) or taking it into account (though no specific examples of this were given). Some adolescents experienced this as negative, describing that they felt like a burden to those close them. One participant experienced this as positive, as it enabled them to build better relationships with their friends. In some cases, family members were perceived as interfering with hypoglycaemia, which resulted in tension and arguments. While some respondents described that others (e.g., teachers, peers, sports trainers) made efforts to accommodate their needs, others described a lack of understanding. This was especially reported at school, where some adolescents mentioned that they were not allowed to eat during class when they had hypoglycaemia, or that their teachers or classmates did not take it seriously.

Another important aspect was how mood changes attributed to hypoglycaemia affected the adolescents' relationships with others. During hypoglycaemia, participants felt easily annoyed by others and, without wanting to, reacted with frustration towards them, which sometimes resulted in arguments and tension. Participants described that having hypoglycaemia affected not only them, but also the people around them. They highlighted that other people were worried or overwhelmed when they had hypoglycaemia, or that others were directly impacted by them having hypoglycaemia. For example, when the hypoglycaemia alarm of their CGM went off at school, this was distracting for their classmates.

Cognitive impact of hypoglycaemia on QoL

Participants described that hypoglycaemia impacted on their ability to concentrate and focus on things they were doing. This was especially experienced at school, during classes or exams and whilst doing homework or studying. Concentration problems also impacted leisure activities, for example when doing sports or playing a musical instrument. This loss of concentration could continue even after the hypoglycemic episode was treated and their glucose levels had returned to target range. Similarly, participants described that when they had hypoglycaemia during the night, they experienced difficulties concentrating the next day.

Behavioural impact of hypoglycaemia on QoL

Respondents described that hypoglycaemia impacted on their day-to-day activities. Sometimes, hypoglycaemia stopped them from doing sports, doing activities with friends, going to school, or playing a musical instrument. In other cases, they were still able to participate, but this was interrupted by hypoglycaemia. Participants described that they had to stop or step out when exercising, to treat hypoglycaemia. They also had to stop studying/working or miss out on class because they had to go to the medical office at school to treat or recover from hypoglycaemia. In addition, they described how hypoglycaemia affected their performance and led to mistakes. This was particularly seen in sports, but also during leisure activities or at school, where hypoglycaemia during exams was reported as negatively affecting their grades. Hypoglycaemia also interrupted activities with friends and family, such as having fun at a party. Older adolescents also mentioned that having sex was interrupted because of hypoglycaemia.

Risk of hypoglycaemia

Impact of reduced freedom on QoL

Participants described that they had to take many precautions to avoid hypoglycaemia. This included planning everything ahead, always bringing/having sugary drinks or food with them, always having to be vigilant, and not being able to fully concentrate because they had to be aware of when they were feeling low. Consequently, participants described they felt a lack of freedom. This was due to a reduced ability to be spontaneous and being unable to do things they wanted in the way they wanted (e.g., when traveling). In addition, they described that sometimes others (usually parents) were worried about them having hypoglycaemia. In some cases, other people's worries limited the adolescent with diabetes. For example, they were not invited for birthday parties because others were afraid of them having hypoglycaemia in that situation.

Impact of worries on QoL

Participants, especially older female adolescents, described that living with the risk of future hypoglycaemia affected them. This was mainly due to worries related to the risk of having hypoglycaemia in various situations (especially while asleep, during sports or at school), or worries about (not) being able to treat hypoglycaemia. Participants also worried about the consequences of hypoglycaemia, such as embarrassing oneself or not being able to complete education.

Impact of suboptimal glucose management on QoL

Some participants reported that the risk of hypoglycaemia sometimes led to suboptimal glucose levels (e.g., intentionally keeping glucose levels higher than recommended or omitting insulin injections), to avoid having to interrupt what they were doing. This was especially seen in the context of parties and alcohol use, where participants described they did not want to be different from their friends. For others, suboptimal glucose levels were attributed to FoH.

Discussion

This online qualitative study shows that both experiencing hypoglycaemia and living with the risk of hypoglycaemia negatively impacts on many domains of life perceived as important for the QoL of adolescents with type 1 diabetes. Across domains of life, the impact of hypoglycaemia related to the experience and consequences (physical, emotional, social, cognitive, and behavioural) of actual episodes as well as to living with the risk of hypoglycaemia and strategies to avoid it (reduced freedom, worries, and suboptimal glucose management). Most participants described that hypoglycaemia impacted on several domains important for their QoL. This impact was mainly described as negative, only a few participants (n=3) reported a positive impact of hypoglycaemia on QoL (e.g., better relationships with friends).

In contrast with some quantitative studies reportedly showing no association between hypoglycaemia and QoL (13, 15, 17), the present qualitative study shows that hypoglycaemia has a considerable negative impact on the lives of adolescents with type 1 diabetes. This discrepancy could possibly be explained by the fact that previous quantitative studies have often claimed to assess QoL but actually assessed other psychological constructs (e.g., diabetes distress) (30). It may also be explained by the inclusion, in the present study, of a QoL measure (“Wheel of Life”) that considers personal priorities, while previous studies might have drawn conclusions using QoL measures that do not take this into account. Although the five most frequently nominated domains important for QoL in this study were similar to those in previous qualitative studies (10, 11), 17 unique domains were selected as important for adolescents’ QoL. However, these domains are rarely assessed in quantitative studies (30). Importantly, neither health nor diabetes were typically nominated as important for QoL, although they are often the focus in quantitative QoL studies (13).

The findings of this study indicate that the relationship between hypoglycaemia and QoL is complex. Although participants were asked to describe the impact of hypoglycaemia on QoL for each domain of life separately, interactions between various domains of life were observed. For example, respondents described that hypoglycaemia negatively impacted their mood, which in turn impacted on their relationships. Furthermore, some adolescents described that they felt like a burden when others had to stop with what they were doing because of their hypoglycaemia. This could be regarded a social impact, but also as an emotional impact as one could *feel* like a burden regardless of the actual impact on others.

There were no differences in responses observed between countries, ages, and genders, except for older female adolescents, who were more likely to describe an emotional impact and an impact of the risk of hypoglycaemia on their life. Whether older female adolescents are more susceptible to these impacts or more willing to articulate them cannot be derived from this study. As previous studies have shown gender differences in both FoH and QoL (31, 32), further studies that explore the (emotional) impact of hypoglycaemia on QoL in male adolescents with type 1 diabetes are needed.

Although the impact of hypoglycaemia on QoL described by some participants aligned closely with previous research about the impact of diabetes more broadly on QoL, such as feeling different and desire to be ‘normal’ (33, 34), self-care activities interfering with other activities (34, 35) and an impact on social relationships (34, 35), unique impacts of hypoglycaemia included feeling embarrassed when having hypoglycaemia, deliberately maintaining high glucose levels, and not being allowed to eat at school to treat hypoglycaemia.

Across various domains, some of the adolescents described that they felt excluded from activities with friends and felt judged or embarrassed when having to treat hypoglycaemia. Previous studies have indicated that exclusion, negative social judgements, and blame are forms of stigma experienced by adults with type 1 diabetes (36, 37). This has psychological, social, behavioural, and medical consequences including emotional distress, non-disclosure, and sub-optimal diabetes management (36, 38). Future studies need to further explore the association between hypoglycaemia and stigma in adolescents with type 1 diabetes.

Strengths and limitations

The main strength of this study was the use of the ‘Wheel of Life’ method that enabled in-depth, personalized assessment of how hypoglycaemia affects areas adolescents defined as important for their QoL. In addition, benefits of an online study including anonymity and flexibility might have increased the chances of adolescents completing it and disclosing personal matters (39). Importantly, the study was positively evaluated by participants. This study also has limitations. First, the sample was self-selected and might have been biased as females were overrepresented and the frequency of SH was relatively high compared to previous studies (12, 13, 40). It could be that adolescents who experience a high impact from hypoglycaemia were more likely to respond, however this could also be the result of a less restrictive definition of SH used in this study, compared to the definition from the International Society of Pediatric and Adolescent Diabetes (3). Future studies need to explore whether findings are transferrable to other samples and settings. Second, given the nature of an online study, there was no opportunity to probe participants’ responses for more detail. Many responses were descriptive, referring to what happened when a person experienced hypoglycaemia (e.g., “*my family is helping me*”). While some adolescents described that they either perceived this positively (because it strengthened their relationships with others) or negatively (because they felt like a burden), many did not describe how they perceived this help. This could be due to the abstract nature of the “Wheel of Life” activity, which required a level of reflection. Though this method has been previously used to assess QoL in adults with diabetes (22), it could be that this method is less suitable for younger adolescents than for older adolescents. Attempts were made to tailor the activity to this age group and no clear differences in length of responses were observed between 12- and 17-year-old adolescents. Third, the sample size was smaller than envisaged and all data were collected before analysis commenced, so it is unclear if data saturation was reached. However, the sample was still relatively large for a qualitative study and included adolescents from four European countries, capturing a broad range of experiences.

Clinical implications

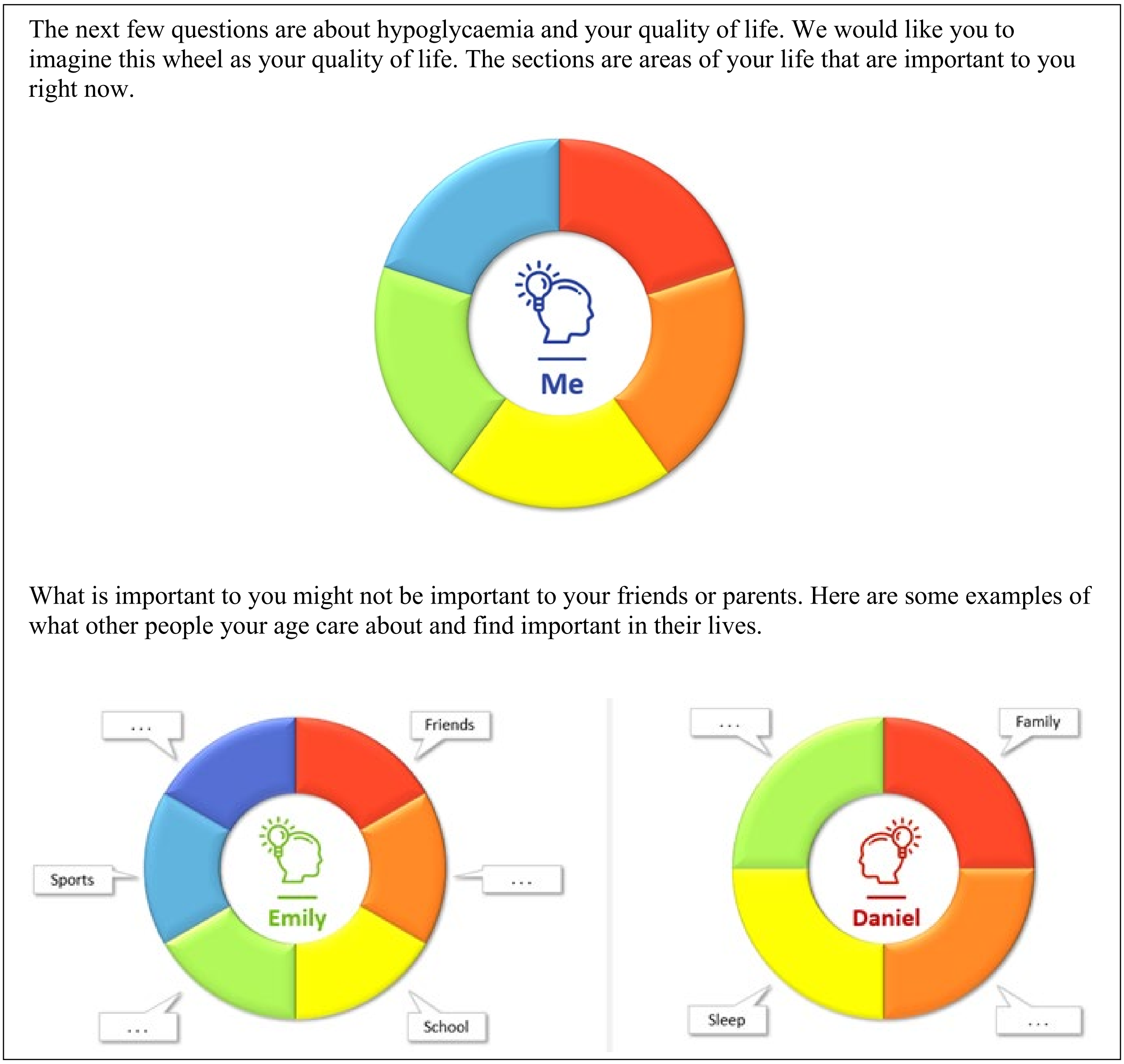
These findings suggest that it is important for healthcare professionals to acknowledge and address the negative impact of hypoglycaemia on adolescents' QoL. Of note, this impact was experienced even though the majority of the adolescents in the study were using insulin pumps or CGM. Moreover, this impact was also reported by adolescents without a history of severe or frequent hypoglycaemia. This is important to consider, as dealing with fear of a potential hypoglycaemic episode in the future requires different support and intervention strategies than dealing with the impact of a current/previous episode.

Healthcare professionals need to keep in mind that QoL is subjective and dynamic; it can be different for different people at different times. Since adolescents might not prioritize diabetes or health for their QoL, they might sometimes compromise their diabetes management to prioritize other areas important for their QoL, such as their friendships. The "Wheel of Life" technique could be used as a tool in clinical practice to facilitate discussion around hypoglycaemia and its impact and to personalize care. Other strategies that can potentially be effective in promoting health outcomes and minimizing the burden of hypoglycaemia for adolescents with type 1 diabetes include interventions that promote social resilience (41), social competence (42), or mindfulness-based stress reduction interventions (43).

Conclusion

This study shows that hypoglycaemia can have a profound negative impact on many domains of life that are important for the QoL of adolescents with type 1 diabetes. These findings suggest that monitoring the impact on QoL of both the experience and risk of hypoglycaemia should have a place in clinical care and guidelines, in addition to biomedical outcomes such as HbA_{1c}. To reduce the burden of hypoglycaemia among adolescents with type 1 diabetes, future studies need to further explore the impact of hypoglycaemia on QoL using appropriate measures that consider the individual aspects of QoL.

Figure 1. Wheel of life with examples as displayed in the survey



The next few questions are about hypoglycaemia and your quality of life. We would like you to imagine this wheel as your quality of life. The sections are areas of your life that are important to you right now.

What is important to you might not be important to your friends or parents. Here are some examples of what other people your age care about and find important in their lives.

Table 1. Adolescents' self-reported demographic and clinical characteristics

	Valid cases	Total N=75	Denmark n=14	Germany n=16	The Netherlands n=21	United Kingdom n=24	P value
Age (years)	74	14.9 (1.7)	13.8 (1.1)	14.2 (2.0)	15.9 (1.2)	15.1 (1.6)	.001[1]
Gender: female	75	73% (55)	43% (6)	69% (11)	91% (19)	80% (19)	.015[1]
Living situation	75						.152
Both parents		71% (53)	50% (7)	88% (14)	67% (14)	75% (18)	
Single parent		23% (17)	36% (5)	13% (2)	19% (4)	25% (6)	
Other		7% (5)	14% (2)	0% (0)	14% (3)	0% (0)	
Diabetes duration (years)	72	5.5 (4.4) R 0-16	6.4 (4.4) R 0-13	6.5 (4.6) R 1-12	5.2 (4.6) R1-15	4.6 (4.3) R 0-16	.465
Insulin administration	69						.021[2]
Multiple daily injections		31% (23)	7% (1)	19% (3)	52% (11)	33% (8)	
Insulin pump		61% (46)	93% (13)	75% (12)	48% (10)	46% (11)	
Glucose monitoring modality	62						.852
Finger prick		4% (3)	7% (1)	0% (0)	5% (1)	20% (1)	
Sensor (CGM or Flash)		81% (61)	50% (7)	88% (100)	95% (20)	83% (20)	
Open-source APS/ artificial pancreas use	73	12% (9)	14% (2)	19% (3)	0% (0)	17% (4)	.230
HbA_{1c}	51						.591
%		7.5 (1.5) R 5.3-14.0	7.0 (0.8) R 6.0-9.1	7.5 (1.2) R 5.8-10.4	7.6 (1.1) R 6.5-10.3	7.8 (2.3) R 5.3-14.0	
mmol/mol		59 (16.3) R 34-130	54 (9.3) R 42-76	58 (13.3) R 40–90	60 (12.3) R 48-89	61 (24.6) R 34-130	
Hypoglycaemia							
Any type in past week: frequency *(M, SD)*	69	4.9 (6.4) R 0-50	4.1 (2.9) R 1-10	5.6 (4.1) R 0-15	4.2 (2.9) R 0-11	5.5 (10.1) R 0-50	.526
≥1 SH (needed hel to treat hypoglycaemia) in past 12 months[8]	75	48% (36)	57% (8)	19% (3)	52% (11)	58% (14)	.070
≥1 SH requiring medical care in past 12 months[9]	75	20% (15)	14% (2)	13% (2)	29% (6)	21% (5)	.645
Awareness of hypoglycaemia							
Hypo-AQ: IA subscale	75	7.1 (2.6) R 2-16	7.4 (1.6) R 4-11	7.1 (3.0) R 3-13	7.6 (2.9) R 3-16	7.8 (2.9) R 3-16	.294
Gold score	75	2.6 (1.0) R 1-6	2.4 (0.9) R 1-4	2.3 (0.6) R 2-4	2.7 (1.2) R 1-6	2.9 (1.1) R 1-5	.245
Gold score ≥4		19% (14)	14% (2)	6% (1)	24% (5)	25% (6)	.440
Psychological comorbid conditions[11]	75						<.001[1,4,6,7]
None		72% (54)	100% (14)	100% (16)	57% (12)	50% (12)	
≥1		28% (21)	0% (0)	0% (0)	43% (9)	50% (12)	
Physical comorbid conditions[11]	75						.227
None		63% (47)	64% (9)	81% (13)	48% (10)	63% (15)	
≥1		37% (28)	36% (5)	19% (3)	52% (11)	38% (9)	

	Valid cases	Total N=75	Denmark n=14	Germany n=16	The Netherlands n=21	United Kingdom n=24	P value
Fear of hypoglycaemia (HFS-SF)	75	10.9 (5.8) R 1-24	8.1 (3.4) R 3-14	8.9 (5.3) R 1-16	6.4 (2.3) R 2-18	15.5 (5.6) R 1-24	<.001[3,4,5]
Evaluation of the survey	73						
Good		64% (48)	57% (8)	75% (12)	52% (11)	71% (17)	
Bad		0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	
Easy		23% (17)	29% (4)	31% (5)	10% (2)	25% (6)	
Hard		17% (13)	29% (4)	13% (2)	29% (6)	4% (1)	
Boring		9% (7)	29% (4)	0% (0)	5% (1)	8% (2)	
Interesting		44% (33)	43% (6)	19% (3)	67% (14)	42% (10)	

Data are mean(SD), range (R) for continuous variables and %(n) for categorical variables

APS: Artificial Pancreas System; CGM: Continuous Glucose Monitoring; SH: Severe Hypoglycaemia; IA: impaired awareness; HFS-SF: Hypoglycaemia Fear Survey-Short Form

[1] Significant difference between Denmark and the Netherlands

[2] Post hoc test revealed no significant differences between countries

[3] Significant difference between United Kingdom and the Netherlands

[4] Significant difference between United Kingdom and Denmark

[5] Significant difference between United Kingdom and Germany

[6] Significant difference between Germany and the Netherlands

[7] Significant difference between Germany and United Kingdom

[8] SH: needed help to treat a hypo (you were conscious but unable to recognize symptoms, ask for help or treat yourself because you were confused)

[9] SH requiring medical care includes passing out due to hypoglycaemia, taken to emergency department after hypoglycaemia and stayed overnight in hospital due to hypoglycaemia

[10] Psychological comorbidities included ADHD, anxiety disorder, mood disorder, eating disorder, autism spectrum disorder

[11] Physical comorbidities included eczema/allergies, celiac disease, thyroid disease, asthma, lactose intolerance, and polycystic ovary syndrome

Table 2. Domains of life nominated by adolescents with type 1 diabetes as important for their quality of life, in descending of total frequency and by country

Area of life	**Total** N=75	**Denmark** (n=14)	**Germany** (n=16)	**The Netherlands** (n=21)	**The United Kingdom** (n=24)
School	68% (51)	57% (8)	75% (12)	62% (13)	75% (18)
Friends	63% (47)	93% (13)	75% (12)	52% (11)	46% (11)
Family	61% (46)	71% (10)	75% (12)	62% (13)	46% (11)
Sleep	59% (44)	50% (7)	63% (10)	48% (10)	71% (17)
Sports	52% (39)	79% (11)	56% (9)	38% (8)	46% (11)
Mood	43% (32)	29% (4)	50% (8)	29% (6)	58% (14)
Hobbies or leisure activities	21% (16)	14% (2)	31% (5)	19% (4)	21% (5)
Parties / going out	16% (12)	7% (1)	19% (3)	10% (2)	25% (6)
Self-confidence	16% (12)	7% (1)	6% (1)	19% (4)	21% (5)
Eating and drinking	15% (11)	21% (3)	19% (3)	10% (2)	13% (3)
Diabetes	12% (9)	0% (0)	6% (1)	29% (6)	8% (2)
Traveling	11% (8)	14% (2)	19% (3)	10% (2)	4% (1)
Pets	7% (5)	21% (3)	6% (1)	5% (1)	0% (0)
Physical health	5% (4)	7% (1)	0% (0)	14% (3)	0% (0)
Work	4% (3)	0% (0)	0% (0)	10% (2)	4% (1)
Sex / relationships	4% (3)	0% (0)	0% (0)	14% (3)	0% (0)
Physical appearance	4% (3)	0% (0)	6% (1)	5% (1)	4% (1)
Religion	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)

Table 3. Overview of key themes, codes and quotes

	Theme	Codes	N[1]	Description	Domains impacted	Sample quotes[2]
Impact of hypoglycaemic episode	*Physical impact*	Sleep	35	Poor sleep, loss of sleep, waking up at night, having to treat at night and nightmares	Hobbies, sleep, and school	*"It affects me a lot because I sleep badly."* M, DK, 15 years old *"I often wake up in the middle of the night low and messes up my sleep."* F, UK, 17 years old *"I have to stay awake for 15 minutes after testing hypo to retest and eat sugar, so I lose sleep."* F, UK, 15 years old
		Tiredness	21	Feeling exhausted, tired, drained and weak from hypoglycaemia or after having had hypoglycaemia at night	Diabetes, hobbies, mood, parties, school, sleep, and sports	*"If I have a hypo I am exhausted for the rest of the day."* F, NL, 13 years old *"I am often tired in the morning due to hypoglycaemia that occurs at night and cannot perform as much at school"* F, GER, 17 years old
		Diet and weight gain	11	Gaining weight, working out for "nothing", no healthy diet when having to eat because of hypoglycaemia	Eating and drinking and physical appearance	*"I work hard to maintain my weight and strength for sport but it sometimes feels as if all the training I do leads to no changes as I usually immediately have to consume the same number of calories I have burnt in order to treat a hypo!"* F, UK, 17 years old *"If I want to be healthy in a day a high sugar and thick carb is not the best for going forward."* M, UK, 15 years old
		Diabetes	10	Impaired awareness of hypoglycaemia (also during sleep), HbA_{1c}	Diabetes and sleep	*"Getting hypos too often and don't feel them coming very well anymore."* F, NL, 17 years old *"I also sometimes get hypos at night; it does not wake me up."* F, NL, 13 years old
		Symptoms	10	Feeling dizzy, ill, bad, shaky	Family, health, mood, school, sleep, and sports	*"I feel ill when I have low blood sugar, and this affects how I act."* F, UK, 13 years old *"My hands are shaking, and my legs hurt. Some hypos make me feel so bad. My body then feels limp and shaky. Even though the hypo is gone, this feeling can sometimes last a day or longer. Because of this I do not feel good / healthy / active."*

Theme	Codes	N[1]	Description	Domains impacted	Sample quotes[2]
					F, NL, 16 years old
Emotional impact	Mood	31	Changes in mood, bad mood, stressed, upset, emotional, confused or anxious when having hypoglycaemia or the next day after nocturnal hypoglycaemia	Diabetes, family, hobbies, mood, school, and sleep	*"Negatively, during fluctuations in my blood sugar I notice that my mood fluctuates enormously."* M, NL, 16 years old *"When I'm low my mood usually gets a lot worse."* F, UK, 17 years old *"When I get a hypo, I often suffer from mood changes and I react angry or sad without wanting to."* F, NL, 13 years old
		17	Feeling irritable, angry or agitated when having hypoglycaemia	Family, friends, and mood	*"I am often cranky because of hypos."* F, NL, 15 years old *"When I am hypo it makes me easily irritable towards others including friends and family"* M, UK, 17 years old
	Frustrations and annoyance	23	Annoyed when having to stop or interrupt activities due to hypoglycaemia, annoyed at having to pay attention to hypoglycaemia, frustrated about having to eat because of hypoglycaemia	Eating and drinking, family, friends, health, hobbies, school, sleep, and sports	*"When I do sports, I get frustrated when I have to sit out to treat and recover from my hypos."* F, UK, 13 years old *"If I want to do something, I always have to pay attention to myself and my blood values, which is very annoying."* F, NL, 13 years old *"When you have low blood sugar it requires what you have to eat, but it is so annoying you have to eat all the time."* M, DK, 15 years old *"Sometimes it's annoying when I'm studying that I get a hypo and then have to concentrate all over again and get into the learning mood again."* M, NL, 16 years old
	Feeling different	13	Not wanting to be different from peers, keeping glucose levels higher because of that, don't like when people ask about it, feeling self-conscious when treating hypoglycaemia or when others are not allowed to eat.	Friends, hobbies, and school	*"I try to not let my levels go lower and try keep them higher when I'm with my friends because I don't want to stand out and be different."* F, UK, 17 years old *"In class, my classmates often look at me strangely when my hypoglycaemia alarm goes off."* F, GER, 14 years old *"During class I sometimes have to eat something because my blood sugar is too low. The rest of the class is not allowed to eat during class so that sometimes feels awkward."*

Theme	Codes	N[1]	Description	Domains impacted	Sample quotes[2]
					F, NL, 16 years old
	Embarrassment	12	Embarrassment about treating hypoglycaemia in front of others, stopping activity, having to eat in class while others are not allowed, behavior during hypoglycaemia,	Friends, school, self-confidence, travel, and work	*“I am often embarrassed to get up in front of my peers and walk out in the middle of a lesson.”* F, UK, 16 years old *“Testing for and treating lows can't be delayed or put off, so it's one of the few parts of diabetes I can never hide, whether it be in front of strangers, or friends, or teachers. It also involves eating and often happens at very awkward times, eating in the middle of class at school or during mass can be quite embarrassing.”* F, UK, 17 years old *“It is also embarrassing when we have stop what we’re doing and treat my hypo, so I often insist to treat them alone.”* *F, UK, 16 years old*
	Reduced enjoyment	10	Not able to enjoy the time, taking away the fun due to hypoglycaemia	Family, friends, hobbies, parties, sports, and travel	*“It's not as fun to do anything with them when I have low blood sugar.”* M, DK, 14 years old *“If I am hypoglycemic, it takes away the fun because I am not able to go along with everything or do not have the energy and then I miss a lot.”* F, GER, 16 years old *“I can't enjoy the time, which makes me sad.”* F, GER, 17 years old
	Burden	8	Feeling like a burden when others have to stop or help	Family, friends, sex and relationships, sleep and sports	*“When we go somewhere, I don't want to be a burden to them by having to stop what we're doing and start eating because I have a hypo.”* F, NL, 17 years old *“My mom does wake up when my pump goes off, then she comes to me and helps me. I think that's super nice, but I think it's a pity that she gets less sleep because of that and I sometimes feel guilty about it.”* F, NL, 13 years old
	Self-confidence	8	Positive (proud when solved hypoglycaemia) and negative (blaming oneself when hypoglycaemia)	Mood and self-confidence	*“When I have or have had a hypo, I think I am doing everything wrong with my diabetes and that I have to do my best more and pay a lot more attention. And that makes me insecure.”* F, NL, 17 years old

Theme	Codes	N[1]	Description	Domains impacted	Sample quotes[2]
					"Positively, I am always proud of myself when I have solved another hypo or other diabetes problem." M, NL, 16 years old
	Worries about other people's reactions	5	Worried that others will judge when hypoglycaemia	Family, friends, and mood	*"When I have a hypo with my Family, I often am afraid that I will just get angry with them or that I will disrupt an activity such as a hike, even though I know that I don't."* F, NL ,13 years old *"I most often avoid telling my friends if my blood sugar is low. I'm afraid they think I'm an inconvenience because I just have to do something else."* F, DK, 15 years old
	Mental health	4	Recurrent hypos having overall effects on emotional wellbeing, not only during hypoglycaemia	Mood and school	*"It affects my mental health a lot as I've broken down in lessons before because of having constant hypos."* F, UK, 15 years old
Social impact	Help and support	43	Others helping with treating, noticing, taking it into account, having sugar with them, having better relationships with them	Family, friends, hobbies, pets, school, sex and relationships, sleep and sports	*"I have good friends and they sometimes notice when I'm too low."* M, GER, 12 years old *"Help me with hypoglycaemia and make sure that I am doing the right thing, e.g., taking breaks when we walk, giving advice on lowering the basal rate or turning off the pump, or giving advice on the amount of carbohydrates I should take."* F, GER, 16 years old *"I don't worry about hypos at night because my mum gets ups very night to check me while I am asleep. I would worry a lot if she didn't. Especially after evening football training."* *"My best friend also has dextrose with him, just in case."* M, GER, 12 years old *"Positive, my friends recognize my hypos. This allows me to build a better relationship with them."* M, NL, 16 years old
	Mood changes affecting relationships	23	Getting annoyed at others easily, grumpy and frustrated with others when low, impacting on relationships	Family, friends, mood, parties, and sleep	*"I get irritable and start saying things I don't mean. My fellow human beings usually react to that and that just makes it worse."* F, GER, 17 years old *"Hypos often make me irritable and emotional which can cause arguments and tension."* F, UK, 16 years old

Theme	Codes	N[1]	Description	Domains impacted	Sample quotes[2]
					"I get upset sometimes at the smallest things my friends say when I have low blood sugar." F, DK, 12 years old
	Others' lack of understanding	19	Others not understanding that hypoglycaemia needs to be treated, not allowed to eat in class or take a break at work during hypoglycaemia, don't take it too seriously	Family, friends, mood, school, sports, and work	*"I remember in the smaller classes where I had to open a fruit bar and the teacher looked at me and said I should be quieter."* F, DK, 15 years old *"Some friends don't understand it that well either. They think you can keep going until we find a better time to eat."* F, NL, 17 years old *"It's hard to me to go upstairs to the staff room and have something to get my sugars back up as we're not meant to go up during shifts especially when we're busy."* F, UK, 16 years old
	Impact on others	15	Others stress when having hypoglycaemia, others overwhelmed when having hypoglycaemia, worries, others disadvantaged	Family, friends, school and sports	*"My family is sometimes stressed about it."* F, NL, 14 years old *"Teachers often find it scary when they experience for the first time that someone gets low blood sugar."* F, NL, 17 years old *"When we are about to go somewhere and I get a hypo, everyone has to wait until my sugars are good and I feel okay again. On vacation, for example, me and my parents were occupied a lot with preventing or treating hypos. This is not always nice for my sister and brother."* F, NL, 16 years old
	Arguments	3	Others getting involved and checking, which leads to tension, frustration leading to arguments (mainly with their mother)	Family and friends	*"My family gets very worried about me having hypos both at night and when I'm away from home, at school or with my friends. This causes tension because they often ask about my blood sugars and try to get involved."* F, UK, 17 years old
Cognitive impact	Concentration problems	35	Not able to concentrate at what you are doing (mostly at school) during and after hypoglycaemia, after nocturnal hypoglycaemia	Hobbies, mood, school and sports	*"It gets harder to concentrate in school when one's blood sugar is low."* M, DK, 14 years old *"I cannot play the clarinet when I'm low or concentrate on my music."* F, DK, 15 years old

Theme	Codes	N[1]	Description	Domains impacted	Sample quotes[2]
					"It is also very difficult to deal with hypos during an exam, for example. Not only does it take time to treat it, but I can no longer concentrate for about 15 minutes after a hypo." F, NL, 16 years old *"It is influenced by the fact that when I have had a hypo at night, I have poor sleep and not enough sleep and that I cannot pay much attention to school that day."* F, NL, 17 years old
Behavioural impact	Interruption of activities	43	Having to stop what you are doing, taking a break because of hypoglycaemia, missing out on things due to treatment of hypoglycaemia, can take a while before able to go back	Family, friends, hobbies, parties, school, sex and relationships, and work	*"When playing football and cycling: I have to take a break until the value is back in the target range. I feel like shit then and would much rather go on."* M, GER, 12 years old *"Do something with the family and you get low blood sugar then you have to stop what you are doing and do something about it, so the low blood sugar actually interrupts the good time you have together."* F, DK, 15 years old *"Constant checking/eating/drinking which can interfere with exercise."* F, UK, 16 years old *"Sometimes I've had to physically leave the classroom for 30 mins as a hypo made me feel extremely upset, dizzy, tired and distraught."* F, UK, 15 years old
	Limited participation	23	Not able to do things you would like to do, not able to participate or join and having to miss out on things	Diabetes, friends, health, hobbies, mood, pets, school, sports, and travel	*"I often can't really participate in sports in the sports club because my bloodsugar doesn't play along."* F, GER, 13 years old *"I cannot go out for walks with my dog as I really like."* M, DK, 14 years old *"Often not in school because of nightly hypoglycaemia and its consequences the next day."* F, GER, 17 years old *"If they are going to do something fun but you can't join because you have a hypo"* F, NL, 17 years old
	Reduced performance	15		School, sports, and work	*"Hypos distract me from my learning and have greatly affected my grades."*

	Theme	Codes	N[1]	Description	Domains impacted	Sample quotes[2]
				Bad grades, lower quality during sports, not efficient, making mistakes at work		F, UK, 16 years old *“If you get hypoglycaemia during a performance or competition, it has a negative effect on performance.”* F, GER, 12 years old
Risk of hypoglycaemia	*Reduced freedom*	-	36	Planning, taking everything into account, having to be careful, taking sugar with you, never fully concentrate because of awareness of low, no spontaneity, uncertainty about being able to treat hypoglycaemia in other situations, not being able to do the things you want to do in the way you would like to do them, worries of others when away, these worries leading to limitations / restrictions being placed on the adolescent with diabetes	Diabetes, family, friends, hobbies, parties, pets, school, sex and relationships, sleep, sports, and travel	*“Unfortunately, I am not allowed to stay overnight, and I only have one friend who invites me for a birthday because they are scared.”* M, GER, 12 years old *“I can never fully concentrate on the lesson because I have to always be aware of how I'm feeling in case I'm low.”* F, UK, 17 years old *“I am also often very occupied with doing everything I can to prevent a hypo during exercise. That takes a lot of effort.”* F, UK, 16 years old *“If I want to do something, I always have to pay attention to myself and my blood values, which is very annoying because I would like to do something like everyone else and that I should not always have to eat.”* F, NL, 13 years old
	Worries	-	29	Worried about having hypoglycaemia in various situations or while asleep, finding treatment, worried about embarrassment, others not knowing what to do, completing education	Diabetes, friends, hobbies, parties, school, sleep, and sports	*“I hardly get any sleep. I have a constant fear of going low in the middle of the night and not feeling it. It's so scary.”* F, UK, 15 years old *“I often worry that I will become hypo when out with friends or in a place where it is hard to sit and treat a hypo.”* F, UK, 16 years old *“When I am in lessons, I get nervous about leaving the class to treat a hypo. I also get very nervous about doing an important test and going low.”* F, UK, 13 years old
	Suboptimal glucose management	-	12	Keeping blood sugar levels higher before activity to prevent having to stop or because of FoH	Friends, health, hobbies, parties, sleep, sports, and work	*“I try to not let my levels go lower and try keep them higher when I'm with my friends because I don't want to stand out and be different. I don't want them to think I can't control it.”* F, UK, 17 years old *“Worried about blood sugar dropping, so I eat carbohydrates without insulin to avoid hypoglycaemia so then go hyperglycaemic, which is bad for my health.”*

Theme	Codes	N[1]	Description	Domains impacted	Sample quotes[2]
					F, UK, 15 years old
					"If I were around 7 before going to sleep, I would already always take the basal off or down. I am very afraid of hypos and I do not like to wake up with a hypo at all." F, NL, 14 years old

[1] N does not reflect the number of people, but the number of meaningful quotes

[2] F, female; M, male; DK, Denmark; Ger, Germany; NL, the Netherlands; UK, United Kingdom

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Authors' contributions

MC, MB, CH, FP, JS were involved in the development of the study concept. MC, MB, JC, SH, SA, BDG, NH, KFG, CH, FP, JS were involved in the design and protocol of the study. MC, MB and JLA collected data. MC and JLA analysed the data. MC prepared the first draft of the manuscript, with input from MB, FP, and JS. All authors are responsible for interpretation of data. All authors reviewed the manuscript for important intellectual content and approved the final version of the manuscript.

Disclosure statement

The authors report no conflicts of interest related to this manuscript

Ethical approval

The study received ethical approval in all participating countries (University of Southern Denmark: 19/78420; UK Health and Social Care: 20-NI-0054; Radboud University Medical Centre; 2020-6587 and German Society for Psychology: HermannsNorbert2020-05-12VA).