Cedar

Healthcare Technology Research Centre

RX139 HERO

Hypoglycaemic episode resource outcomes project report

Authors: Dr James Evans
Ruth Poole
Dr Grace Carolan-Rees
Dr Alistair Ray

Date: 02/02/18

Version: V1.0

Summary

The Hypoglycaemic Episode Resource Outcomes (HERO) project had two main aims:

- to determine healthcare resource use caused by hypoglycaemic episodes in patients with type 1 diabetes
- to present results on the effect of fear of hypoglycaemia on individuals with type 1 diabetes

The project used linked healthcare records obtained from the SAIL databank in order to determine the number of hypoglycaemic episodes in patients with type 1 diabetes. These data were combined with type 1 registration data from the National Diabetes Audit in order to determine the cumulative incidence of hypoglycaemia in type 1 diabetes.

In order to obtain information on the impact of fear of hypoglycaemia on individuals with type 1 diabetes, a systematic review was carried out. The systematic review included studies presenting results for FoH in adults with type 1 diabetes, children with type 1 diabetes and parents of children with type 1 diabetes.

This report presents the results of Cedar's analysis of linked healthcare records and systematic review to answer the research recommendations from NICE DG21 "Integrated sensor-augmented pump therapy systems for managing blood glucose levels in type 1 diabetes (the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system)".

Contents

List of tables

List of tables

Abbreviations

A&E	Accident and Emergency
ALF	Anonymous linking field
ANOVA	Analysis of variance
ASI	Anxiety sensitivity index
ASSIA	Applied Social Sciences Index and Abstracts
AUDIT	Alcohol use disorders identification test
BNI	British Nursing Index
CAV	Cardiff and Vale
CCI	Charlson co-morbidity index
CCG	Clinical commissioning group
CEA	Cost-effectiveness analysis
CG	Clinical guidance
CGM	Continuous glucose monitor
CIDS	Confidence in diabetes self-care
CINAHL	Cumulative Index of Nursing and Allied Health Literature
CSII	Continuous subcutaneous insulin infusion
DAC	Diagnostic advisory committee
DEMS	Diabetes electronic management system
DFRQ	Diabetes family responsibility questionnaire
DG	Diagnostic guidance
DM	Diabetes mellitus
DQOL	Diabetes quality of life
EDDS	Emergency department dataset
EED	Economic Evaluation Database
EQ-5D	EuroQoL-5D
EMR	Electronic medical record
FCQ	Fear of complications questionnaire
FoH	Fear of hypoglycaemia
GAD	Generalised anxiety disorder
GP	General practitioner
HADS	Hospital anxiety and depression scale
HERO	Hypoglycaemic Episode Resource Outcomes
HES	Hospital episode statistics
HFS	Hypoglycaemia fear survey
HFS-P	Hypoglycaemia fear survey for parents
HFS-P-YC	Hypoglycaemia fear survey for parents of young children
HQIP	Healthcare Quality Improvement Partnership
HIRU	Health Information Research Unit
HMIC	Health Management Information Consortium
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HSCL-25	Hopkins Symptom Checklist-25 item
HypoA-Q	Hypoglycaemia Awareness Questionnaire
HTA	Health Technology Assessment
IDDM	Insulin dependent diabetes mellitus

IAH	Impaired awareness of hypoglycaemia
ICD-10	International classification of diseases, version 10
IGRP	Information Governance Review Panel
IPG	Interventional procedure guidance
LAS	London Ambulance Service
LHB	Local health board
MH	Mild hypoglycaemia
NaDIA	National Diabetes Inpatient Audit
NDA	National Diabetes Audit
NDFA	National Diabetes Footcare Audit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPID	National Pregnancy in Diabetes
NWIS	NHS Wales Informatics Service
PAID	Problem Areas in Diabetes Scale
PDQOL	Parent Diabetes Quality of Life Questionnaire
PedsQL	Paediatric Quality of Life Inventory
PEDW	Patient episode database for Wales
PIP	Paediatric Inventory for Parents
PREM	Patient reported experience measure
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROM	Patient reported outcome measure
PSS	Perceived stress scale
QALY	Quality adjusted life year
QoL	Quality of life
R&D	Research and development
RCT	Randomised controlled trial
SAIL	Secure Anonymised Information Linkage
SD	Standard deviation
SED	Self-efficacy for diabetes scale
SES	Socio-economic status
SH	Severe hypoglycaemia
SLC	Seizures or loss of consciousness
SMBG	Self-monitoring of blood glucose
SPS	Social phobia scale
SPSS	Statistical package for the social sciences
SQL	Structured query language
STAIC	State-Trait Anxiety Inventory for Children
STPI	State-Trait Personality Inventory
SURE	Specialist Unit for Review Evidence
T1D	Type 1 diabetes
T2D	Type 2 diabetes
UHB	University health board
UHW	University Hospital of Wales
UK	United Kingdom
USA	United States of America

VAS	Visual analogue scores
W-BQ28	Wellbeing Questionnaire-28
WDS	Welsh demographic service
WHO-5	World Health Organisation well-being index
WoS	Web of Science

HERO – Hypoglycaemic Episode Resource Outcomes

1 Introduction

1.1 Project aims

The HERO project aims to address recommendations raised by the diagnostic advisory committee (DAC) for further research for the development of diagnostics guidance 21 (DG21): Integrated sensor-augmented pump therapy systems for managing blood glucose levels in type 1 diabetes (the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system).

The two main aims of the HERO project were as follows:

- to assess the impact of episodes of hypoglycaemia in patients with type 1 diabetes (T1D) on healthcare resource use
- to determine the impact of fear of hypoglycaemia (FoH) on an individual with T1D

This report presents the results of Cedar's work on the impact of episodes of hypoglycaemia on healthcare resource use in people with T1D. The report also presents a review on the impact of FoH on an individual with T1D. The report presents the methods undertaken in order to address the aims, Cedar's results and a discussion of these results.

1.2 Diabetes

Diabetes is a metabolic disorder which leads to high blood glucose caused by an abnormal metabolism of carbohydrates. This high blood glucose leads to a range of complications including diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, cardiovascular disease, diabetic ketoacidosis, hyperglycaemia and hypoglycaemia. It is currently estimated that there are around 3.5 million people in the UK living with diabetes (Diabetes UK Facts and Stats: 2015).

There are two main types of diabetes:

- Type 1 diabetes
- Type 2 diabetes

1.2.1 Type 1 diabetes

T1D is an autoimmune disease whereby the body's β-cells of the islets of Langerhans in the pancreas are attacked by the body's immune system. This attack leads to the destruction or damage of the β-cells resulting in a reduction and eventual elimination of their ability to produce insulin (van Belle 2011). Subsequently the individual's body loses its ability to control blood glucose levels. The person's blood glucose levels become too high in the absence of this control. Therefore, insulin therapy is administered in an effort to control blood glucose levels. It is currently estimated that around 10% of all diabetes diagnoses are T1D. With the current estimate of 3.5 million people living with diabetes in the UK, around 350,000 people are living with T1D in the UK.

1.2.2 Type 2 diabetes

Type 2 diabetes (T2D) arises from the interplay between environmental, genetic and behavioural risk factors. People with T2D show insulin insensitivity as a result of insulin resistance, decreasing insulin

production and eventual failure of the β-cells of the pancreas. Unlike T1D, a number of lifestyle factors, including a sedentary lifestyle, are associated with the development of T2D (Olokoba et al. 2012). It is currently estimated that around 90% of all diabetes diagnoses are T2D. With the current estimate of 3.5 million people living with diabetes in the UK, around 3,150,000 people are living with T2D in the UK.

1.3 Hypoglycaemia

Hypoglycaemia occurs when blood glucose is too low. For people with T1D blood glucose is controlled through insulin administration. In these people there is a risk of using too much insulin and causing a drop in blood glucose. A person is deemed to be hypoglycaemic if their blood glucose falls below 4 mmol/L (NHS Choices). Initial symptoms of hypoglycaemia include:

- feeling hungry
- sweating
- tingling lips
- dizziness
- feeling tired
- palpitations
- turning pale

It is possible for friends and family to spot these initial signs of hypoglycaemia and to administer treatment (eating or drinking a fast acting carbohydrate) to normalise the person's blood glucose levels. These are often termed mild hypoglycaemic events and usually do not require additional treatment from a medical professional. However, if left untreated more serious symptoms can develop and this is called severe hypoglycaemia. The symptoms include:

- blurred vision
- confusion
- slurred speech
- seizures
- loss of consciousness
- coma

If a person is experiencing severe hypoglycaemia it will often require treatment from a medical professional. This treatment may be administered by paramedics or the person may require hospitalisation. Severe hypoglycaemic events can lead to coma and in some instances death.

1.3.1 Fear of hypoglycaemia

FoH is where a person is afraid/worried about hypoglycaemia. Excessive FoH can lead an individual to adopt poor adherence behaviours such as maintaining an elevated blood glucose level or over-treating early symptoms of hypoglycaemia (Cox 1987). It has been argued that FoH arises from "concerns regarding insulin injections, dietary restrictions, risk of future complications and employment prospects" (Strachan 2005). FoH can have a detrimental effect on the quality of life (QoL) of an individual. In addition, FoH is not restricted to the individual at risk of hypoglycaemia but can also affect friends and family. This can have a detrimental effect on their lives also.

2 Project methods

2.1 Project approvals

2.1.1 Local project approval

Cedar sought local project approval from Cardiff and Vale University health board (CAV UHB). The project was discussed with the CAV UHB research and development (R&D) department. The R&D department advised Cedar that using linked data to determine the impact of hypoglycaemic episodes on healthcare resource use falls under service evaluation. However, using patient reported outcome measures (PROM) to assess FoH was deemed to be research and would require full research approvals. Cedar obtained service evaluation approval from CAV UHB in order to determine the impact of hypoglycaemic episodes on healthcare resource use and decided to submit an application for research approval for FoH determination if appropriate at a later date (Cedar did not pursue this (see section 2.5)).

2.1.2 London Ambulance Service

Cedar contacted the London Ambulance Service (LAS) to determine whether the information we required was held by the service and also to determine the feasibility of sharing any information. The LAS held some of the information Cedar required and was able to share the information subject to approval. The LAS provided an application form to complete and return. Cedar completed the necessary application form and provided evidence that local R&D designated the project as service evaluation. The project was then approved and Cedar was able to receive the necessary information from the LAS.

2.1.3 SAIL databank

This project required the use of routinely-collected data. The Secured anonymised information linkage (SAIL) databank holds patient-level data for the population of Wales. Applications to use SAIL data are reviewed by an independent Information Governance Review Panel (IGRP), which includes patient/public representation. Cedar has an agreement in place with the SAIL databank for NICE commissioned projects. Therefore, our project proposals are subject to a fast-track approval system. In the application Cedar had to specify the datasets we required and justify what the dataset would be used to gain IGRP approval. Cedar also requested the use of a dataset outside of SAIL databank's core datasets, the Brecon Register of Children with Diabetes (Brecon register). This required an additional approval process (see section 2.1.4). Cedar received approval for the project once the additional approvals for the Brecon register were granted.

2.1.4 Brecon Register of Children with Diabetes

The Brecon register is outside of the SAIL databank's core datasets and therefore requires additional approvals if it is to be used. In order to gain approval for the use of this dataset, the HERO project needed to be presented to a data guardian for the register. Cedar also had to agree to present the project to a lab group at the University Hospital of Wales (UHW) and also to present the project to the Brecon Group upon completion. Once Cedar agreed to the requests of the Brecon data guardian, use of the dataset was granted. The SAIL databank was then able to finalise the project approval through their IGRP process.

2.2 Linked data from the SAIL databank

The SAIL databank holds routinely-collected, patient-level data for the population of Wales. Analysts at the SAIL databank are able to link datasets using a unique, anonymised identifier for an individual. This identifier is known as the Anonymous Linking Field (ALF). The following datasets, held at the SAIL databank, were used for this project:

- Brecon Register of Children with Diabetes (Brecon register) – not a core dataset
- Patient Episode Database for Wales (PEDW) – core dataset
- Primary Care general practitioner (GP) dataset (GP dataset) – core dataset
- Emergency department Data Set (EDDS) – core dataset
- Welsh Demographic Service (WDS) – core dataset

2.2.1 Cedar's proposed SAIL data workflow

Cedar held many meetings with the analysts assigned to this project in the first few weeks following the project's approval. This included a detailed description of what Cedar required and how this would be achieved.

Cedar's initial proposed workflow using SAIL's datasets for T1D diagnosis has been presented in Figure 1. For this workflow Cedar envisaged using the PEDW, EDDS and GP dataset to obtain a diagnosis of T1D and to then determine the number of hypoglycaemic events in each dataset. Demographic information (e.g. death, gender, birth and age) would then be obtained from the WDS for patients identified in the datasets to produce a data extract.

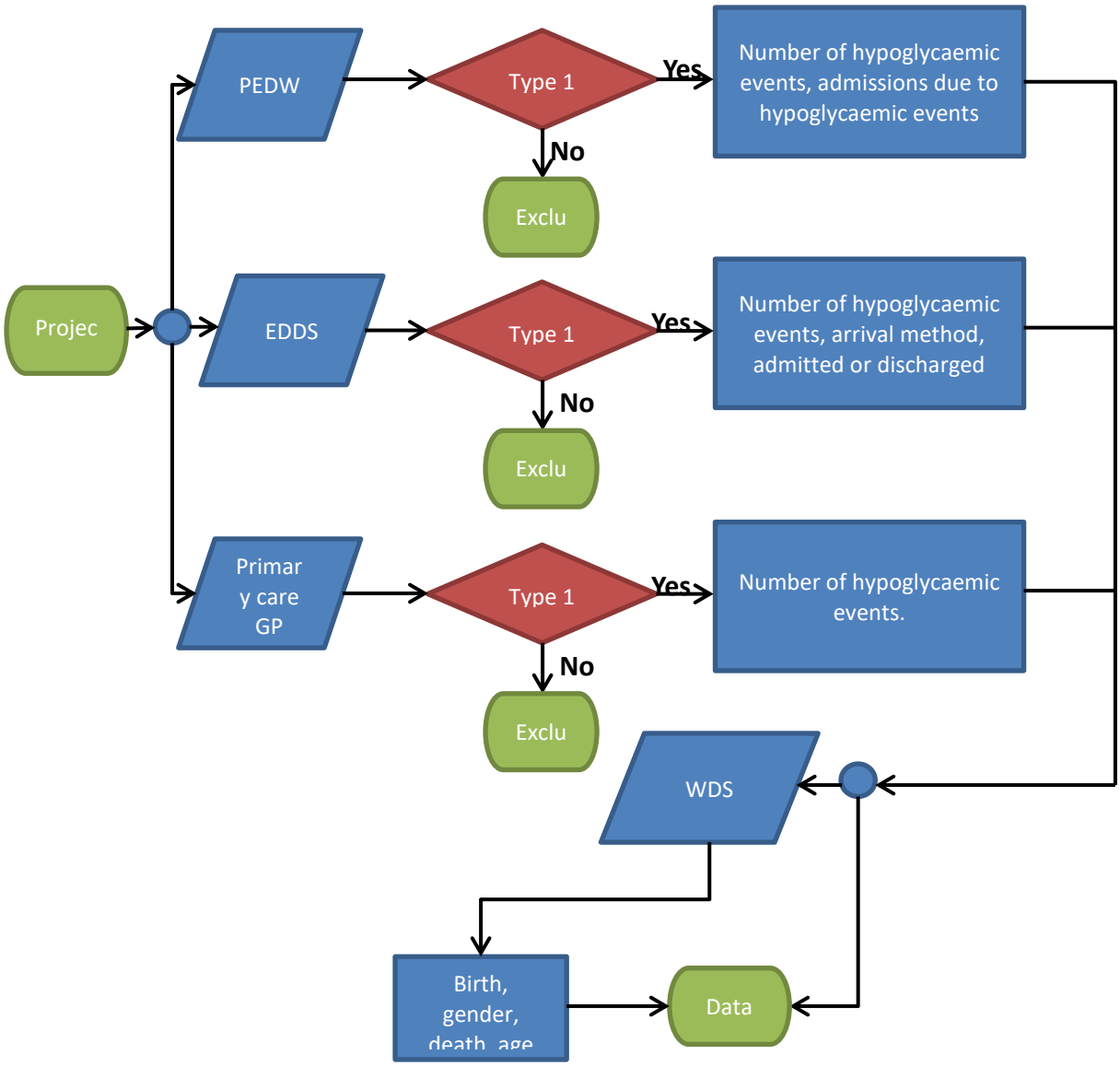

Figure 1| Cedar's proposed workflow at the start of the project using SAIL datasets as the source of T1D diagnosis.

Cedar also envisaged using the Brecon register for T1D diagnosis and then to determine the number of hypoglycaemic events in the PEDW, EDDS and Primary GP dataset (Figure 2). For this workflow patients with T1D diagnosed in the Brecon register were be linked to the PEDW, EDDS, GP dataset and WDS. This would allow Cedar to determine the number of hypoglycaemic episodes and to obtain demographic information for these patients in a data extract.

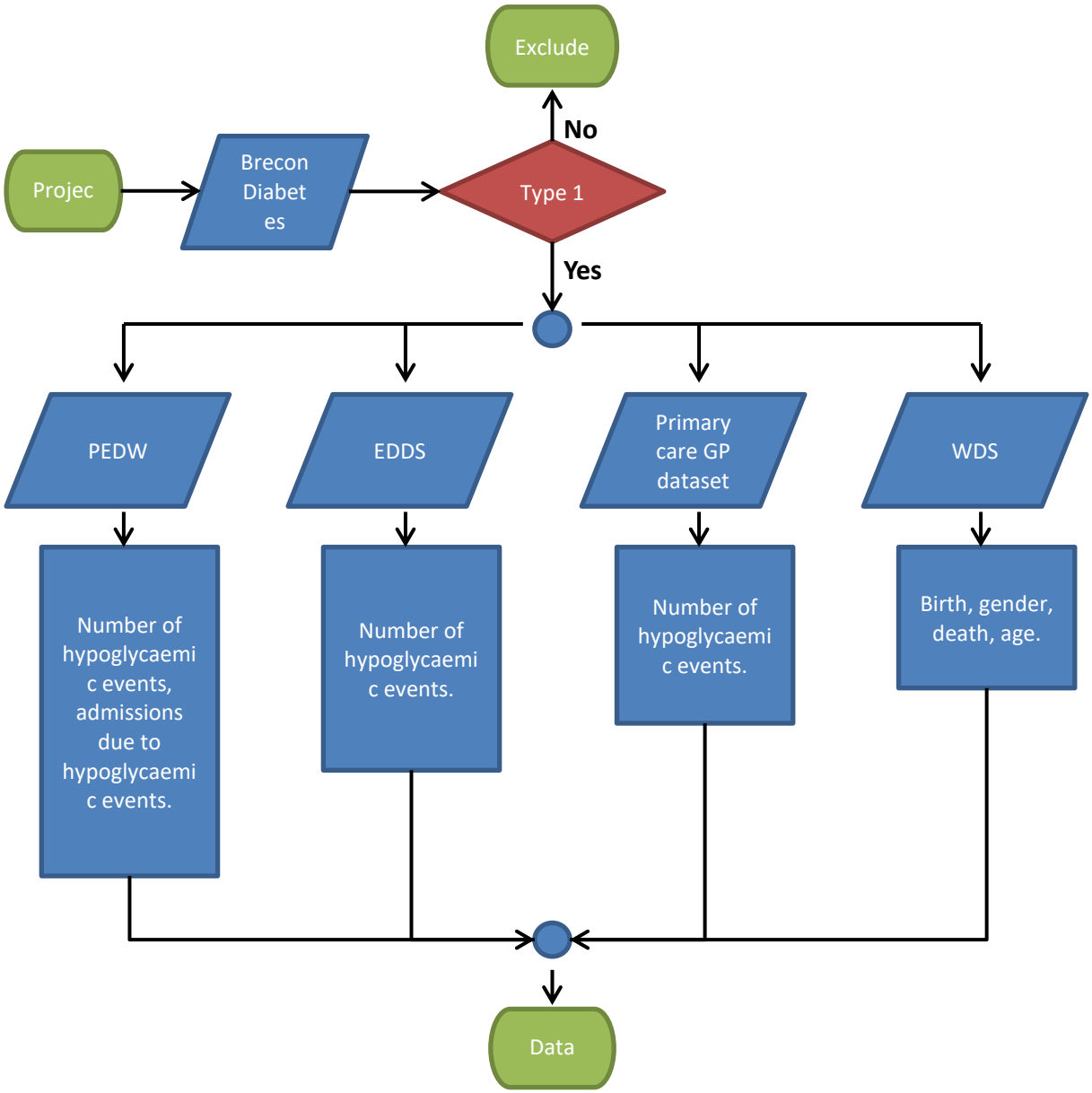

Figure 2| Cedar's proposed workflow at the start of the project using the Brecon register as the source of T1D diagnosis.

2.2.2 Final SAIL data workflow

2.2.2.1.1 EDDS

Following discussions between Cedar and SAIL analysts it was decided that the use of the EDDS would not be feasible for this project. The method of recording information in the EDDS was not granular and did not provide the necessary information to determine if a person had T1D or a hypoglycaemic episode. The final SAIL data workflow therefore did not include the EDDS (Figure 3).

The EDDS codes diabetes under an "Endocrinological Conditions" category in its "Accident and Emergency Diagnosis Types" record ID. However, the type of diabetes is not specified. Furthermore, no code for hypoglycaemia exists. There are codes for Glasgow coma score under the "Head injury" category and there are codes for "Seizure/convulsion" under the "Neurological conditions" category. However, these did not appear to be appropriate to Cedar and the SAIL analyst. This was further confounded by the lack of granularity with regards to diabetes type. A full list of the codes used in the EDDS under its "Accident and Emergency Diagnosis Types" record ID has been presented in Appendix 1.

2.2.2.1.2 Brecon Register of Children with Diabetes

Following discussions between Cedar and SAIL analysts it was decided that the Brecon register would be used for validation purposes. The Brecon register is a register of children with diabetes in Wales and was set up in 1996 (see section 2.2.6). Therefore, the register does not contain information on children born before 1996. Cedar felt that using this database for T1D diagnosis would lead to patients with T1D being missed once linked with PEDW and GP dataset. It was therefore decided that the register could be used to validate both of these datasets by providing an estimate of diagnosis error (Figure 4).

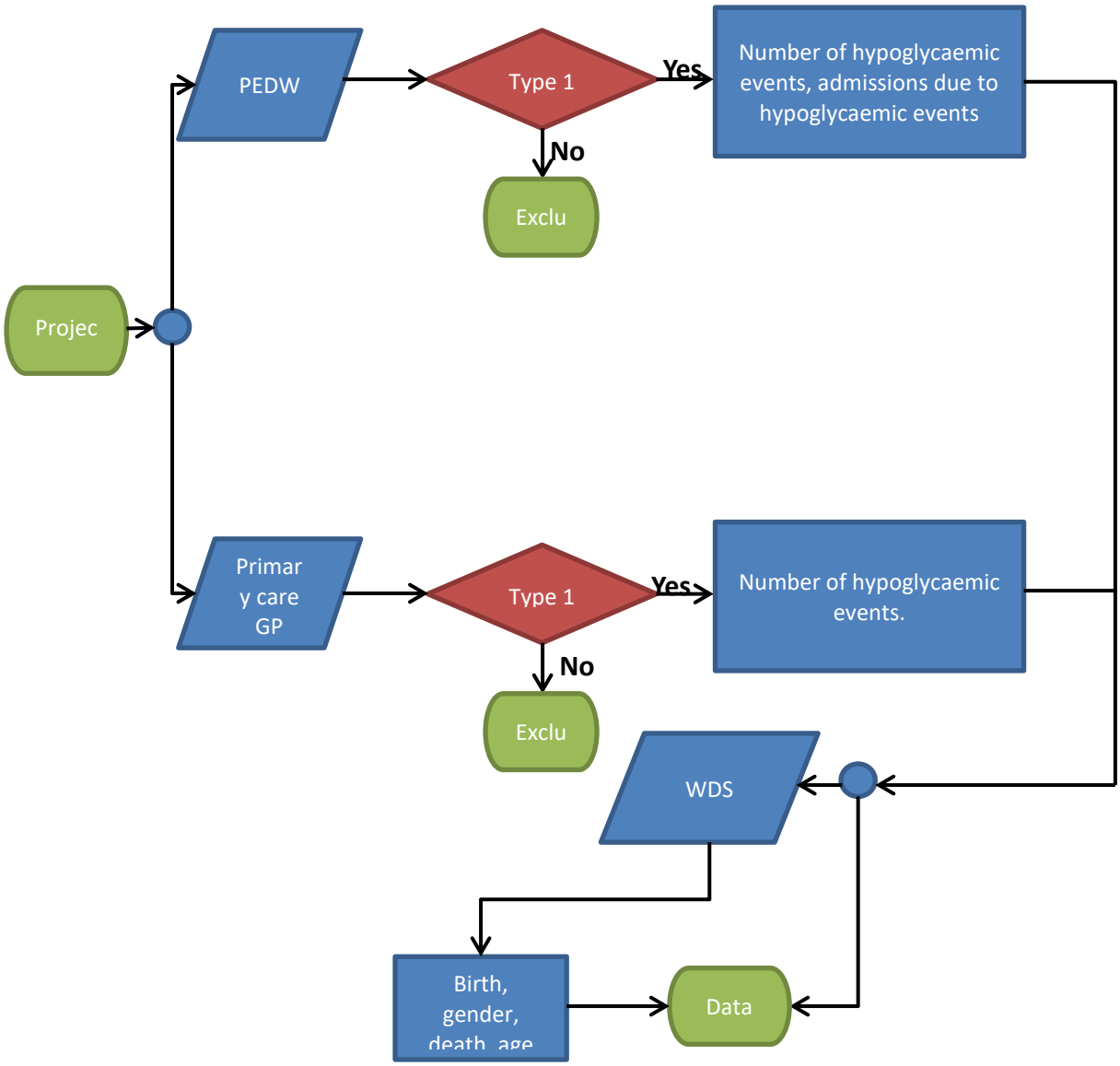

Figure 3| Final data workflow used by SAILanalsyt and Cedar.

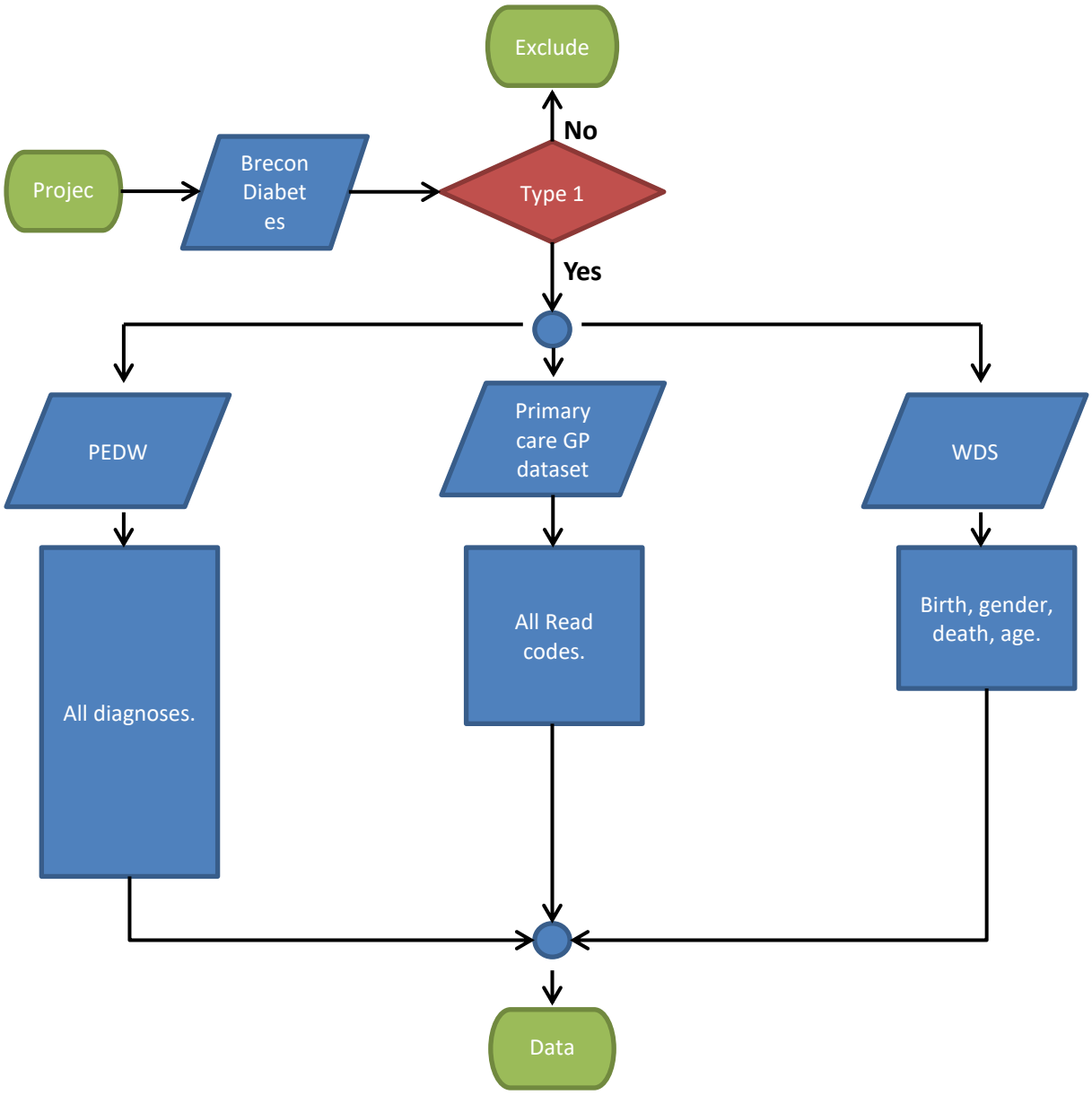

Figure 4| Final Brecon register data workflow used by SAIL analyst and Cedar.

2.2.3 Work carried out by Cedar and the SAIL analyst for each dataset.

2.2.3.1 PEDW data

The PEDW dataset contains NHS Wales hospital admissions, including inpatients and day-cases. The dataset contains clinical and attendance information for all hospital admissions across Wales including diagnoses and operations performed. Data collection and coding are carried out at each hospital whereby hand written patient notes are transcribed by a clinical coder into medical coding terminology. The ICD-10 coding system is used for the PEDW dataset.

2.2.3.1.1 Identification of ICD-10 codes

Cedar liaised with the NHS Wales Informatics Service (NWIS) in order to identify relevant ICD-10 codes. NWIS identified codes for the following diagnoses:

- T1D
- Hypoglycaemia
- Insulin and oral hypoglycaemic drug
- Accidental poisoning

In addition to identifying individual codes, NWIS were able to advise on combining ICD-10 codes in order to identify hypoglycaemic episodes in people with T1D. For the PEDW dataset there is a convention for coding hypoglycaemia in patients with T1D which NWIS shared with Cedar. The combinations were checked by Prof. John Gregory, a Professor in paediatric endocrinology at the UHW, for applicability. Combinations of ICD-10 codes were grouped into 4 categories:

- hypoglycaemic coma in patient with T1D
- hypoglycaemia (without coma) in patient with T1D
- hypoglycaemic coma in patient with T1D following accidental overdose of insulin
- hypoglycaemia (without coma) in patient with T1D following accidental overdose of insulin.

A full list of the ICD-10 codes and the combinations used has been presented in Appendix 2. The ICD-10 code combinations were then shared with analysts at SAIL in order to obtain the necessary information.

2.2.3.1.2 Work carried out by the SAIL analyst

The PEDW cohort was based on patient spell data with admissions between 01/01/2010 and 31/12/2015. The SAIL analyst then joined the cohort to episode data to produce “flags” in the dataset based on the 4 ICD-10 code categories identified by Cedar. It is worth noting that T1D diagnoses were not separated from hypoglycaemia diagnoses. A new dataset was created with the 4 categories identified by Cedar, each with a binary coding (0 = ICD-10 codes do not match flag, 1 = ICD-10 codes match flag). Data were then collated in a new dataset by summing the number of times an individual matched the flags within a year (effectively summing the number of times “1” appeared in each of the 4 categories for an individual). We were therefore able to determine the number of hypoglycaemic episodes experienced by an individual within a year. The final PEDW dataset contained a single row for each identified individual with the number of hypoglycaemic episodes experienced annually from 01/01/2010-31/12/2015.

2.2.3.2 Work carried out by Cedar analyst

The final PEDW dataset was imported into SPSS 22 (IBM Corporation). The dataset was reduced by removing individuals where the 4 categories identified by Cedar were empty. Therefore, those who did not have a diagnosis of T1D and hypoglycaemia were removed. The dataset was then split into 5 new datasets for each year (2010-2015). Frequency tables were produced for each of the 4 categories in each of the year datasets. The frequency tables were imported into Microsoft Excel to calculate the total number of hypoglycaemic episodes which occurred for each year. The data were presented in tables and bar plots.

2.2.4 Primary care GP dataset

The Primary care GP dataset combines information from individual GP practices. Each patient has an electronic health record at their GP practice. This record includes test results, diagnoses, prescribed treatment and referrals. Data entry is carried out by a GP during a patient consultation and test results are electronically transferred from secondary care systems. Read codes are used for coding in this dataset. Read codes are not as precise as the ICD-10 codes used in PEDW. Local Read codes are sometimes used and two different versions of Read codes may be used (version 2 and version 3).

2.2.4.1 Identification of Read codes

NWIS clinical coders were unable to offer advice on coding in the Primary care GP dataset as Read codes are entered at individual GP practices. In addition, multiple Read codes may be used for the same diagnosis/procedure. Therefore, Cedar carried out its own search for Read codes that could be used for this project. We combined Read codes identified using the NHS Read code browser, 2 published papers (Khunti et al. 2015 and Zhong et al. 2017) and Read codes identified in the National Diabetes Audit (NDA) 2011-2012 (available at: http://content.digital.nhs.uk/media/13053/2011-2012-Primary-Care-Extraction-Specification/pdf/CASU_NDA_2011-2012_primary_care_extraction_specification_v7.9.pdf). Version 2 Read codes were also screened for version 3 codes using the NHS Read code browser.

Read codes were grouped into 5 categories:

- T1D
- Hypoglycaemia
- Hypoglycaemia with coma
- Other hypoglycaemia
- T1D with hypoglycaemic coma (a specific, single Read code).

A full list of Read codes used can be found in Appendix 3 – Read codes used by Cedar and the SAIL analyst for the GP dataset.

2.2.4.2 Work carried out by SAIL analyst

The GP patient table and GP event tables were imported by the SAIL analyst and merged. Event dates between 01/01/2010 and 31/12/2015 were considered. The SAIL analyst searched this dataset for all the Read codes identified by Cedar and produced a list to show which codes were identified within the dataset. Cedar then removed any unused codes and split identified combinations of Read codes into the 5 categories noted above. The SAIL analyst reduced the number of records in the merged GP dataset by only including records where Read codes matched those supplied by Cedar.

The analyst created 5 “flags” (categories), based on the categories supplied by Cedar, each with a binary coding (0 = Read codes do not match flag, 1 = Read codes match flag). Data were then collated in a new dataset by summing the number of times an individual matched the flags within a year (effectively summing the number of times “1” appeared in each of the 5 categories for an individual). The final GP dataset contained a single row for each identified individual with the number of visits to the GP for hypoglycaemia or visit due to their T1D annually from 01/01/2010-31/12/2015.

2.2.4.3 Work carried out by Cedar analyst

Initial investigation of the dataset by the Cedar analyst showed individuals with Read codes for T1D in one year followed by Read codes for hypoglycaemia in another year. Therefore, a new binary variable was created to identify if an individual had a Read code for T1D from 2010-2015 (0 = “no T1D Read code from 2010-2015”, 1= “≥1 T1D Read code from 2010-2015”). Due to the variability in coding using Read codes, the Cedar analyst also created binary variables for a T1D diagnosis from PEDW or from the Brecon register (0= “no T1D diagnosis”, 1= “T1D diagnosis”. For individuals with a Read code for T1D from 2010-2015 in the GP dataset, T1D diagnosis from PEDW or T1D diagnosis from the Brecon register it was assumed that any subsequent hypoglycaemia Read codes were as a result of their T1D.

Individuals with 0s in the new variables created by the Cedar analyst were removed from the dataset leaving only individuals with T1D. The dataset was then split into 5 new datasets for each year (2010-2015). Frequency tables were produced for each of the 5 categories in each of the year datasets. The frequency tables were imported into Microsoft Excel to calculate the total number of hypoglycaemic episodes which occurred for each year. The data were presented in tables and bar plots.

2.2.5 Calculation of mean number of hypoglycaemic episodes per person using PEDW and GP dataset data

The mean number of hypoglycaemic episodes per person was calculated for PEDW and GP datasets for each year. This was calculated by dividing the number of hypoglycaemic episodes for each year by the number of individuals who had a hypoglycaemic episode.

2.2.6 Brecon Register of Children with Diabetes

The Brecon register of children with Diabetes (Brecon register) was set up by the Brecon Group in 1996 and is a register of children with diabetes in Wales. Capture-recapture techniques have shown that the register has <97% completeness. This register was used by Cedar as a means to validate the GP and PEDW datasets.

2.2.6.1 Work carried out by SAIL analyst

The SAIL analyst linked the patients with T1D from the Brecon dataset to the PEDW and Primary care GP cohorts previously generated by the analyst (from 01/01/2010-31/12/2015). For the PEDW dataset all diagnoses from hospital admissions by patients in the Brecon register were exported into a new table for analysis by Cedar. For the GP dataset all Read codes (events) generated from GP visits by patients in the Brecon register were exported into a new table for analysis by Cedar.

2.2.6.2 Work carried out by Cedar on the Brecon PEDW validation dataset

The Cedar analyst copied all diagnoses into a single column in Microsoft Excel. This single column of diagnoses was imported back into SPSS 22 (IBM Corporation) where a frequency table was created. ICD-10 codes not relating to diabetes were then removed to leave a frequency table of diabetes ICD-10 codes. The Cedar analyst then split the ICD-10 codes into the following categories:

- T1D
- T2D
- Other specified diabetes
- Gestational diabetes
- Pre-existing T1D in pregnancy
- Pre-existing T2D in pregnancy
- Unspecified pre-existing diabetes in pregnancy
- Unspecified diabetes in pregnancy

The Cedar analyst calculated the proportion of ICD-10 codes in each of the categories in order to determine an estimate of diabetes misdiagnosis in the PEDW dataset. Data were presented in tables.

2.2.6.3 Work carried out by Cedar on the Brecon GP validation dataset

The GP dataset contains a description column for each Read code. The Cedar analyst created a frequency table of the Read code descriptions in the dataset. The frequency table was manually searched and Read code descriptions were categorised as follows:

- Generic diabetes Read codes
- T1D Read codes
- T2D Read codes.

The Cedar analyst calculated the proportion of Read codes in each of the categories in order to determine an estimate of diabetes misdiagnosis in the GP dataset. The data were presented in tables.

2.2.7 Demographic information using WDS

The WDS holds administrative data on individuals that use NHS services in Wales. The data in this dataset are obtained from GP practices.

2.2.7.1 Work carried out by SAIL analyst

Individuals identified in both the PEDW and GP datasets were linked to demographic information held in the WDS. Linking these datasets allowed information on age and gender to be merged with PEDW and GP datasets.

2.3 London Ambulance Service

An analyst from the LAS R&D department provided data on the number of hypoglycaemic episodes from 01/11/2011-31/10/2016. It is worth noting that the analyst was not able to obtain the reason for the hypoglycaemic episode as the database which holds this information does not contain that level of information. Therefore, the data are not likely to be restricted to hypoglycaemic episodes in

people with T1D. The data were presented by gender and age. Data on whether the patient was conveyed to hospital or not were also presented.

2.3.1 Work by Cedar analyst

The Cedar analyst reworked the data to give the total number of hypoglycaemic episodes in 2012-2015. Data were presented in the form of tables and bar plots where appropriate.

2.4 Diabetes audits

Annual clinical audits of diabetes care in England and Wales have been conducted as part of the National Clinical Audit Programme. The programme is managed by the Healthcare Quality Improvement Partnership (HQIP) and is funded by NHS England. Audits concerning diabetes are part of the National Diabetes Audit (NDA) programme and are available online (http://content.digital.nhs.uk/nda). The NDA programme comprises a number of audits including:

- Core NDA
- National Diabetes Inpatient Audit (NaDIA)
- National Pregnancy in Diabetes (NPID)
- National Diabetes Footcare Audit (NDFA)

2.4.1 Core National Diabetes Audit

For this project, data from the Core NDA were used in order to determine the number of T1D registrations in Wales. Individual data submitted by Clinical Commissioning Groups (CCGs) in England were also used in order to determine the number of T1D registrations in London, specifically the CCGs covered by the LAS. This was used by Cedar alongside data obtained from the LAS, in order to determine the incidence of hypoglycaemic episodes requiring treatment from an ambulance. In addition, the number of T1D registrations in England has been presented by Cedar.

2.4.2 National Diabetes Inpatient Audit

The NaDIA 2016 report (available from: https://digital.nhs.uk/media/30626/NaDIA-2016-Full-Report/Any/nati-diab-inp-audi-16-rep) was used by Cedar to present data on the numbers of T1D inpatients having one or more severe hypoglycaemic episode from 2010-2016 (no audit was carried out in 2014).

2.5 Fear of hypoglycaemia

2.5.1 All Wales Patient Reported Outcome Measures, Patient Reported Experience Measures and Effectiveness programme

Cedar researched the feasibility of using data from the All Wales PROMs, PREMs and Effectiveness programme (https://proms.nhs.wales) to obtain information on FoH for this project. A team of Cedar Researchers is contributing to the design, analysis and reporting of this programme. However, following discussions with the researchers at Cedar it was noted that PROMs and PREMs for people with diabetes are not currently being collected. Therefore, the information required was not available. Cedar therefore conducted a systematic review of the literature in order to obtain the necessary information (see section 2.5.2).

2.5.2 Systematic review of the literature

Due to the lack of available data from the All Wales PROMs, PREMs and Effectiveness programme Cedar conducted a systematic review in order to obtain the necessary information on FoH for this project. The literature search conducted by Cedar's information specialist was kept purposely broad in order to identify information on the incidence of hypoglycaemia in people with T1D in the UK and any UK based studies on its associated resource use. The literature search was conducted in Applied Social Sciences Index and Abstracts (ASSIA), British Nursing Index (BNI), Cumulative Index of Nursing and Allied Health Literature (CINAHL), Cochrane Library (Health Technology Assessment (HTA) and NHS Economic Evaluation Database (EED) only), EconLit, Embase, Health Management Information Consortium (HMIC), Medline, Medline in Process, PsycINFO, Pubmed ('epub ahead of press'), Scopus, Web of Science (WoS), Cost-effectiveness Analysis (CEA) registry, EconPapers and IDEAS. A full search strategy and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram has been presented in Appendix 5 – Search strategy for Cedar's systematic review.

2.6 Calculation of hypoglycaemia cumulative incidence

2.6.1 Calculation of hypoglycaemia incidence using SAIL and NDA data

The number of hypoglycaemic episodes in people with T1D identified in the PEDW datasets and the number of GP visits for hypoglycaemia in people with T1D was combined for each year. The number of people with T1D was obtained from NDA data for 2015-2016 for Welsh Local Health Boards (LHB) (available from: https://digital.nhs.uk/media/30457/National-Diabetes-Audit-Report-1-Wales-LHB-Level-Spreadsheet-2013-15/Any/nati-diab-audi-rep1-wal-lhb-data-tab-2014-16_v2). The reason for using data from 2015-2016 was due to the 100% participation rate across Wales for this audit year and this therefore gives a better indication of the number of people in Wales with T1D. The cumulative incidence was calculated by dividing the number of hypoglycaemic episodes for 2015 by the number of people with T1D in Wales.

2.6.2 Calculation of hypoglycaemia incidence using LAS and NDA data

The LAS covers a total of 32 CCGs across London. The number of people with T1D was obtained from NDA data for 2015-2016 for individual CCGs (available from: https://digital.nhs.uk/media/30456/National-Diabetes-Audit-Report-1-England-CCG-GP-Level-Spreadsheet-2014-16/Any/nati-diab-audi-rep1-eng-ccg-data-tab_2014-16_v2). The reason for using data from 2015-2016 was due to a higher participation rate then previous years and this therefore gives a better indication of the number of people in London with T1D. The cumulative incidence was calculated by dividing the number of attendances for hypoglycaemic episodes for 2015 by the number of people with T1D in the London area for 2015-2016.

2.7 Data visualisation

Bar plots for this project were generated using the ggplot2 package (Wickam 2009) in R statistical software (R Core Team 2015). Each plot was generated using a custom script. Results from the NaDIA 2016 were reproduced in Microsoft Excel.

3 Results

3.1 Individuals identified in PEDW and GP datasets

A total of 1,677,327 unique individuals were identified in the PEDW dataset whilst 2,048 unique individuals were identified in the GP dataset. A total of 8,842 individuals appeared in both datasets (Figure 5). The GP dataset was reduced by the SAIL analyst to only include individuals where T1D or hypoglycaemia Read codes were present and this lead to the lower number of individuals in the Venn diagram presented. The format of the GP dataset is different to that of the PEDW dataset and the GP dataset was reduced in this manner to make the dataset useable for the analyst at Cedar.

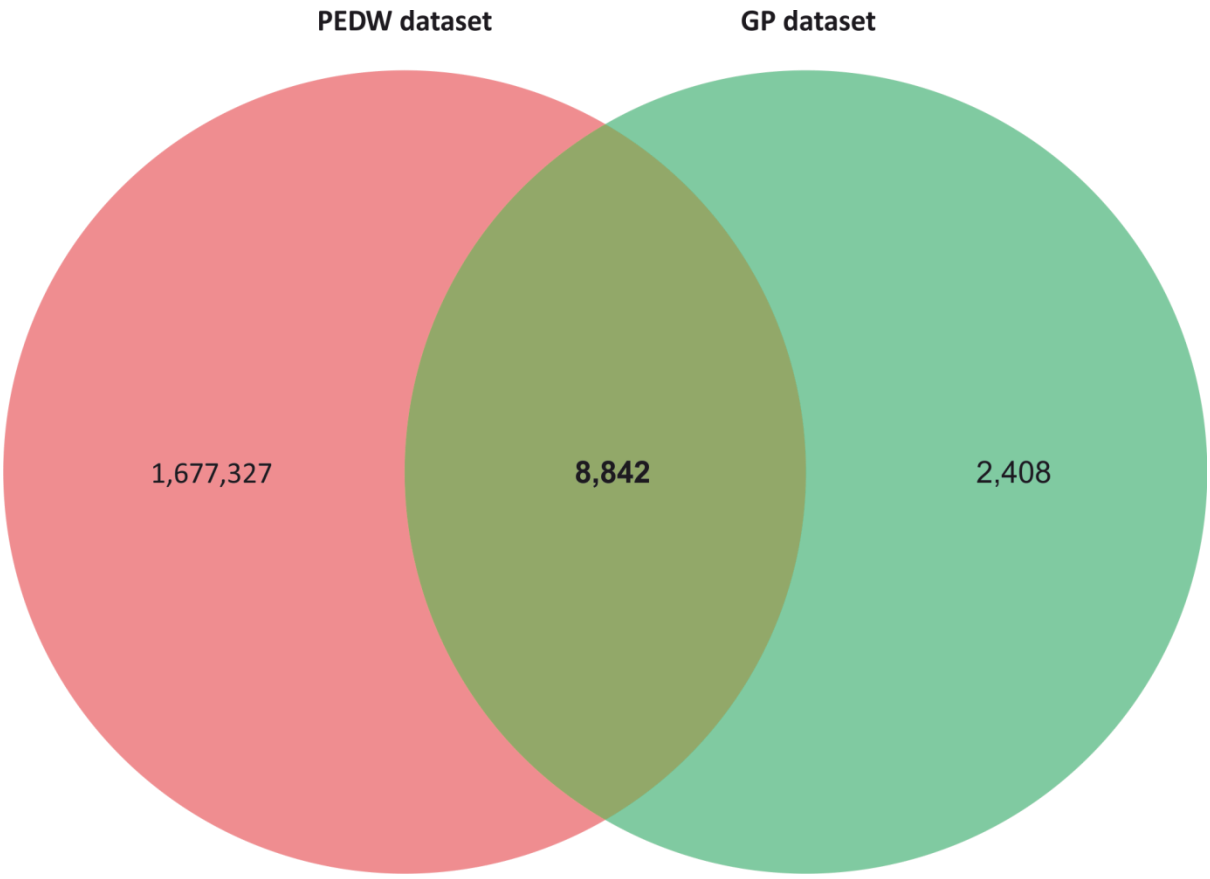

Figure 5| Venn diagram of individuals identified in PEDW and GP datasets and the number of individuals identified in both datasets.

3.2 Hypoglycaemic episodes in patients with Type 1 Diabetes requiring admission to hospital (PEDW data)

The following results present number of hypoglycaemic episodes in patients with T1D requiring admission to hospital (PEDW) data from 2010-2015. Additional analyses based on age and gender have also been presented. The results have been presented in the form of bar plots. However, the Cedar analyst has also created tables for the data and these have been presented in Appendix 4 – Data tables for the number of hypoglycaemic episodes identified in data obtained from the SAIL databank.

3.2.1 PEDW annual results

During the period of 2010-2015 there were a total of 3,661 hypoglycaemic episodes in patients with T1D requiring admission to hospital. The average annual number of hypoglycaemic episodes across the 6 years of data was 610 (SD±77.8), with a low of 505 in 2015 and a high of 705 in 2014 (Figure 6).

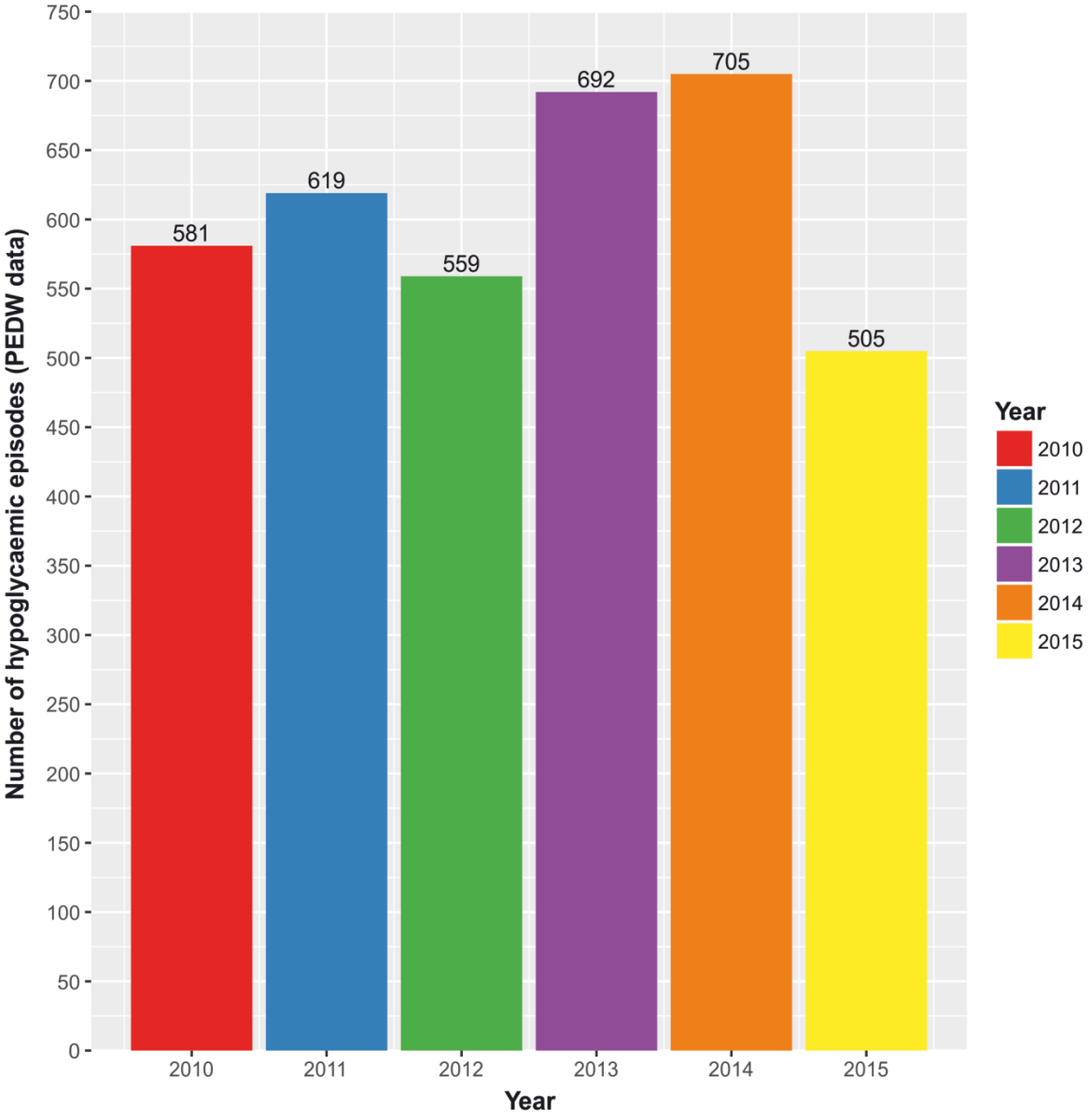

Figure 6| The number of hypoglycaemic episodes in people with T1D requiring admission to hospital between 2010-2015**.**

3.2.2 PEDW results by gender

Of the 3,661 hypoglycaemic episodes during 2010-2015, 1,856/3,661 (50.7%) were observed in males, 1,746/3,661 (47.7%) were observed in females and in 59/3,661 (1.6%) the gender was unknown (Figure 7). However, analysing the data annually shows that females had a higher number of hypoglycaemic episodes than males in 2010, 2011 and 2013 whilst males had a higher number of hypoglycaemic episodes in 2012, 2014 and 2015. The reason for males having a higher number of hypoglycaemic episodes across all 6 years is due to the difference between the numbers of males and females having hypoglycaemic episodes in 2012 and 2014. During 2012 a total of 303 hypoglycaemic episodes occurred in males whilst 241 occurred in females. During 2014 a total of 394 hypoglycaemic episodes occurred in males whilst 303 occurred in females (Figure 8).

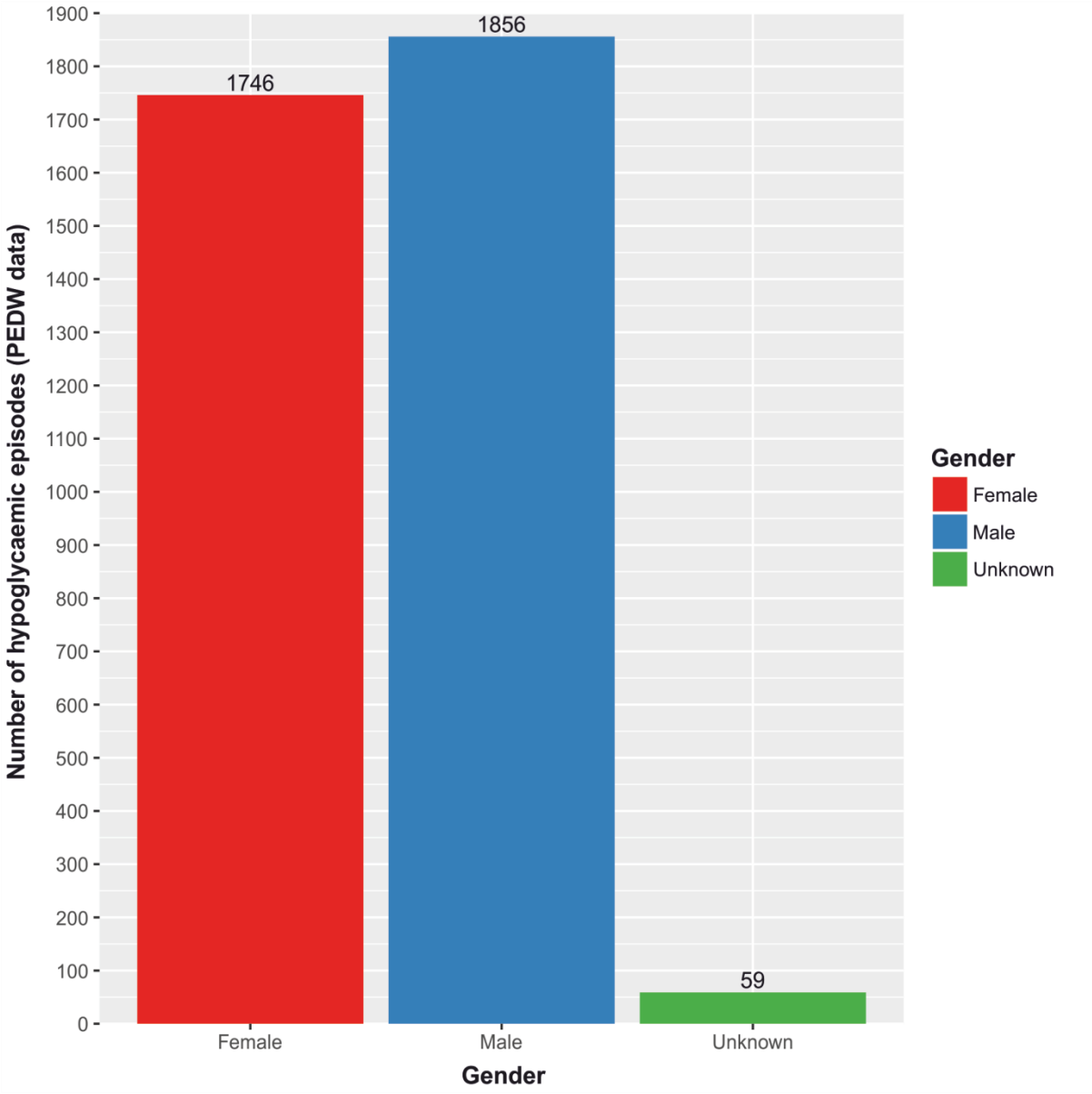

Figure 7| Gender differences in the number of hypoglycaemic episodes in people with T1D requiring admission to hospital between 2010-2015.

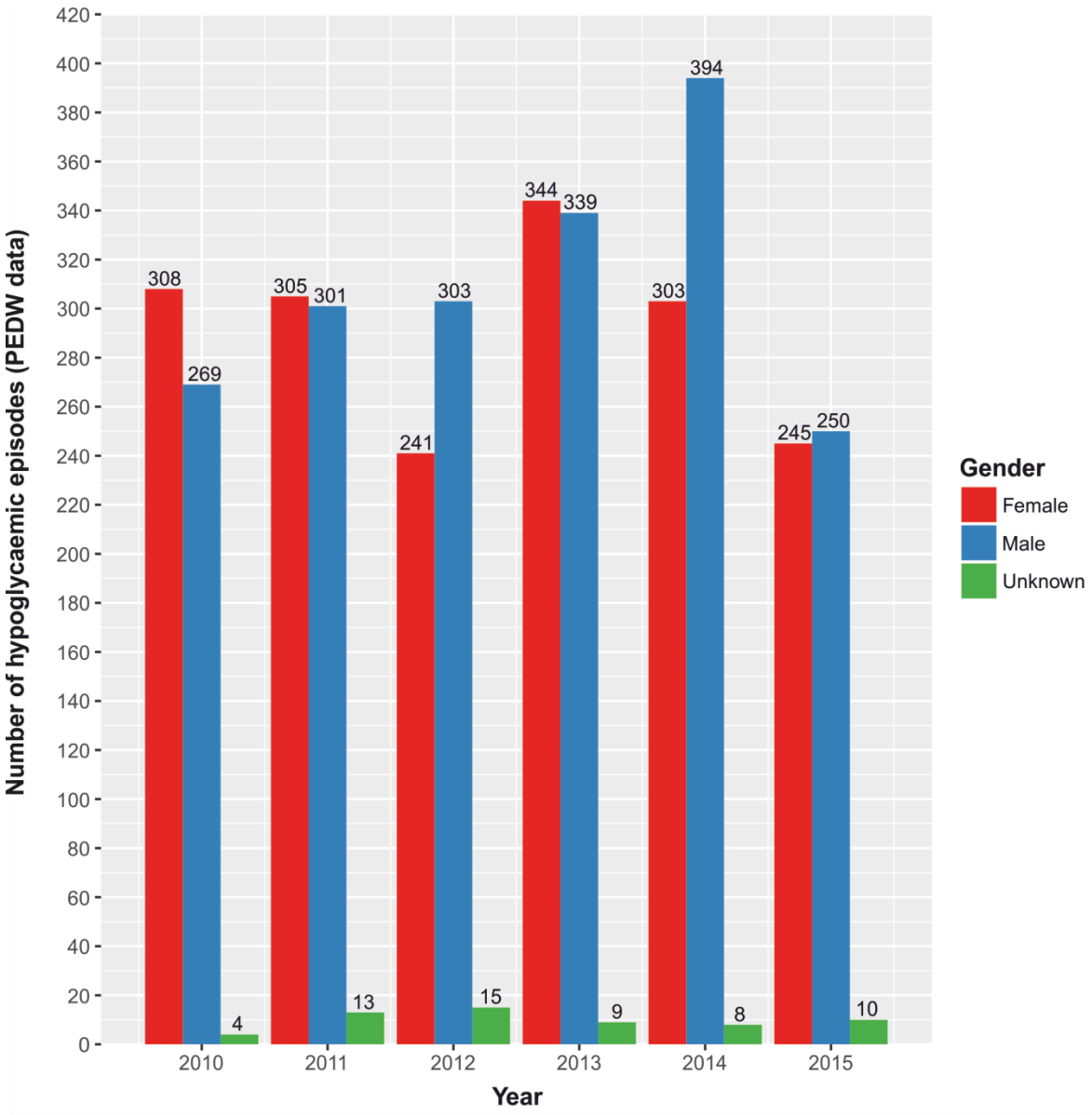

Figure 8| Annual gender differences in the number of hypoglycaemic episodes in people with T1D requiring admission to hospital between 2010-2015.

3.2.3 PEDW results by age

Over the period of 2010-2015 the highest number of hypoglycaemic episodes was observed in the 75+ age group. 599/3,661 (16.4%) of hypoglycaemic episodes were observed in this group. Excluding those with unknown age, the lowest number of hypoglycaemic episodes was observed in the 65-74 age group with 382/3,661 (10.4%) of all hypoglycaemic episodes (Figure 9)

When the data were analysed annually, the highest number of hypoglycaemic episodes was observed in the 75+ age group for 2010, 2013, 2014 and 2015. In 2011 and 2012 the highest number of hypoglycaemic episodes was observed in the 16-24 age group and 45-54 age group respectively (Figure 10)

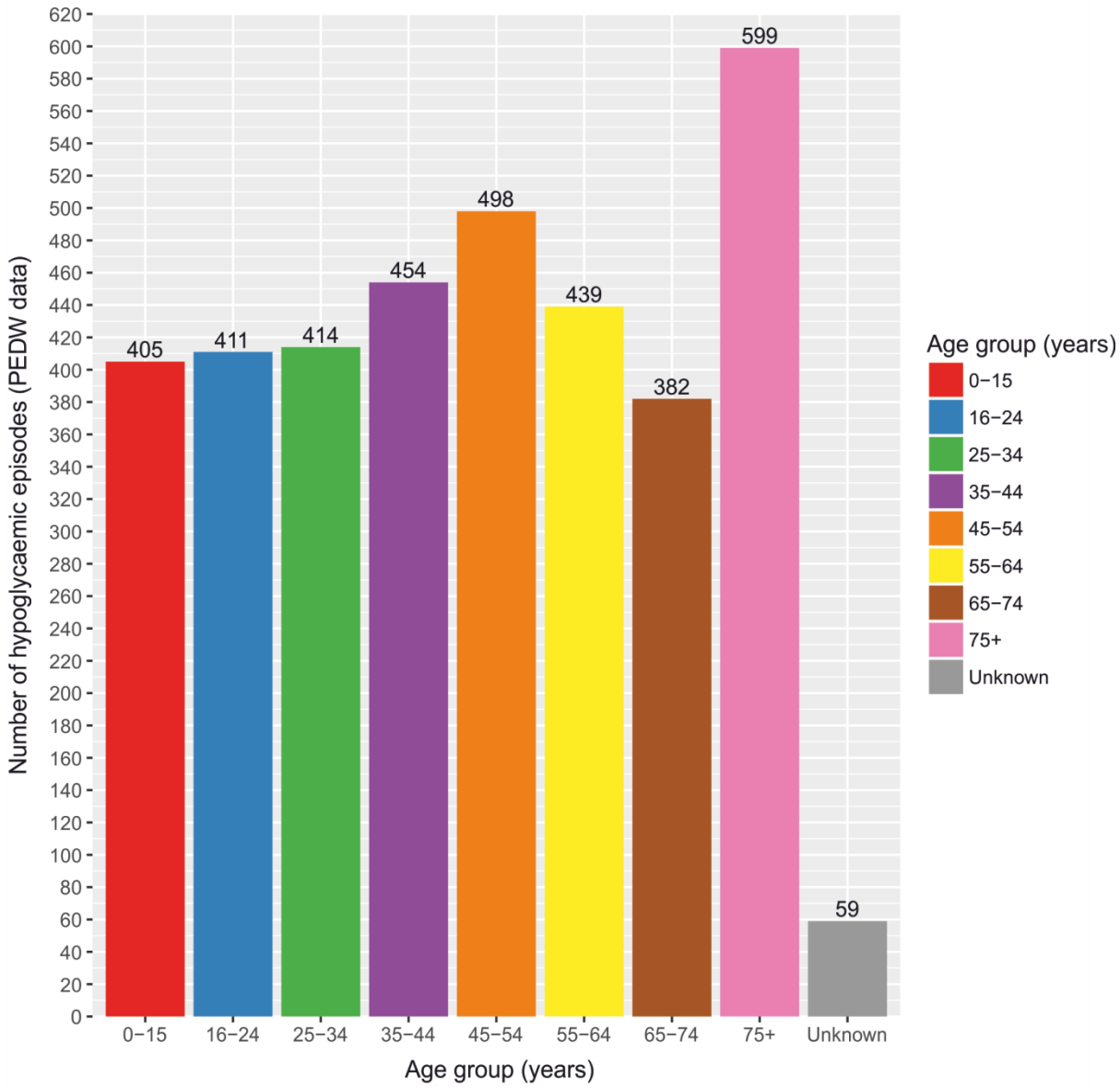

Figure 9| Age group differences in the number of hypoglycaemic episodes in people with T1D requiring admission to hospital between 2010-2015.

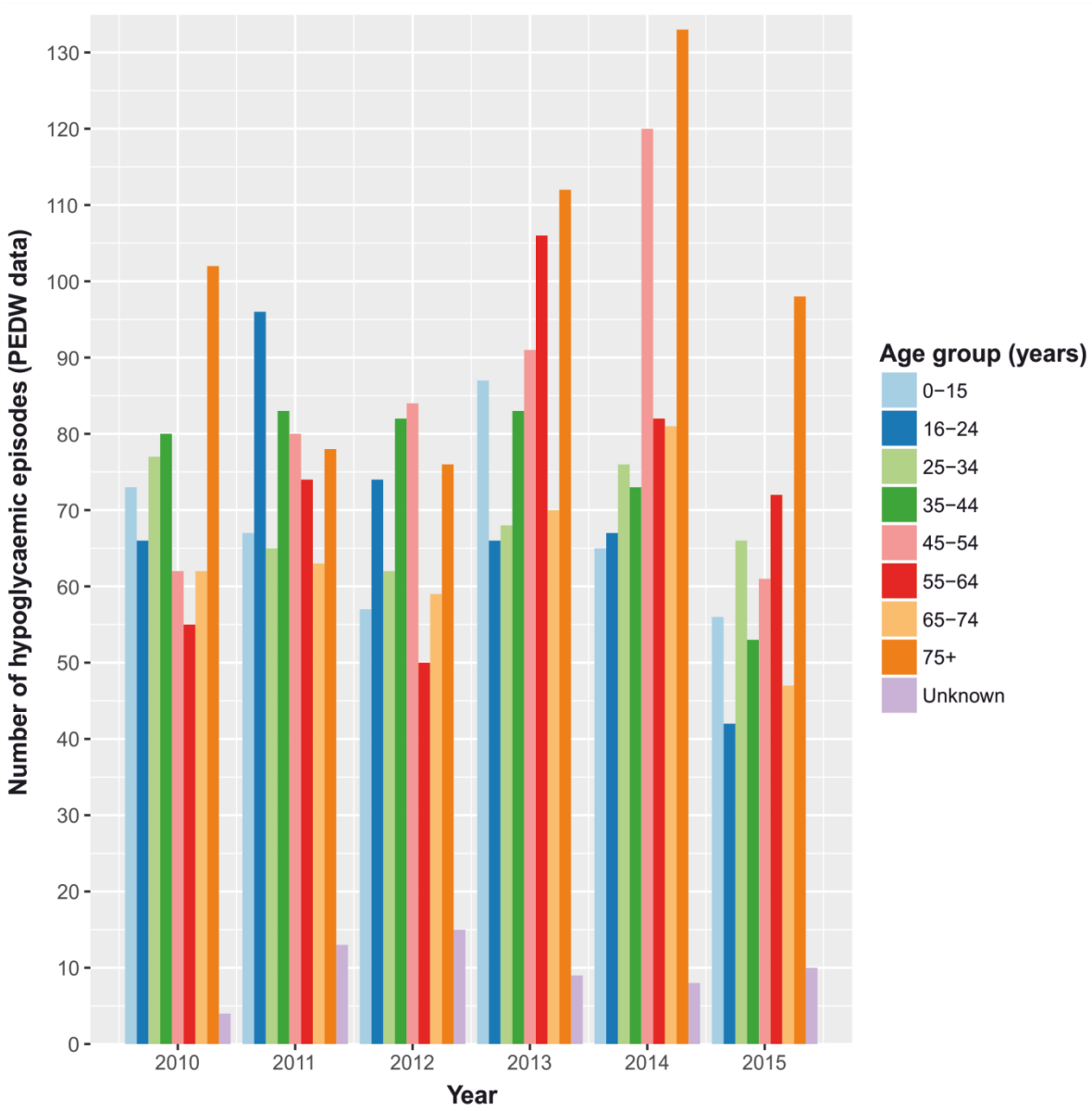

Figure 10| Annual age group differences in the number of hypoglycaemic episodes in people with T1D requiring admission to hospital between 2010-2015.

3.3 Hypoglycaemic episodes in patients with Type 1 Diabetes resulting in a visit to a GP (GP dataset)

The following results present the results for the number of GP visits as a result of a hypoglycaemic episode in patients with T1D (GP dataset) from 2010-2015. Additional analyses based on age and gender have also been presented. The results have been presented in the form of bar plots. However, the Cedar analyst has also created tables for the data and these have been presented in Appendix 4 – Data tables for the number of hypoglycaemic episodes identified in data obtained from the SAIL databank

3.3.1 GP dataset annual results

During the period of 2010-2015 there were a total of 1,210 GP visits due to a hypoglycaemic episode in patients with T1D. The average annual number of GP visits due to a hypoglycaemic episode across the 6 years of data was 202 (SD±54), with a low of 119 in 2015 and a high of 281 in 2013 (Figure 11).

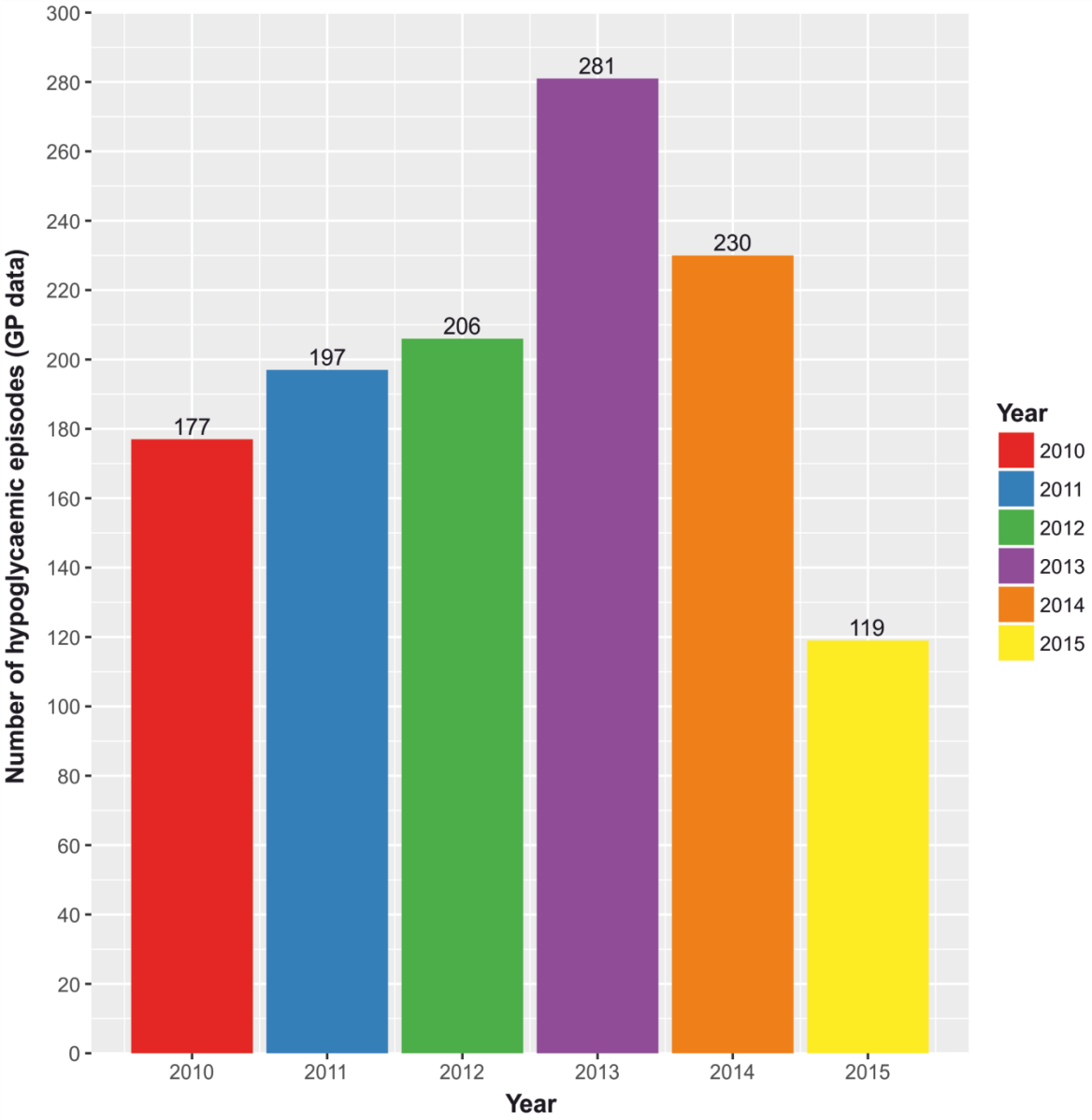

Figure 11| The number of hypoglycaemic episodes in people with T1D requiring a visit to the GP between 2010-2015

3.3.2 GP dataset results by gender

Of the 1,210 GP visits for a hypoglycaemic episode during 2010-2015, 684/1,210 (56.5%) were by males, 524/1,210 (43.3%) were by females and in 2/1,210 (0.2%) the gender was unknown (Figure 12). Analysing the data annually showed that males had a higher number of visits to the GP for a hypoglycaemic episode than females across all years. (Figure 13)

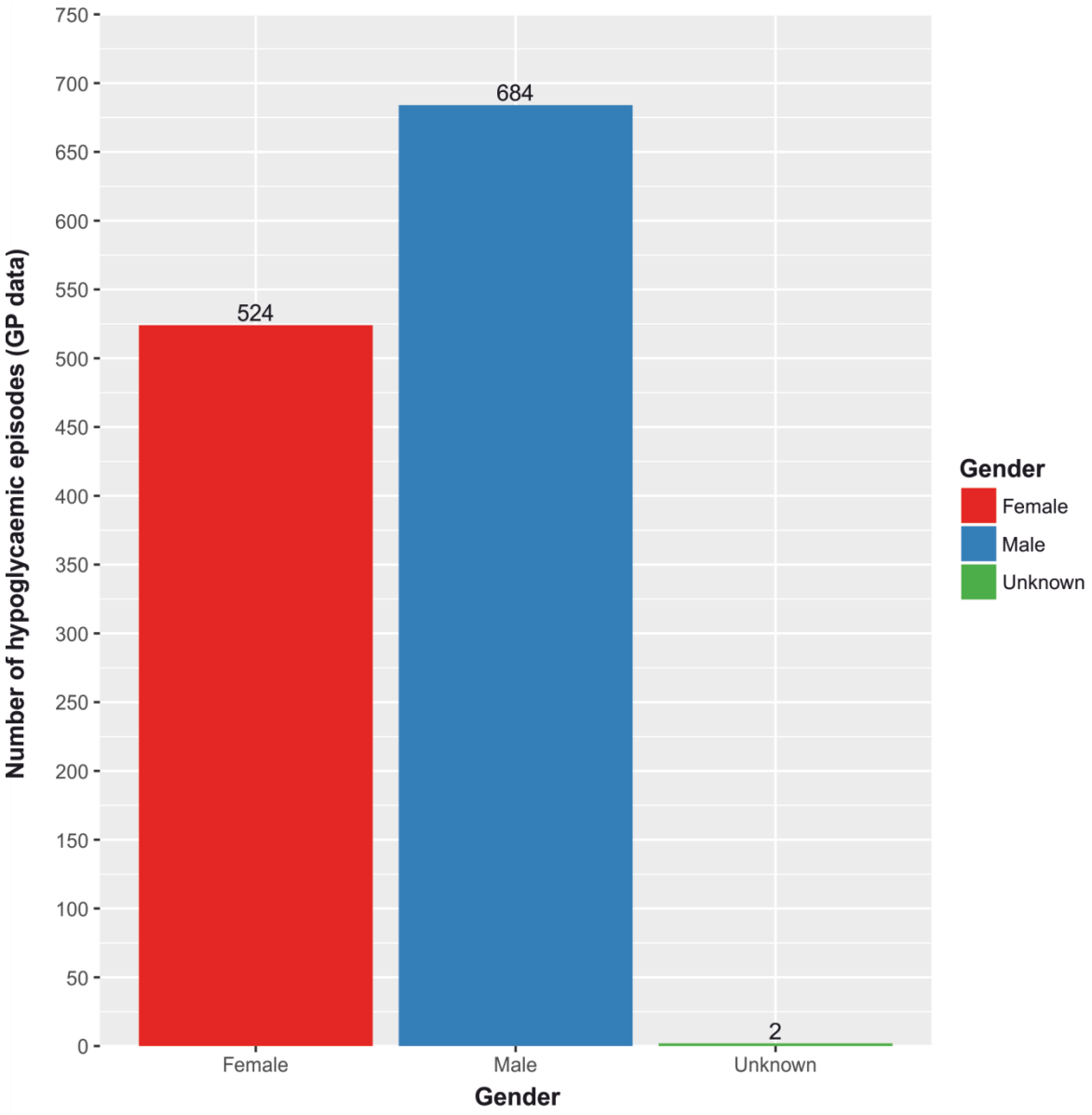

Figure 12| Gender differences in the number of GP visits due to a hypoglycaemic episode in people with T1D from 2010-2015

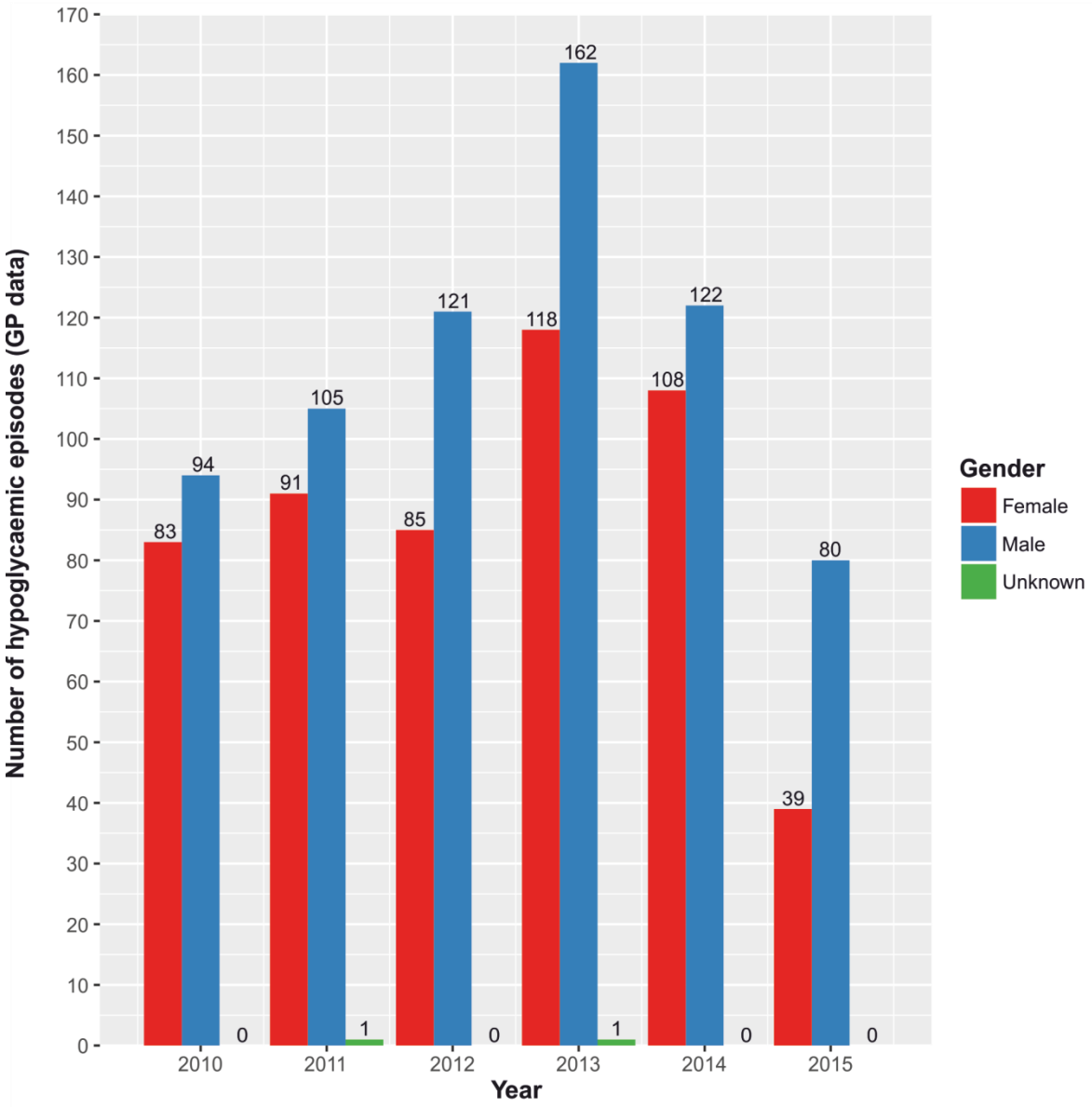

Figure 13| Annual gender differences in the number of GP visits due to a hypoglycaemic episode in people with T1D from 2010-2015.

3.3.3 GP dataset results by age

Over the period of 2010-2015 the highest number of GP visits due to a hypoglycaemic episode was observed in the 45-54 age group, 199/1,210 (16.4%) of hypoglycaemic episodes were observed in this group. Excluding those with unknown age, the lowest number of GP visits due to a hypoglycaemic episode was observed in the 0-15 age group with 111/1,210 (9.2%) of all hypoglycaemic episodes (Figure 14)

When the data were analysed annually, the highest number of GP visits due to a hypoglycaemic episode was observed in the 75+ age group for 2011, 2012 and 2014. In 2010 the highest number GP visits due to a hypoglycaemic episode was observed in the 25-34 age group. The 45-54 age group had the highest number of GP visits due to a hypoglycaemic episode in 2013 and 2015 (Figure 15).

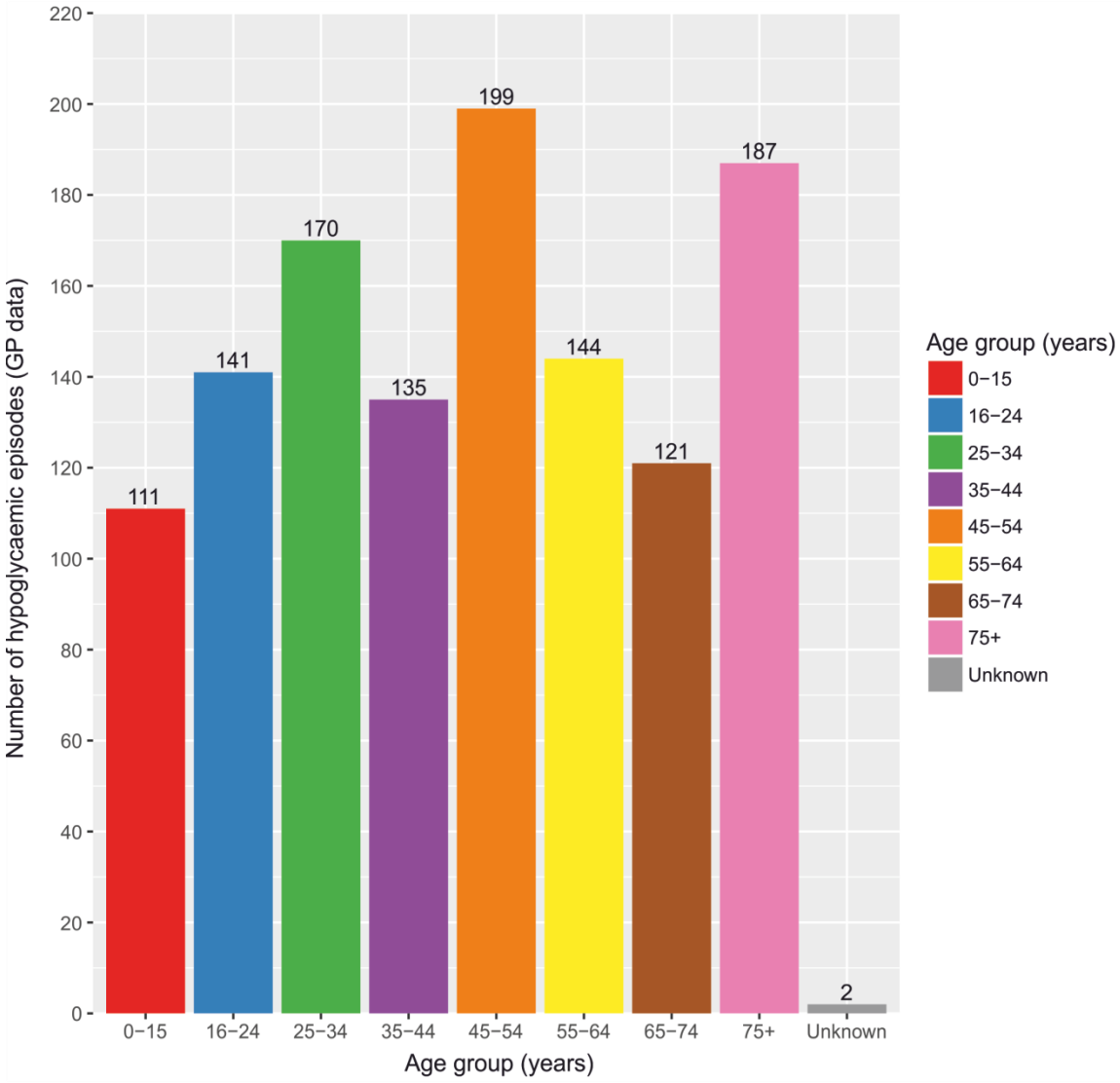

Figure 14| Age group differences in the number of GP visits due to a hypoglycaemic episode in people with T1D between 2010-2015

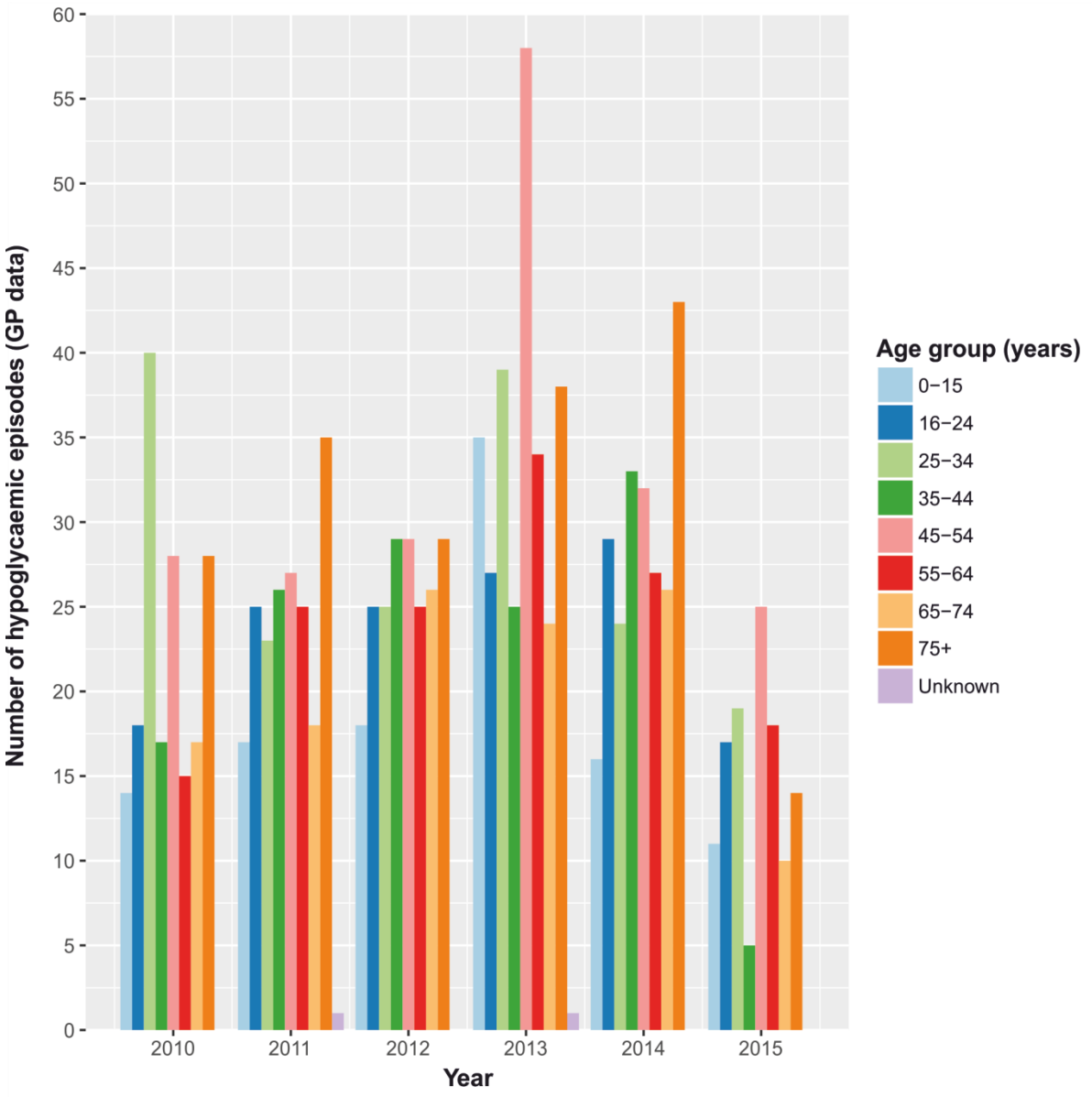

Figure 15| Annual age group differences in the number of GP visits due to a hypoglycaemic episode in people with T1D from 2010-2015.

3.4 Individual perspective analysis of PEDW and GP datasets

Both PEDW and GP datasets were analysed from the perspective of the individuals (patients) from 2010-2015. In total, 1,307 individuals with T1D had at least one hypoglycaemic episode requiring admission to hospital and 339 individuals with T1D had at least one hypoglycaemic episode requiring a visit to the GP. In addition, a total of 436 individuals required treatment from a GP and requiring admission to hospital for a hypoglycaemic episode (Figure 16).

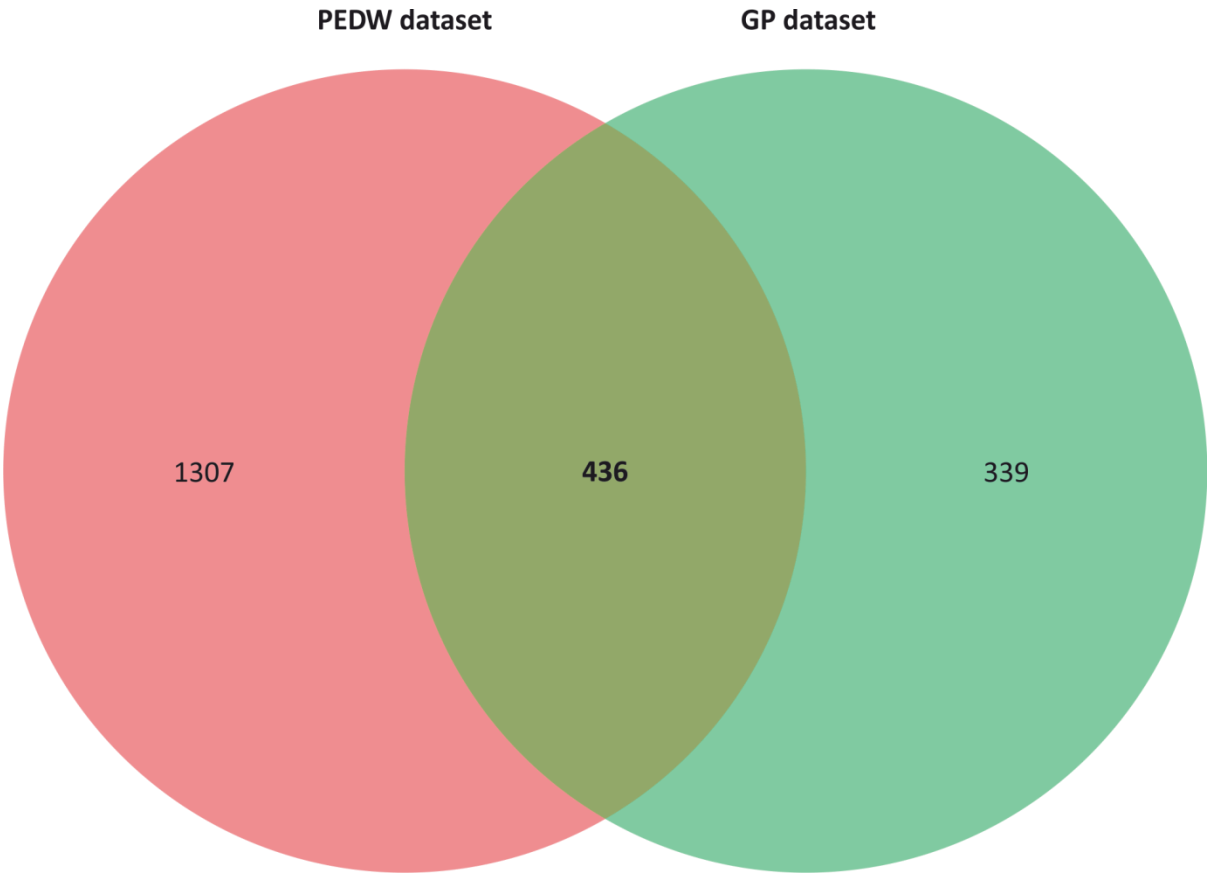

Figure 16| Venn diagram of the number of individuals having a hypoglycaemic episode requiring admission to hospital (PEDW) and a GP visit (GP dataset) and the number of individuals requiring both.

3.4.1 Individual level analysis of the PEDW dataset

The average number of individuals experiencing at least one hypoglycaemic episode each year was 350 (SD±44.4) with a high of 400 individuals observed in 2013 and 2014 and a low of 290 in 2015. A number of individuals experienced more than one hypoglycaemic episode in a year with a high of 164 individuals in 2013 and a low of 120 in 2010. The mean number of hypoglycaemic episodes requiring admission to hospital per person per year ranged from a low of 1.63 (SD±1.24) in 2012 to 1.84 (SD±2.25) in 2010 (Table 1).

Table 1| Analysis of the PEDW dataset from an individual perspective

PEDW				
Year	Number of individuals having a hypoglycaemic episode	Number of individuals having 1 hypoglycaemic episode	Number of individuals having >1 hypoglycaemic episode per year	Mean number of hypoglycaemic episodes per person(±SD)
2010	315	195	120	1.84 (2.25)
2011	352	199	153	1.76 (1.22)
2012	344	219	125	1.63 (1.24)
2013	400	236	164	1.73 (1.24)
2014	400	249	151	1.76 (1.42)
2015	290	177	113	1.74 (1.31)

3.4.2 Individual analysis of the GP dataset

The average number of individuals requiring at least one GP visit for a hypoglycaemic episode each year was 164 (SD±42.1) with a high of 225 individuals observed in 2013 and a low of 101 in 2015. A number of individuals required more than one GP visit for a hypoglycaemic episode in a year with a high of 35 individuals in 2013 and a low of 15 in 2015. The mean number of GP visits due to a hypoglycaemic episode per person per year ranged from 1.18 (SD±0.48) in 2015 to 1.26 (SD±1.09) in 2010.

Table 2| Analysis of the GP dataset from an individual perspective

GP				
Year	Number of individuals visiting the GP due to hypoglycaemia per year	Number of individuals visiting the GP once due to hypoglycaemia per year	Number of individuals visiting the GP more than once due to hypoglycaemia per year	Mean number of visits to the GP for a hypoglycaemic episode per person(±SD)
2010	140	117	23	1.26 (1.09)
2011	160	132	28	1.23 (0.59)
2012	168	137	31	1.23 (0.53)
2013	225	190	35	1.25 (0.96)
2014	188	160	28	1.22 (0.61)
2015	101	86	15	1.18 (0.48)

3.5 Validation of PEDW and GP datasets

3.5.1 Validation of the PEDW dataset

The Cedar analyst carried out validation of the PEDW dataset as described in section 2.2.6.2. Analysis of 10,245 individuals from the Brecon register identified in the PEDW dataset showed a total of 10,058 ICD-10 codes related to diabetes. The results suggested that patients with T1D were misdiagnosed in 2.2% of cases. The Cedar analyst also noted that 9.7% of the cases were diagnosed as "pre-existing T1D in pregnancy". Therefore, a correct diagnosis of T1D was given in 97.8% of cases. However, it is worth noting that ICD-10 codes for "pre-existing T1D in pregnancy" were not identified by the Cedar analyst for this project (Table 3).

Table 3| Validation of the PEDW dataset using data from the Brecon register

PEDW dataset	
Diagnosis	**ICD-10 codes (%)**
T1D	88.1
T2D	1.7
Other specified diabetes	0.1
Gestational diabetes	0.1
Pre-existing T1D in pregnancy	9.7
Pre-existing T2D in pregnancy	0.1
Unspecified pre-existing diabetes in pregnancy	0.0
Unspecified diabetes in pregnancy	0.2
Total IDC-10 codes for diabetes	**10058**

3.5.2 Validation of the GP dataset

The Cedar analyst carried out validation of the GP dataset as described in section 2.2.6.3. Analysis of 1,196,690 Read codes identified for individuals from the Brecon register showed a total of 2,609 Read codes for diabetes. The results suggested that the correct Read code was applied in 72.6% of instances. Read codes for T2D were assigned in 4.7% of instances and a large percentage (22.7%) of generic diabetes Read codes were assigned to patients with T1D (Table 4).

Table 4| Validation of the GP dataset using data from the Brecon register

GP	
Read code	**Read codes (%)**
Generic diabetes	22.7
T2D	4.7
T1D	72.6
Total Read codes for diabetes	**2609**

3.6 Hypoglycaemic episodes requiring an ambulance (London Ambulance Service data)

Cedar obtained information on the number of hypoglycaemic episodes attended by the LAS from 01/11/2011-31/10/2016. The information supplied by the LAS included all attendances for hypoglycaemia and therefore included patients who do not have T1D.

3.6.1 Annual results for ambulance attendances

In the period of 01/11/2011-31/10/2016 the LAS attended a total of 54,062 hypoglycaemic episodes. From 2012-2015 the LAS attended a total of 42,965 hypoglycaemic episodes. The highest number was 11,355 in 2014 and the lowest was 10,182 in 2012 (Figure 17)

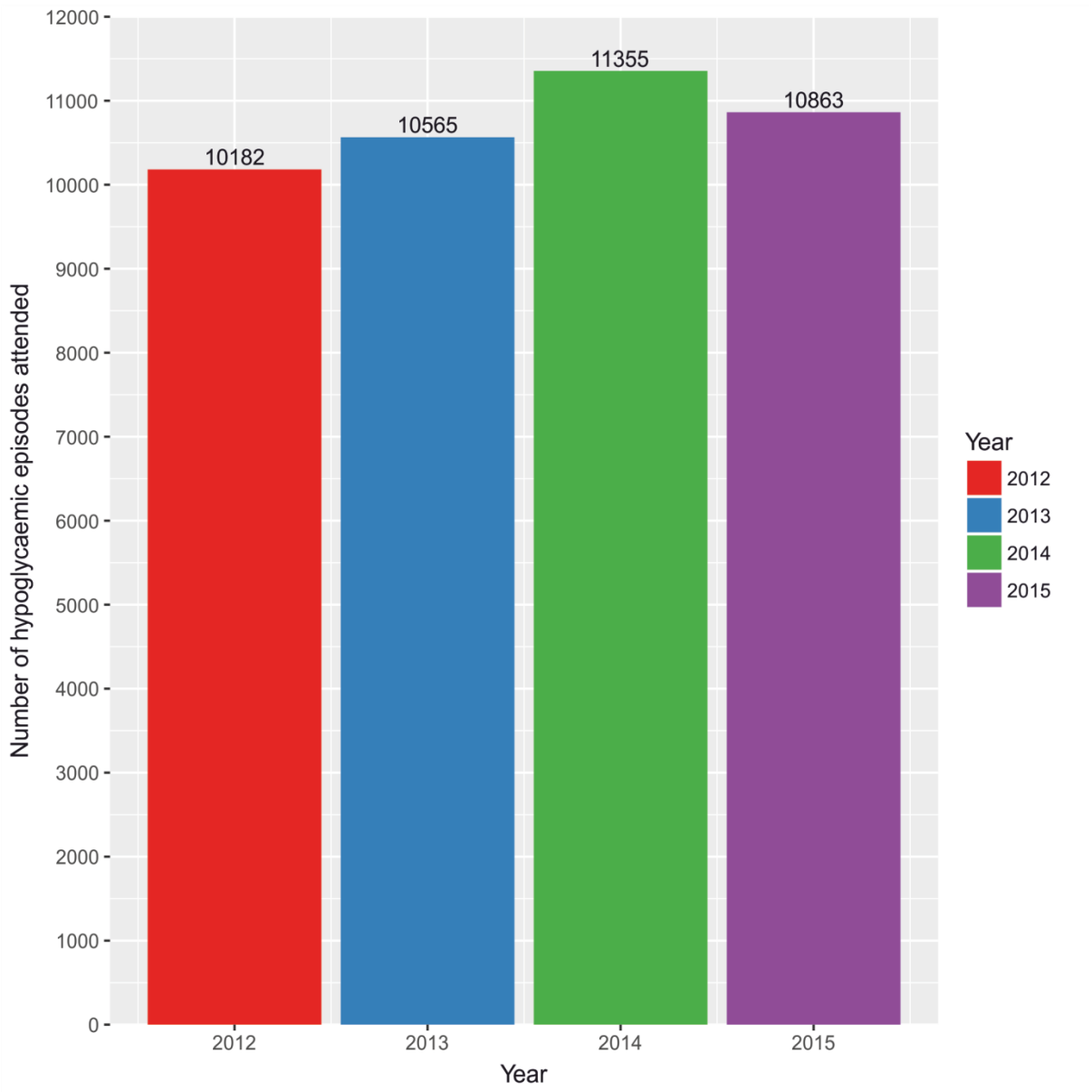

Figure 17| The number of hypoglycaemic episode attendances by the LAS from 2012-2015.

3.6.2 Ambulance attendance results by gender

Analysis of the total number of ambulance attendances from 01/11/2011-31/10/2016 by gender showed that the number of attendances for males was higher than females (30,615/54,062 (56.6%) vs. 22,932/54,062 (42.4%) respectively). In a number of attendances (515/54,062 (1%)) the gender was unknown (Figure 18)

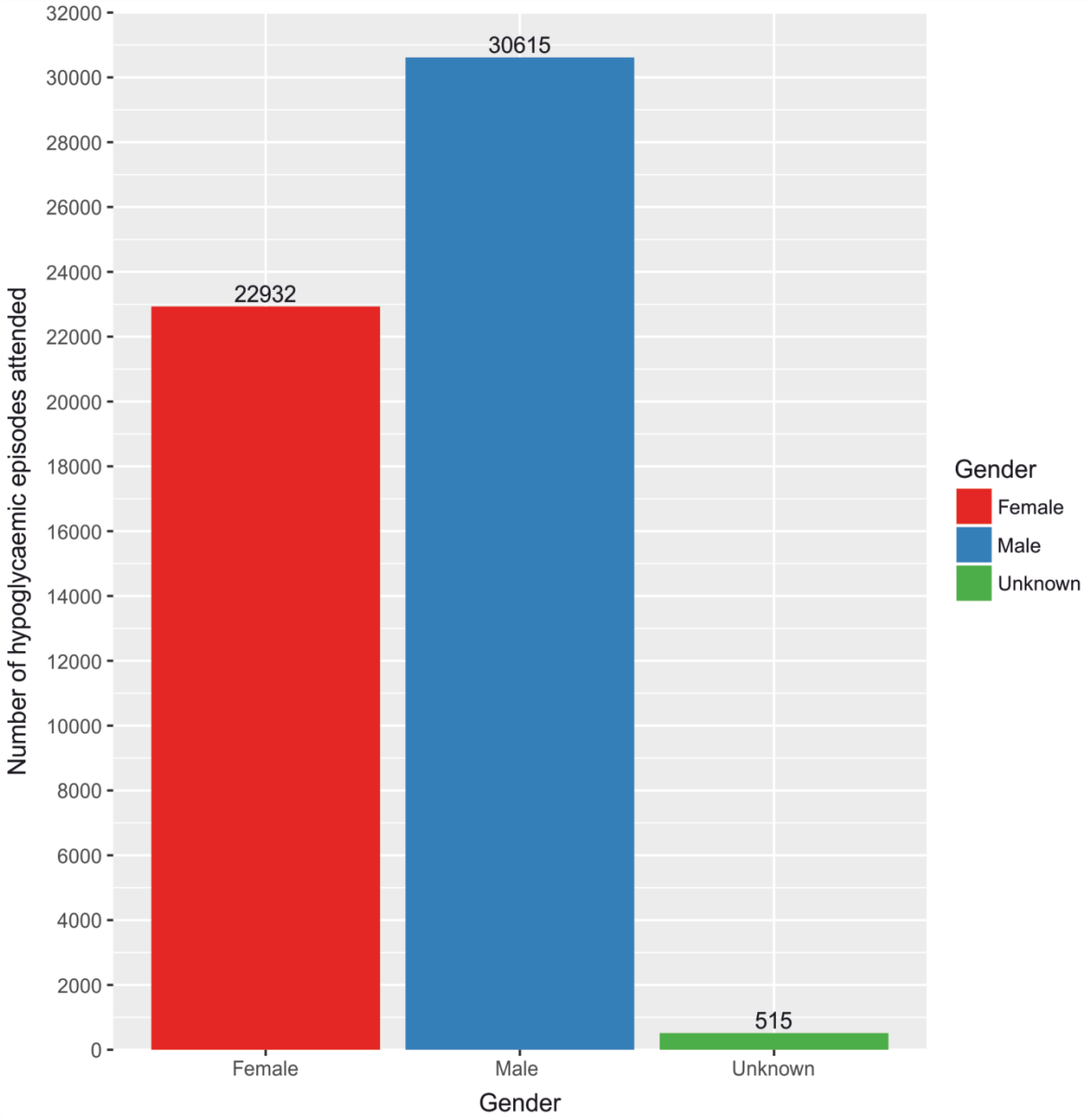

Figure 18| The number of attendances by the LAS due to a hypoglycaemic episode from 2012-2015 by gender.

3.6.3 Ambulance attendance results by age

For the period of 01/11/2011-31/10/2016, the highest number of attendances in male individuals was for the 75-79 age group (years) with 3,113/30,615 (10.2%) attendances. For females, the highest number of attendances was for the 80-84 age group (years) with 2,689/22,932 (11.7%) attendances. When the data were analysed by age group only, and not by age group and gender, the age group with the highest number of attendances was 75-79 years with 5585/54062 (10.3%). The age group with the lowest number of attendances was the >100 years with 55/54062 (0.1%) (Table 5).

Table 5| The number of attendances by the LAS for a hypoglycaemic episode by age group (years) and gender.

	Gender			
Age group (years)	Male	Female	Unknown	Total attendances per age group
0-4	532	437		969
5-9	124	111	2	237
10-14	192	225		417
15-19	517	461		978
20-24	1034	920	2	1956
25-29	1424	1008	3	2435
30-34	1445	1043	1	2489
35-39	1398	1031		2429
40-44	1655	950	1	2606
45-49	1930	1088	2	3020
50-54	2568	1296	2	3866
55-59	1935	1264	4	3203
360-64	2350	1332	2	3684
65-69	2299	1528	3	3830
70-74	2626	1850	5	4481
75-79	3113	2468	4	5585
80-84	2801	2689	4	5494
85-89	1627	1808	1	3436
90-95	588	924	1	1513
95-99	103	245	1	349
>100	11	44		55
Unknown	343	210	477	1030
Total	**30615**	**22932**	**515**	**54062**

3.6.4 Care pathway for attendances

The data provided by the LAS contained information on the care pathways individuals followed once an ambulance had been in attendance for the period of 01/11/2011-31/10/2016. The majority of patients (29,967/54,061, 55.43%) were taken to accident and emergency (A&E). However, a number of patients were not conveyed and were not referred (14,693/54,061, 27.18%). Therefore, the ambulance crew were responsible for treating or assisting the individual (Table 6).

Table 6| Care pathway for individuals having a hypoglycaemic episode which was attended by the LAS.

Care Pathway	Count	Percentage
None	179	0.33%
Cancelled	67	0.12%
Care Pathway - conveyed	1457	2.70%
No patient	76	0.14%
Patient not conveyed	14693	27.18%
Patient not conveyed - referred	7525	13.92%
Taken to A&E	29967	55.43%
Unknown	98	0.18%
Total	**54062**	**100%**

3.7 Hypoglycaemia cumulative incidence using Welsh data

The core NDA dataset contains data on the number of diabetes registrations and a participation rate across England and Wales. Welsh data can be viewed by LHB which presents the number of T1D registrations and the participation rate for each LHB. During the period of 2015-2016, the participation rate across Wales was 100% and the number of T1D registrations (number of people with T1D) was 14,406 (Table 7).

Table 7| Type 1 diabetes registration and LHB participation rate for Wales during 2015-2016

LHB	LHB participation rate (%)	LHB T1D registrations
Betsi Cadwaladr University LHB	100	3615
Hywel Dda LHB	100	1824
Abertawe Bro Morgannwg University LHB	100	2486
Cardiff and Vale University LHB	100	1883
Cwm Taf LHB	100	1336
Aneurin Bevan LHB	100	2612
Powys Teaching LHB	100	647
Wales	**100**	**14406**

Average participation rate (%)	Total Welsh T1D registrations (according to GP registrations)
100	14403

In 2015 there were a total of 505 hypoglycaemic episodes requiring admission to hospital (PEDW data) and a total of 119 GP visits due to a hypoglycaemic episode (GP dataset). The cumulative incidence for hypoglycaemic episodes requiring admission to hospital (PEDW data) and GP visits due to a hypoglycaemic episode were 3.5% and 0.83% respectively. With results from both datasets combined the cumulative incidence of hypoglycaemia in T1D for Welsh patients was 4.33% (Table 8).

Table 8| The cumulative incidence of hypoglycaemia in 2015 using Welsh data obtained from SAIL and NDA data for 2015-2016

Data source	Number of hypoglycaemic episodes	Number of T1D registrations	Hypoglycaemia cumulative incidence for 2015-2016
Inpatient (PEDW)	505	14406	**3.5%**
GP (GP dataset)	119	14406	**0.83%**
Combined datasets	624	14406	**4.33%**

3.8 Hypoglycaemia cumulative incidence using LAS data

The core NDA dataset contains data on the number of diabetes registrations and participation rate across England and Wales. English data can be viewed by CCG which presents the number of T1D registrations and the participation rate for each CCG. The LAS covers a total of 32 CCGs across London. During the period of 2015-2016, the participation rate across the CCGs covered by the LAS was 82.7% and the number of T1D registrations (number of people with T1D) was 23,977 (Table 9).

In 2015, the LAS attended a total of 10,863 hypoglycaemic episodes. The cumulative incidence for hypoglycaemic episodes requiring an attendance from the LAS was 45.3% in 2015-2016 (Table 10). It is worth noting that the number of LAS attendances due to a hypoglycaemic episode may include people who do not have T1D and therefore, the cumulative incidence may be an over-estimate.

Table 9| Type 1 diabetes registration and participation rate for CCGs covered by the LAS during 2015-2016

CCG	CCG participation rate (%)	CCG T1D registrations
NHS Barking and Dagenham	90	512
NHS Barnet	90.3	1171
NHS Bexley	100	898
NHS Brent	30.3	127
NHS Bromley	93.3	1311
NHS Camden	80.6	532
NHS Central London (Westminster)	82.9	546
NHS City and Hackney	100	840
NHS Croydon	80.7	964
NHS Ealing	88.5	1196
NHS Enfield	63.3	580
NHS Greenwich	32.5	303
NHS Hammersmith and Fulham	100	688
NHS Haringey	95.2	752
NHS Harrow	79.4	611
NHS Havering	83.3	950
NHS Hillingdon	87	883
NHS Hounslow	98.1	999
NHS Islington	73.5	605
NHS Kingston	100	628
NHS Lambeth	100	1158
NHS Lewisham	100	945
NHS Merton	20.8	150
NHS Newham	100	784
NHS Redbridge	91.1	726
NHS Richmond	21.4	157
NHS Southwark	100	967
NHS Sutton	83.3	659
NHS Tower Hamlets	100	664
NHS Waltham Forest	93.2	824
NHS Wandsworth	88.6	1084
NHS West London	100	763
England	**81.4**	**203037**
	Average participation rate across CCGs (%)	**Total London T1D registrations**
	82.7	**23977**

Table 10| The cumulative incidence of hypoglycaemia requiring an ambulance in 2015 using LAS and NDA data from 2015-2016

Number of attendances due to a hypoglycaemic episode	Number of T1D registrations	Hypoglycaemia cumulative incidence for 2015-2016
10863	23977	45.3%

3.9 Summary of the NaDIA 2016

The NaDIA forms a part of the NDA programme and provides a snapshot of diabetes inpatient care across Wales and England. A total of 209 sites across England Wales took part in the 2016 audit. The audit showed that around 1 in 6 hospital beds are occupied by an individual with diabetes (all types). The audit showed the prevalence of hypoglycaemic episodes (blood glucose measurement of ≤3.9 mmol/L) in inpatients with diabetes (all types) has fallen from 2011 to 2016 (Figure 19). However, 20% of inpatients with diabetes still have a hypoglycaemic episode during their hospital stay. No audit was carried out in 2014.

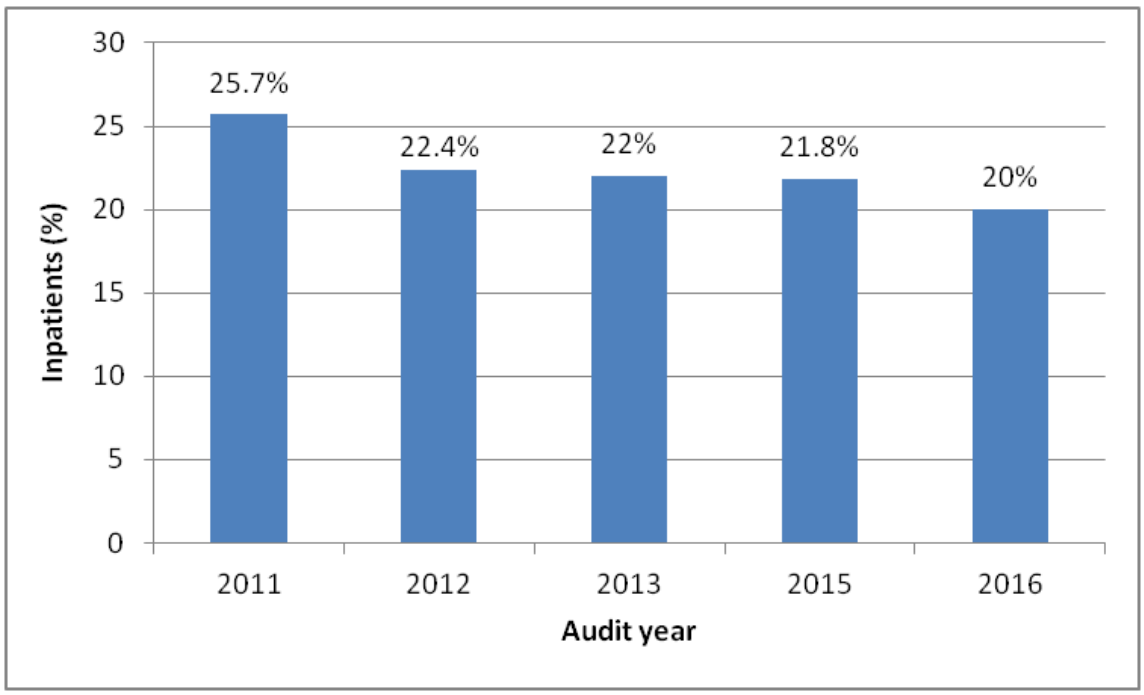

Figure 19| Inpatients with diabetes (all types) having one or more hypoglycaemic episode in the last 7 days in England and Wales (figure recreated by Cedar analyst from data presented in NaDIA 2016).

The percentage of inpatients with T1D who have one or more severe hypoglycaemic episode (blood glucose measurement of <3.0 mmol/L) was lower in 2016 than previous years. However, 26.9% of inpatients with T1D had a severe hypoglycaemic episode during their hospital stay in 2016 (Figure 20)

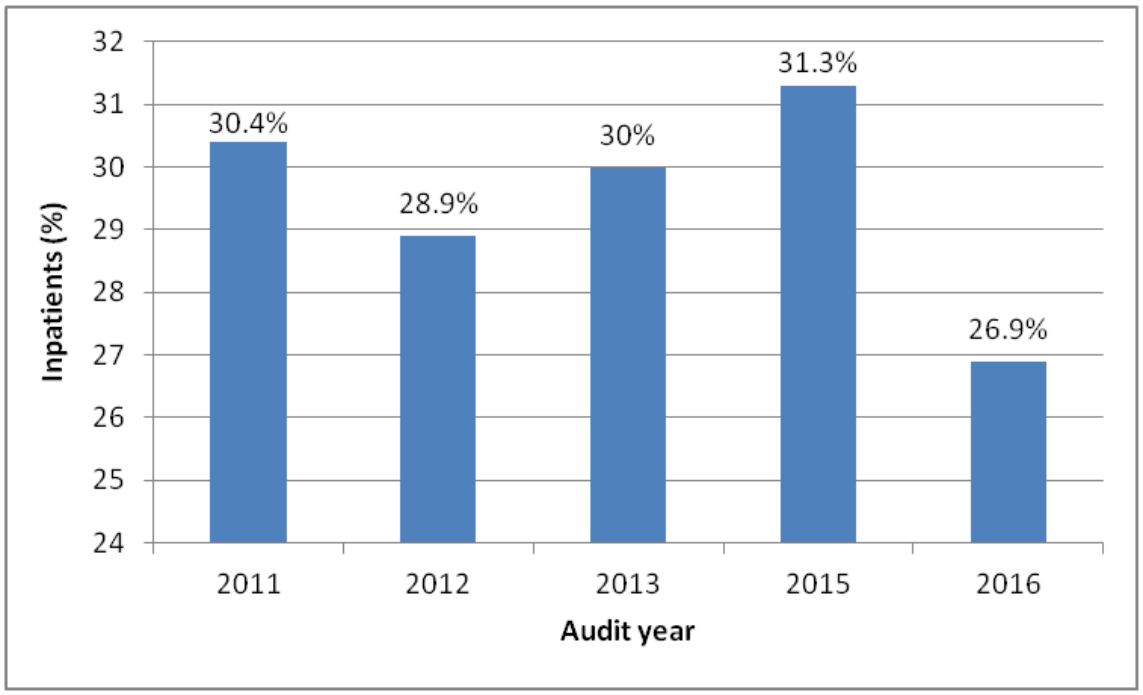

Figure 20| Inpatients with T1D having one or more hypoglycaemic episode in the last 7 days in England and Wales (figure recreated by Cedar analyst from data presented in NaDIA 2016).

3.10 Fear of hypoglycaemia systematic review

3.10.1 Literature search

The Cedar analyst, in partnership with an information specialist, carried out a systematic review of the literature on fear of hypoglycaemia. The search strategy followed, a PRISMA diagram and critical appraisal checklists have been presented in Appendix 5 – Search strategy for Cedar's systematic review. The literature search returned a total of 2,193 studies which was reduced to 2,111 studies following the removal of duplicates. The studies were then screened by title and abstract where 2,071 were excluded leaving 40 studies to be screened at full text. 26/40 studies were excluded with reasons to leave a total of 14 studies for the systematic review.

3.10.2 Summary of included studies

The majority of the included studies were of good quality. Seven studies reported FoH in children/adolescents or adults with T1D (Table 11) and seven studies reported FoH in parents of children with T1D or where FoH has been reported for both children with T1D and their parents (Table 12).

The majority of the studies (n=12) were cross-sectional in design. One systematic review and one qualitative study were also included. The included studies were based in the USA (n=4), Sweden (n=3), Norway (n=2), Australia (n=2), Canada (n=1) and the UK (n=1). The systematic review included studies from multiple countries. Participants in the studies were adults with T1D (n=6), parents of children with T1D (n=5), children and adolescents with T1D (n=1), adolescents with T1D and their parents (n=1) and children with T1D and their parents (n=1).

3.10.3 Questionnaires used

A number of different questionnaires were utilised in the included studies in order to assess FoH, hypoglycaemia unawareness and QoL.

3.10.3.1 Hypoglycaemia fear survey

The hypoglycaemia fear survey (HFS) was developed by Cox et al. (1987) and contains a total of 23 items measuring FoH. The survey is made up of two subscales: the behaviour subscale and worry subscale. Both subscales contain different items which were designed to cover different facets of FoH. The behaviour subscale aims to determine the actions taken by individuals in order to avoid low blood sugar whilst the worry subscale aims to determine the concerns individuals may have regarding their diabetes. The survey makes use of a 5-point Likert scale from 1-5 where 1 = "never" and 5 = "very often". Scores for subscales are usually presented separately to give an indication of the hypoglycaemic avoidance behaviours followed by individual and also to give an indication of the level of worry the individual has. Further versions of the HFS have since been developed including the HFS-II (Gonder-Frederick et al. 2011), HFS-P (parent), HFS-P-YC (parent of young children).

3.10.3.2 Perceived stress scale

The perceived stress scale (PSS) was developed by Cohen et al. (1983). The questionnaire is designed to determine the extent individuals appraise various life situations as stressful. There are different versions of this questionnaire including 14 and 10 item versions. Each item is measured using a 5-point Likert scale from 0-4 where 0 = "never" and 4 = "very often".

3.10.3.3 Social phobia scale

The social phobia scale (SPS) was developed by Mattick and Clarke (1998). The SPS is used to assess the fear of being scrutinised whilst carrying out normal activities such as eating or drinking. The SPS contains a total of 20 items measured through a 5-point Likert scale from 0-4 where 0 = “not at all” and 5 = “extremely”.

3.10.3.4 Hospital anxiety and depression scale

The hospital anxiety and depression scale was developed by Zigmond and Snaith (1983) and is used to determine patient anxiety and depression levels. The questionnaire contains 14 items, 7 for anxiety and 7 for depression. Each item is measured using a 4-point Likert scale from 0-3 where 0 = “no, not at all” and 3 = “yes, definitely”.

3.10.3.5 Anxiety sensitivity index

The anxiety sensitivity index (ASI) was developed by Reiss et al. (1986) and is used to measure anxiety sensitivity in individuals. The questionnaire contains 16 items which are measured using a 5-point Likert scale from 0-4 where 0= “very little” and 4 = “very much”.

3.10.3.6 Fear of complications questionnaire

The fear of complications questionnaire (FCQ) was developed by Taylor et al. (2005). The questionnaire was designed to measure fear of complications in T1D. The questionnaire contains 15 items which are measured on a 4-point Likert scale from 0-3 where 0 = “never” and 3 = “always”.

3.10.3.7 State-trait personality inventory, trait anxiety subscale

The state-trait personality inventory (STPI) was developed by Spielberger (1979). The STPI is made up of 80 items with eight 10 item subscales and aims to measure stat and trait anxiety, anger, curiosity and depression. The anxiety subscale contains 10 items which are measured using a 4-point Likert scale from 1-4 where 1 = “not at all” and 4 = “very much so”.

3.10.3.8 State-trait anxiety inventory for children

The state-trait anxiety inventory for children (STAIC) is a 40 item questionnaire which is split into two 20 item subscales. The questionnaire measures state and trait anxiety in children through a 3-point Likert scale from 1-3 where 1 = “hardly ever” and 3 = “often”.

3.10.3.9 Paediatric quality of life inventory

The paediatric quality of life inventory (PedsQL) was developed by Varni et al. (1999) and is a 23 item questionnaire administered to parents to determine their view on their child’s QoL. The questionnaire is made up of 4 subscales which include physical functioning, emotional functioning, social functioning and school functioning. Items are scored using a 5-point Likert scale from 0-4 where 0 = “never” and 4 = “almost always”.

3.10.3.10 Parent diabetes quality of life

The parent diabetes quality of life (PDQOL) questionnaire was developed by Vandagriff et al. (1992) and consists of a total of 48 items. The questionnaire aims to determine a parent’s satisfaction with their child’s T1D, the impact T1D has on their lives and any worries the parent may have regarding their child’s T1D through the use of 3 subscales. Items are scored using a 5-point Likert scale.

3.10.3.11 Diabetes family responsibility questionnaire

The diabetes family responsibility questionnaire (DFRQ) was developed by Anderson et al. (1990). The questionnaire contains 19 items in order to determine the level of responsibility parents have in managing their child's diabetes. Items are scored using a 3-point Likert scale from 1-3 where 1 = "parent takes or initiates responsibility almost all of the time" and 3 = "child takes or initiates responsibility almost all of the time".

3.10.3.12 EQ-5D instrument

The EuroQol-5D (EQ-5D) instrument is a measure of health outcome and was first introduced in 1990. Different versions of EQ-5D exist including a 3 level version (EQ-5D-3L), a 5 level version (EQ-5D-5L) and a version suitable for a child (EQ-5D-Y). The instrument comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The 3 level version utilises a 3-point Likert scale indicating no problems, some problems and extreme problems. The 5 level version utilises a 5-point Likert scale indicating no problems, slight problems, moderate problems, severe problems and extreme problems. EQ-5D can be used to calculate quality adjusted life years (QALYs).

3.10.4 Studies reporting FoH in adults

A total of 6 studies presented results for FoH in adults. The study by Anderbro et al. (2010) suggested a difference between men and women in terms of FoH. Women scored significantly higher than men on the HFS worry and aloneness subscale indicating a higher FoH in women than men. The study showed that frequency of severe hypoglycaemia (SH) and the number of symptoms during mild hypoglycaemia (MH) were associated with FoH for men and women.

In another study by the same authors (Anderbro et al. 2015) women scored significantly higher on the HFS worry subscale than men but there was no significant difference between males and females on the behaviour subscale. The study showed that frequency of SH, nocturnal hypoglycaemia, self-monitoring of blood glucose, and the number of symptoms experienced during MH were all positively associated with HFS score.

Differences between males and females in terms of FoH were also observed in the study by Gjerlow et al. (2014). Mean scores across all items of the HFS worry survey were significantly higher in women than men. HFS worry items with the highest mean scores were the same in men and women and included “becoming hypoglycaemic while sleeping” and “not having food available”. However, women scored higher than men in all HFS worry items. In 5/18 items women scored significantly higher than males, these included: “interferes with important things”, “upset and difficult”, “difficulty thinking clearly”, “lightheaded or dizzy” and “passing out in public”.

A study by Hendrieckx et al. (2014) showed that participants who had at least one SH event in past 6 months reported greater diabetes-related distress, greater FoH, lower general emotional well-being and lower diabetes specific positive well-being. The authors compared participants experiencing SH and those not reporting SH. Participants experiencing SH were more worried about hypoglycaemia and made more behavioural changes to avoid hypoglycaemia than those not reporting SH. In addition, the authors carried out regression modelling which showed that more frequent SH was associated with impaired awareness of hypoglycaemia, greater FoH and lower diabetes specific positive well being.

Differences in FoH have been observed between patients with T1D and T2D (Leiter et al. (2005). Following a mild or moderate hypoglycaemic episode a higher percentage of patients with T2D reported an increase in FoH than patients with T1D. However, following a severe hypoglycaemic episode a higher percentage of patients with T2D reported a greater FoH than patients with T1D. The study also suggested that patients with T1D modified their insulin dose following a severe or mild/moderate hypoglycaemic episode. Patients with T1D also reported consuming additional food following a hypoglycaemic episode.

One final study reported on FoH in adults only (McCoy et al. 2013). This study showed that SH did not have a significant association with HRQoL impairment or self-rating of health as measured by the EQ-5D utility index in patients with T1D. However, a non-significant increase in FoH was observed in T1D patients reporting SH compared to those who reported no/mild hypoglycaemia. A comparison of patients with T1D and T2D showed that general FoH was significantly higher in patients with T1D than those with T2D. Confidence in the ability of the patient to recognise and manage a hypoglycaemic event was significantly lower in patients with T1D than those with T2D.

3.10.5 Studies reporting FoH in children and adolescents

One study presented results for FoH in children and adolescents with T1D without results for their parents (Nordfeldt and Ludvigsson 2005). The study utilised visual analogues scores (VAS) from 0-100 (low to high). VAS scores of perceived problem were significantly higher for SH than MH, indicating that children/adolescents found SH to be more of a problem than MH. The study also investigated perceived disturbance through the use of a VAS. The highest number of patients indicating >50 mm on the VAS for perceived disturbance was observed for risk of SH. In addition, perceived disturbance was higher for SH with unconsciousness than SH without unconsciousness, MH and diabetic ketoacidosis. Results also showed that a shorter duration of T1D was weakly correlated with greater perceived disturbance in school/day-care. VAS scores were also collected for FoH. The majority of the participants indicated >50 mm on the VAS for SH with unconsciousness. Similarly to the results presented for perceived disturbance, fear of SH with unconsciousness was correlated with shorter T1D duration. Analysis of life satisfaction and QoL (measured through EQ-5D) with hypoglycaemia showed no correlation between life satisfaction or QoL and the number of incidents of SH within the last year. However, higher annual mean HbA1c was correlated with perceived worse health. QoL (measured through EQ-5D) for patients who had SH within the last year was significantly lower than in patients who did not have SH.

3.10.6 Studies reporting FoH in children/adolescents and their parents

Two studies reported results on FoH in children/adolescents and their parents (Gonder-Frederick et al. 2006 and Johnson et al. 2013).The study by Gonder-Frederick et al. (2006) showed a difference between girls and boys in terms of FoH. HFS worry subscale scores were significantly higher for girls than boys. The study also showed that adolescents with a history of SH with unconsciousness had significantly higher HFS total scores than those who did not. The study also included analysis of FoH in parents of adolescents with T1D. HFS Total and worry subscale scores were significantly higher for parents whose adolescents had experienced a hypoglycaemic episode at school.

The study by Johnson et al. (2013) presented results for children and their parents. Analysis of parents' FoH and their report of their children's QoL showed a significant association. Results showed that parents with the highest FoH reported lower QoL scores for their children compared to those in the lower fear quartile. No association between history of any episode of SH and the parents' perception of their children's QoL was observed. FoH was significantly higher in parents whose children had experience a severe hypoglycaemic event than those who did not. Analysis of HbA1c concentrations and parents' FoH showed no association. For children in the study, a significant association between increased FoH and reduced QoL was observed. Similar to the results of their parents no association between history of SH and QoL was observed in children. However, analysis of HbA1c concentrations showed that children with the highest FoH score had a higher HbA1c concentration compared to children in the lowest FoH quartile. Unlike their parents, episodes of SH were not associated with the children's FoH score.

3.10.7 Studies reporting FoH in parents of children with T1D

A total of 5 studies reported on FoH in parents of children with T1D (Barnard et al. 2010, Haugstvedt et al. 2010, Herbert et al. 2014, Lawton et al. 2015 and Streisand et al. 2005). The study by Barnard et al. (2010) is a systematic review of FoH in parents of children with T1D. The systematic review analysed results from 6 studies. A full description of the results has been presented in Table 12.

Briefly however, one of the included studies showed that mothers of young children with T1D reported significantly higher FoH and HFS behavioural subscale scores than fathers but no significant difference in HFS worry subscale scores. Another study reported lower levels of FoH in fathers. One study showed that hypoglycaemia severity caused higher FoH than hypoglycaemia frequency, especially if the parent's child had experienced a hypoglycaemic seizure. Barnard et al. (2010) state this was in agreement with another study which showed FoH did not relate to the number of hypoglycaemic episodes over the past 12 months in mothers. Results from another included study showed that parents of children who had experienced a hypoglycaemic seizure during the past year had higher FoH than parents whose children did not. This result was also supported in another included study where mothers whose children had a history of passing out had significantly higher HFS scores than mothers whose children had never lost consciousness. One study showed no significant correlation between HFS scores in parents and PDQOL general worry about their child having diabetes. The most common fears relating to hypoglycaemia reported by parents were: a feeling a child will have a low blood glucose level whilst asleep or away from a parent. Another study further reported that FoH in mothers was related to the degree of distress over hypoglycaemic episodes that occurred when their children were asleep or in social situations. The review also presented results on hypoglycaemia avoidance behaviours. Ones study included by Barnard et al. (2010) showed that parents of children with higher than average blood glucose levels engaged in frequent hypoglycaemia avoidance behaviours. Mothers' higher scores in the HFS behavioural subscale were thought to indicate behaviour to avoid hypoglycaemia. Another study presented common strategies for hypoglycaemia prevention and included: carrying fast-acting sugar, checking blood glucose often when attending long events, avoiding being away from their child when they suspect their child's blood glucose may go low and feeding the child at the first sign of hypoglycaemia. Furthermore another study reported that parents often carry out nocturnal blood glucose blood monitoring.

In a study by Haugstvedt et al. (2010) significant associations between parental HFS worry subscale score and HbA1c were observed. In addition, a parent reported co-morbid disease and a higher frequency of parent reported problematic hypoglycaemic episodes during the previous year were also associated with a higher score on the worry subscale. Parental HFS behaviour subscale scores were significantly higher in parents of children receiving insulin injections than the parents of children using subcutaneous insulin infusion devices. The study also showed that frequency of blood glucose measurements were positively associated with parental HFS behavioural subscale scores. Gender differences were also analysed by the authors and showed that mothers scored significantly higher on the HFS worry and behavioural subscales than fathers. However, the study showed considerable symptomatic emotional distress in mothers and fathers.

Herbert et al. (2014) investigated the relationship between school/day-care experiences of parents with young children with T1D. The study showed that school/day-care functioning scores of the PedsQL tool were negatively correlated with parent's worry as determined using the HFS-P-YC questionnaire. According to the authors this indicates that parents who perceived their children as having higher school/day-care functioning had less FoH and better T1D-realated QoL. The results from the study also indicated that child school/day-care functioning and hypoglycaemia worry were significantly associated with parent T1D-related QOL. Therefore, parents of children who

experienced greater hypoglycaemia worry with worse school/day-care functioning experienced poorer T1D-related QoL.

The study by Lawton et al. (2015) is different in study design to the other included studies. This study uses qualitative methodologies in order to explore the difficulties in trying to achieve and maintain recommended blood glucose levels faced by parents of children with T1D. The study authors identified themes from the in-depth interviews they carried out. Themes included 'FoH', 'children are unreliable reporters of hypoglycaemia', 'monitoring and supervision', 'school/nursery and other settings outside of the home' and 'home and away targets'. A full data extraction of the results has been presented in Table 12. However, a few key points from each theme will be discussed here. The 'FoH' theme presents the thoughts of parents who described an ever-present concern about hypoglycaemia. One parent stated, "you have that underlying nervousness all the time that something might happen". Parents also feared finding their child unconscious or dead in bed with one parent stating, "you're scared to go into her room in the morning, every morning". Under the 'children: unreliable reporters of hypoglycaemia' theme parents spoke about their worries of hypoglycaemia being driven or compounded by their child's difficulties detecting and reporting low blood glucose. Parents described situations where children did not notice their blood glucose levels dropping because they were enjoying an activity they were doing at the time and didn't notice or didn't want to tell their parents in case they had to stop the activity they were enjoying. The 'monitoring and supervision' theme presents parents' approaches to monitoring their child's blood glucose levels. Parents described making use of blood glucose monitoring devices in addition to recognising behaviour and physical changes which could signal the onset of hypoglycaemia. For their monitoring approaches to be successful parents spoke of the need for their child to be under their close supervision. This often means that parents give up work, take on part time employment or make changes to other aspects of their lives. The 'school/nursery and other settings outside the home' theme highlighted the lengths parents go to in order to manage their child's blood glucose level. One parent described how they would go to their child's school every day to adjust the basal rate on their child's pump. Parents also described how they would ask for school dinner menus to determine the carbohydrate contents of their child's lunch and that they made extensive use of texting or phone calls to advise staff on the correct dose of insulin to administer. Parents described changes in weather and unawareness from other parents or grandparents as being a source of anxiety. Finally, the majority of parents described using two sets of blood glucose targets in the 'home and away targets' theme. The parents described tight targets when their child was under direct parental supervision and loose targets when their child was not under direct supervision. Examples of where a loose target would be used included when their child attended school/playgroups and when older children went out to play unsupervised. Parents stated they elevate blood glucose levels purposely because they lacked confidence in their own child and teachers to recognise hypoglycaemia. Parents also elevated blood glucose levels to avoid distressing others.

The study by Streisand et al. (2005) carried out bivariate and multivariate analyses to investigate the stress faced by parents and to explore the psychological and behavioural correlates of their stress. Bivariate analysis showed that parents of younger children, non-Caucasian parents, those from lower socio-economic status families, from single parent families and those with children not using an insulin pump reported more frequent paediatric parenting stress. Multivaraite analysis showed

that parents with lower self-efficacy, greater responsibility for the child's diabetes management, and greater FoH experienced more frequent stress related to parenting their children with diabetes.

Table 11| Studies reporting fear of hypoglycaemia in children/adolescents and adults with T1D.

Study details	Population and Setting	Study Methodology	Outcomes and methods of analysis	Results	Notes
Anderbro *et al*. (2010) **Study design:** Cross-sectional study. **Country:** Sweden	**Aim of study:** To examine the fear of hypoglycaemia and its association with demographic and disease-specific variables in a large and unselective population of adult patients with Type 1 diabetes (T1D). **Setting:** Questionnaires completed by Swedish patients at home. **Participants:** 1,387 patients were sent the questionnaire with 764 responding. **Inclusion criteria:** T1D, age ≥ 18 years, onset of diabetes before 30 years of age and duration of diabetes of ≥ 1 year. **Exclusion criteria:** Not reported.	**Method of selection:** Participants (n=1,387) were identified from diabetes registries at two university hospitals in Stockholm, Sweden. All patients who met the inclusion criteria were sent the questionnaire. **Method of data collection:** The questionnaire contained a Swedish version of the previously published Hypoglycaemia Fear Survey (HFS). The survey is made up of 3 subscales: the worry, behaviour/avoidance and aloneness subscales. For this study the behaviour/avoidance subscale was omitted. Demographic data, duration of diabetes and median HbA1c was obtained from medical records. 21 questions were also added in order to capture disease-specific factors such as frequency and severity of hypoglycaemic events, unawareness of hypoglycaemia, pharmacological treatment and daily self-monitoring of blood glucose (SMBG).	**Outcomes:** Number of severe hypoglycaemic (SH) episodes, history of nocturnal hypoglycaemia and fear of hypoglycaemia (FoH). **Follow-up period:** No follow-up. **Method of analysis:** Difference between groups were analysed through χ^2 tests and unpaired t-tests with an alpha value of 0.05. Multiple linear regression was used to analyse answers from the HFS.	764/1387 eligible participants returned the sent questionnaire. **Demographic results:** Significant differences were observed between the responders (n=764) and non-responders (n=623). Non-responders were younger, more often were men, had higher HbA1c levels and had shorter duration of diabetes than the responders. **Fear of hypoglycaemia:** Women (n=384) scored significantly higher ($p<0.01$) than men (n=380) on the HFS worry subscale and aloneness subscale indicating a higher FoH in women than men. Factors associated with FoH for both men and women included 'Frequency of SH' and 'Number of symptoms during mild hypoglycaemia (MH)'. For men HbA1c, 'Hypoglycaemic unawareness', 'Frequency of moderate hypoglycaemia' and 'Frequency of SMBG' were also factors. For the HFS worry subscale the 'Frequency of SH' and 'Number of symptoms during mild hypoglycaemia' were factors for men and women. For men, the factor 'Hypoglycaemic unawareness' also showed an association with the score and, for women, the third factor was 'Hypoglycaemic symptoms during hyperglycaemia'	**Conclusions:** The study shows the complex relation between FoH and several disease-specific factors, of which frequency of SH is the most important one. The authors also documented gender differences in FoH with different patterns of associated factors, which may suggest that male and female patients use somewhat different strategies to avoid hypoglycaemic episodes. **Limitations:** This study was cross-sectional. The authors identify that there was a significant difference between responders and non-responders in terms of demographic characteristics. The authors also highlight that their models are of little predictive value as the adjusted R^2 values were not high.
Anderbro *et al*. (2015)	**Aim of study:**	**Method of selection:**	**Outcomes:**	469/764 contacted patients returned the sent questionnaire.	**Conclusions:**

Study design: Cross-sectional study. **Country:** Sweden	To examine the association between FoH in adults with T1D with demographic, psychological (anxiety and depression), and disease-specific clinical factors (hypoglycaemia history and unawareness, HbA1c), including SH, and differences in patient subgroups categorized by level of FoH and risk of SH. **Setting:** Questionnaire completed by Swedish patients at home. **Participants:** 764 people with T1D. **Inclusion criteria:** T1D, age ≥18 years, and diabetes duration ≥1 year. **Exclusion criteria:** Not reported.	All patients (n = 764) who participated in a previous FoH study (Anderbro *et al*. 2010) were sent a consent form and a set of questionnaires by post. All participants had T1D, were age ≥18 years, and diabetes for ≥1 year. **Method of data collection:** The questionnaire contained the Swedish translation of the HFS. The survey contained two subscales (worry and behaviour). In addition the questionnaires contained a number of tools to measure different types of psychological stress including: the perceived stress scale (PSS), the social phobia scale (SPS), the hospital anxiety and depression scale (HADS), the anxiety sensitivity index (ASI), the fear of complications questionnaire (FCQ). Alcohol habits were assessed by using the alcohol use disorders identification test (AUDIT). There was also a diabetes history questionnaire which assessed variables such as frequency and severity of hypoglycaemia, hypoglycaemic unawareness and daily SMBG.	Number of severe hypoglycaemic episodes, history of nocturnal hypoglycaemia and HFS results. **Follow-up period:** No follow-up. **Method of analysis:** Multiple linear regression analyses were used to analyse results from the HFS in conjunction with demographic, clinical and psychological variables. Differences between groups were analysed through χ^2 tests, unpaired t-tests or analysis of variance (ANOVA) tests. Sub-group comparisons were carried out following the creation of 4 sub-groups: low fear/low SH risk, low fear/high SH risk, high fear/low SH risk and high fear/high SH risk.	**Demographic results:** There were some significant differences between the responders (n=469) and non-responders (n=275). The non-responders had higher HbA1c (p=0.031), were younger (p=0.037) and had a shorter duration of diabetes (p=0.032). **HFS and demographic variables:** Gender was the only demographic variable associated with HFS scores, with women (*m* = 14.6, SD = 10.5) scoring higher than men (*m* = 11.4, SD = 9.2) on the worry (*t* = 3.397, p = 0.001), but not the behaviour subscale (*m* = 18.8, SD = 5.9 for women; *m* = 18.1, SD = 6.1 for men) (*t* = 1.121, p = 0.263). **HFS and clinical variables:** HFS scores, including frequency of SH, nocturnal hypoglycaemia, and SMBG and the number of symptoms experienced during mild hypoglycaemia were positively associated with HFS scores. **HFS and psychological variables:** The ASI, HADS anxiety subscales and the SPS were positively associated with HFS scores. **Sub-group analyses:** Patients were categorised into 4 sub-groups: low fear/low SH risk (n=136), low fear/high SH risk (n=25), high fear/low SH risk (n=101) and high fear/high SH risk (n=52). ANOVA showed a significant subgroup effect for all psychological measures, as well as for number of symptoms during mild hypoglycaemia and A1c For all anxiety-related measures, both groups with high FoH showed significantly higher scores than the low FoH groups, regardless of SH risk (p<0.001 in each instance). The same difference was found for depression, with both high FoH groups showing significantly higher scores on the HADS depression subscale. No subgroup effect was found for frequency of exercise or nights spent alone.	These findings highlight the complexity of FoH and its relationship with psychological and diabetes-related clinical factors. There is a strong link between FoH and non-diabetes related anxiety, as well as hypoglycaemia history. Comparison of patient subgroups categorized according to level of FoH and SH risk demonstrated the complexity of FoH and identified important differences in psychological and clinical variables, which have implications for clinical interventions. **Limitations:** The authors identify that there was a moderate response rate and that by their definition the majority of patients were at low risk for SH. In addition there is large heterogeneity in terms of the numbers of patients who fall into each sub-group. This should be kept in mind whilst interpreting the ANOVA results. The study design is cross-sectional and therefore it is not possible to draw causal conclusions. Psychological, demographic and diabetes-related clinical outcomes

		Median HbA1c levels during the past two years were calculated from patient medical charts.			may drive FoH or FoH may be the driver.
Gjerlow *et al*. (2014) **Study design:** Cross-sectional **Country:** Norway.	**Aim of study:** To investigate specific fears related to hypoglycaemia in adults with T1D and to investigate how aspects of FoH may differ between genders. **Setting:** Study invitations and questionnaires were sent to patients attending an outpatient clinic in St. Olavs Hospital, Trondheim, Norway. **Participants:** 636 adults with T1D. **Inclusion criteria:** Adults aged 18-75 years and diabetes duration of 2 years. **Exclusion criteria:** None reported.	**Method of selection:** All patients meeting the inclusion criteria and treated at the centre were mailed a questionnaire. **Method of data collection:** FoH was assessed using the Norwegian version of the HFS-II-Worry questionnaire. Clinical characteristics were obtained using another questionnaire and included questions on history of SH. Awareness of hypoglycaemia was also determined. Data obtained from the questionnaire were supplemented with data from hospital records.	**Outcomes:** FoH and gender differences in FoH. **Follow-up period:** Not reported. **Method of analysis:** The Mann-Whitney *U* test was used to examine if HFS-II-worry scores differed between genders. Statistical significance was corrected for multiple comparisons using a Bonferroni correction. For each item the proportions of women and men with high scores were calculated and a χ^2 test used to determine if proportions differed between men and women. The independent samples t-test was used to analyse differences in age, diabetes duration and HbA1c between responders and non-responders within each gender.	445/636 contacted patients gave informed consent and returned the questionnaire. **Demographic and clinical characteristics of responders and non-responders:** - Women: Responders (n=216): mean age (years) 40.6 (SD±14.4); diabetes durations (years) 23 (SD±11.9); HbA1c 8.1 (SD±1.1). Non-responders (n=76): mean age (years) 37 (SD±12.9); diabetes duration (years) 19.9 (SD±12.1); HbA1c 8.7 (SD±1.6). - Men: Responders (n=229): mean age (years) 43.4 (SD±14.1); diabetes duration (years) 22.5 (SD±12.7); HbA1c 7.9 (SD±1.2). Non-responders (n=103): mean age (years) 35.3 (SD±12.4); diabetes duration (years) 18.7 (SD±10.5); HbA1c 8.3 (SD±1.4). **Mean differences by gender:** The mean score across all items in the HFS-II-worry was 2.46 (SD±0.8) in women and 2.22 (SD±0.74) in men ($p<0.001$). The items with the highest mean scores were the same in men and women: "becoming hypoglycaemic while sleeping" (3.14 in women, 2.93 in men) and "not having food available" (2.98 in women and 2.69 in men). Women scored numerically higher than men in all items and in 5/18 items the gender difference was statistically significant (mean scores presented): "interferes with important things" (2.96 in women, 2.54 in men; $p<0.001$), "upset and difficult" (2.44 in women, 2.06 in men; $p=0.001$), "difficulty thinking clearly" (2.68 in women, 2.3 in men; $p<0.001$), "lightheaded or dizzy" (2.18 in women, 1.81 in men; $p<0.001$), "passing out in public" (2.2 in women, 1.87 in men; $p=0.002$). **High scores by gender:**	**Conclusions:** Women expressed higher number of concerns for hypoglycaemia than men. The highest scores for women and men occurred in the same items, but the largest gender differences appeared in other items, including some items related to social esteem. The results may be useful for providing individualised advice for patients with T1D to diminish their FoH and improve their glycaemic control. **Limitations:** The authors highlight that the responders had no opportunity to express specific concerns about hypoglycaemia other than those included in the HFS-II-worry.

				For each item, the proportion of women and men with high scores was calculated. The items having largest proportions of high scores were similar in women and men: "becoming hypoglycaemic while sleeping" (40% of women, 33% of men), "not having food available" (28% of women, 21% of men) and "low blood glucose interfering with important things" (31% of women, 19% of men).In all items except one ("having hypoglycaemia while driving") the proportion with high scores was higher in women than in men.	
Hendrieckx *et al*. (2014) **Study design:** Cross-sectional **Country:** Australia.	**Aim of study:** To investigate SH in adults with T1D and its associations with impaired awareness of hypoglycaemia (IAH), clinical, psychological and socio-demographic factors**.** **Setting:** Questionnaire booklets completed in one of three specialist clinics by patients. Data collections took place between October and December 2011 (site 1), and between February and May 2012 (sites 2 and 3). Patients were also permitted to complete the questionnaire booklet at home and returned it by post or on their next visit. **Participants:**	**Method of selection:** Upon arrival in the clinic all participants who met the study's inclusion criteria were invited to participate in the study by a research assistant and/or diabetes nurse educator or endocrinologist (sites 1 and 2), clinical researcher and/or endocrinologist (site 3), who provided attendees with written information and answered questions about the study. **Method of data collection:** The questionnaire booklet included seven pages of questions; four pages focused on hypoglycaemia (recall of events, IAH and FoH) with the remaining pages focused on psychological well-being and demographic/clinical questions. The booklet contained: items derived from the Hypoglycaemia Awareness	**Outcomes:** Prevalence of self-reported SH, IAH and psychological measures (including general emotional well-being, diabetes-related distress, diabetes-specific positive well-being, FoH). **Follow-up period:** No follow-up. **Method of analysis:** Comparative analysis was carried out by splitting the participants into two groups (participants with a Gold score of ≥4 (IAH) and those with scores <4 (no IAH)). Groups were compared using the χ^2 test, the Student's t-test or Mann–Whitney U-test, according to whether data were categorical/continuous and normally distributed. Logistic regression was conducted to establish factors associated with the occurrence of SH (one or more SH versus none in past	444/502 eligible adults invited to take part consented and completed the questionnaire. 22 questionnaires were discarded due to missing data to give a final number of 422. **Associations between SH, socio-demographic and clinical characteristics:** Participants who experienced at least one SH event were younger at diabetes onset, had longer diabetes duration and were more likely to have IAH than those who did not report SH in the past 6 months. In addition participants who experienced at least one SH event experienced fewer symptoms of hypoglycaemia and relied more often on others to recognise a hypoglycaemic event than those not reporting SH. **Association between SH and psychological outcomes:** Participants who reported at least one SH event in the past six months reported greater diabetes-related distress ($t = -3.46$, $df = 414$, $p < 0.001$), greater FoH ($t = -5.22$, $df = 97.6$, $p < 0.001$), lower general emotional well-being ($t = 3.35$, $df = 415$, $p < 0.001$) and lower diabetes-specific positive well-being ($t = 3.36$, $df = 414$, $p < 0.001$). Groups differed on both behavioural and worry subscales of the HFS: participants experiencing SH were more worried about hypoglycaemia ($t = -6.35$, $df = 417$, $p < 0.001$) and made more behavioural changes to avoid hypoglycaemia ($t = -3.18$, $df = 103.3$, $p < 0.001$) than those not reporting SH. After controlling for diabetes duration and age at onset greater IAH, greater FoH and lower diabetes-specific	**Conclusions:** One in five Australian adults with T1D experienced a SH event in the past six months, which was associated with IAH, longer diabetes duration and impaired psychological well-being. The study indicates that it is important to assess hypoglycaemia, IAH, and psychological well-being as part of the routine diabetes clinic, to identify those requiring additional support and to inform tailored medical, educational or therapeutic interventions. **Limitations:** The authors highlight that the self-reported nature of the questionnaires has not been validated against objectively collected data on patient hypoglycaemic episodes.

	502 people T1D attending one of three specialist clinics. **Inclusion criteria:** Patients were eligible if they were aged ≥18 years, had been diagnosed with T1D for more than six months and were able to complete the survey in English without assistance. **Exclusion criteria:** Patients who visited clinic more than once during the 12 week study period were not approached on subsequent visits.	Questionnaire (HypoA-Q), Gold score (IAH assessment), through the World Health Organisation well-being index (WHO-5) (general emotional well-being assessment), the Problem Areas in Diabetes Scale (PAID) (diabetes-related stress assessment), the diabetes-specific positive well-being subscale of the Wellbeing Questionnaire-28 (W-BQ28) (diabetes-specific positive well-being) and the HFS which included the worry and behaviour subscales. The questionnaire booklet also collected information on age, gender, education, living situation, age at diabetes onset, diabetes duration, insulin delivery regimen (number of insulin injections/continuous subcutaneous insulin infusion (CSII)). The type of insulin used by the patient and the most recent HbA1c were retrieved from medical records.	6 months). In addition, to account for the skewed distribution, a log-linear negative binominal regression was conducted.	positive well-being were significantly associated with the occurrence of SH ($\chi^2 = 75.28$, df = 7, $p < 0.0001$). The negative binominal regression generated the same result ($\chi^2 = 143.2$, df = 7, $p < 0.0001$): more frequent SH was associated with IAH ($p < 0.001$), greater FoH ($p < 0.001$) and lower diabetes-specific positive well-being ($p < 0.05$). Age at diabetes onset contributed significantly to the final model ($p < 0.05$).	
Leiter *et al*. (2005) **Study design:** Prospective, cross-sectional.	**Aim of study:** To assess the impact of mild, moderate and SH and fear of future hypoglycaemic episodes on adults with T1D or insulin-treated T2D.	**Method of selection:** At each site, upon arrival at a scheduled clinic visit, a research assistant provided all patients meeting the inclusion criteria with details about the study. To be	**Outcomes:** Number of hypoglycaemic episodes (mild, moderate and severe), glucose monitoring, changes to insulin regimen following a hypoglycaemic episode and	335/345 eligible patients were enrolled on the study. This number included people with T1D (n=202) and insulin-treated T2D (n=133). **Fear of hypoglycaemia** Following a mild or moderate hypoglycaemic episode, more T1D patients reported increased fear of future hypoglycaemia (37.8%) than insulin-treated T2D patients	**Conclusions:** This study has shown that fear of hypoglycaemia significantly affects patient health outcomes such as glycaemic control and management, self-

Country: Canada	**Setting:** The study was conducted in four Canadian centres between July to December 2003; 2 sites in Quebec and 2 sites in Ontario. **Participants:** 345 people with T1D or T2D. **Inclusion criteria:** Male and female patients ≥18 years of age, with a diagnosis of T1D or T2D, treated with insulin alone or in combination with oral agents for ≥1 year, and able to provide informed consent were screened for enrolment. **Exclusion criteria:** No exclusion criteria were presented.	included in the study, all participants or their legal guardian provided written informed consent. **Method of data collection:** Enrolled patients completed the 30 minute questionnaire whilst waiting for their clinic appointment. The self-administered questionnaire collected data on frequency of hypoglycaemia, impact of hypoglycaemia on behaviour and glycaemic management, cost of diabetes management and post-hypoglycaemia lifestyle infringements. On the self-administered questionnaire, patients recorded the frequency of mild or moderate hypoglycaemic episodes experienced during the preceding 1 month, and the frequency of SH experienced during the preceding 12-month period and lifetime. For each patient providing consent, data regarding glycaemic control, co-morbidities, diabetes-related complications and current treatment were collected by the research assistant from the patient's medical chart and recorded on a separate physician data collection form. Data collected	changes to lifestyle following a hypoglycaemic episode. **Follow-up period:** No follow-up. **Method of analysis:** All data were recorded on a database. However, no information has been provided on how the data were analysed or what statistical tests were carried out.	(29.9%). However, subsequent to a severe hypoglycaemic episode, 84.2% of T2D vs. 63.6% of T1D patients reported greater fear of future hypoglycaemia. **Changes to insulin regimen and lifestyle following a hypoglycaemic episode** Patients with T1D "sometimes" or "always" modified their insulin dose 78.5% of the time following severe and 74% of the time following mild or moderate hypoglycaemia. Patients with T2D reported "sometimes" or "always" modifying their insulin dose 57.5% of the time following severe and 43% of the time following mild or moderate hypoglycaemia episodes. Following hypoglycaemia, the most frequent lifestyle changes reported by patients with T1D were modification of insulin dose (74.1% for mild or moderate and 78.2% for severe), followed by consumption of additional food (66.8% for mild or moderate and 70.9% for severe).	treatment modifications and post-episode lifestyle infringements, all resulting in the utilization of considerable personal and healthcare resources. **Limitations:** The authors noted that the generalisability of the results may have been affected by excluding patients who did not speak English or French. Additionally, the majority of the patients were recruited from diabetes specialist clinics and were likely aware of the value of regular visits to their physician. Furthermore, a participation bias may exist as those who volunteered to participate may have been more concerned and knowledgeable about their disease and its management than the general population. There is no information on how data were handled and no description of the statistical analyses undertaken.

		included: patient demographics, laboratory values, treatment information (diabetes medication and dose), method of administration (injection, oral or pump), frequency of administration, complications and co-morbidities.			
McCoy et al. (2013) **Study design:** Cross-sectional **Country:** USA	**Aim of study:** To establish the prevalence of self-reported hypoglycaemia among ambulatory patients with diabetes and assess its impact on health-related quality of life (HRQoL). **Setting:** Postal surveys were sent to participants. **Participants:** 875 adults with diabetes mellitus. **Inclusion criteria:** ≥18 years old with established diabetes mellitus. **Exclusion criteria:** No exclusion criteria reported.	**Method of selection:** Adults with established diabetes mellitus were identified on the basis of an index diabetes related clinical encounter with a healthcare professional documented in the Diabetes Electronic Management System (DEMS) between August 1 2005 and June 30 2006. **Method of data collection:** Participant demographics and most recent HbA1c were recorded in the electronic medical record (EMR) and DEMS. Diagnoses were extracted from the International Classification of Diseases (ICD)-9 codes and EMR review. Administrative and EMR data were used to derive the Charlson co-morbidity index (CCI) for the 1 year prior to survey disbursement. The self-administered postal survey was designed to assess the frequency of	**Outcomes:** Prevalence of patient-reported hypoglycaemia, patient well being and health related quality of life, anxiety and FoH. **Follow-up period:** Not reported. **Method of analysis:** Uni-variate analyses were performed to obtain descriptive statistics of individual variables. Measures of association were tested using bi-variate analyses (two-sample *t* test for continuous variables and χ^2 test for categorical variables). Multi-variable analysis was used to adjust for factors potentially contributing to hypoglycaemia, including age, gender, duration of diabetes and CCI.	418/875 patients completed and returned the postal survey. **Differences between responders and non-responders** There was no difference between responder and non-responders with respect to gender, diabetes type or CCI. However, responders were somewhat older, had longer duration of diabetes and had a slightly lower HbA1c compared to non-responders. **Baseline characteristics** - Mean age (years) = 65.6 (SD±14.3) - Number of men (%) = 233 (55.7%) - Number with T1D (%) = 92 (22%) - Mean diabetes duration (years) = 19.4 (SD±13.5) - Mean HbA1c = 7.4 (SD±1.1) - Mean CCI = 2.0(SD±1.8) **Prevalence of self-reported hypoglycaemia** One or more episodes of SH over the preceding 6 months was reported by 81 (19.4%) respondents: 26 with T1D (28.3%) and 55 with T2D (16.9%) (p=0.02). Among patients with T1D only age was positively correlated with increased self-report of SH (p=0.049). **Patient well-being and health related quality of life** SH, in T1D, did not have a significant association with HRQoL impairment or self-rating of health as measured by the EQ-5D utility index. **Anxiety and fear of hypoglycaemia** There was a non-significant increase in FoH in patients with T1D reporting SH compared to those reporting no/mild hypoglycaemia. However, FoH was generally	**Conclusions:** Self-report of hypoglycaemia is common and is associated with increase FoH and impaired HRQoL and may also promote counterproductive health behaviours, particularly in patients with T2D. Self-efficacy is decreased in T1D patients who reported SH, which highlights the need for timely interventions. **Limitations:** By focusing on self-report of hypoglycaemia, not all hypoglycaemic events experienced by patients, with little or no hypoglycaemia awareness could be detected. The study relied on voluntary mailed questionnaires and so has the potential for response bias.

		hypoglycaemia, generalised anxiety, FoH, self-efficacy in hypoglycaemia detection/management and HRQoL. The concepts were measured using the following instruments: EQ-5D, HFS, generalised anxiety disorder (GAD)-7 survey, 3 questions adapted from the confidence in diabetes self-care (CIDS) survey, a self-rating of health across 5 dimensions and frequency of hypoglycaemia in the prior 6 months (defined as mild and/or severe). Additional questions queried mode of diabetes management and frequency of SMBG.		higher in patients compared with those with T2D ($p<0.001$). Confidence in the ability to recognise and manage hypoglycaemic event (self-efficacy) was significantly lower in patients in with T1D reporting SH than those reporting no/mild hypoglycaemia (10.4 vs. 8.9 respectively; p=0.02).Nearly all patients with T1D reported regular glucose self-monitoring regardless of history of hypoglycaemia.	
Nordfeldt and Ludvigsson (2005) **Study design:** Cross-sectional **Country:** Sweden	**Aim of study:** To explore the occurrence of fear and other disturbances of SH, and their average perceived magnitude in comparison to other aspects of T1D, in children and adolescents with modern intensive treatment including active education and psychological support. **Setting:** Questionnaires were mailed to children and adolescents with T1D. **Participants:**	**Method of selection:** Eligible children and adolescents diagnosed in the catchment area belonging to the University of Linköping, Sweden were invited to participate. **Method of data collection:** Clinic visits were scheduled at 3 month intervals where SH was prospectively self-reported on a long-term basis by the patients and/or families at every visit. Questionnaires were sent to eligible patients and the person most responsible for treatment was asked to respond. The questionnaire	**Outcomes:** Perceived problem, perceived disturbance, fear and quality of life. **Follow-up period:** Not reported. **Method of analysis:** Non-parametric Friedman, Wilcoxon signed rank Mann-Whitney *U* and Spearman rank correlation tests were used. The χ^2 test was used for proportions. Significance level was p=0.05.	74/112 patients returned the questionnaire.. **Difference in the characteristics of responders and non-responders** Responders and non-responders did not differ significantly in age, sex, age of T1D onset, duration of T1D or proportion with SH within the last year. However, responders had slightly lower yearly mean HbA1c than non-responders (median 6.8 vs. 7.3 respectively; p=0.021) and lower yearly mean insulin dose (median 0.89 vs. 1.01 respectively; p=0.045). **Clinical characteristics at baseline** - Mean age (years) = 12.1 (SD±3.8) - Mean T1D onset age (years) = 6.8 (SD±3.6) - Mean T1D duration (years) = 5.3 (SD±3.4) - Mean insulin (U/kg x d) = 0.97 (SD±0.28) - Mean yearly HbA1c = 6.8 (SD±0.9). **Perceived problem**	**Conclusions:** SH frequently causes fear and various disturbances in spite of active education and psychosocial support. There is a potential for increased quality of life from interventions targeted at the prevention of SH. Further research and improved strategies for the prevention of SH are needed. **Limitations:** The study population was too small for stratification by age, insulin types and regimes or other factors. It may be beneficial to study

	112 children and adolescents with T1D. **Inclusion criteria:** <19 years and with a T1D duration of >1 year after onset. **Exclusion criteria:** No exclusion criteria were presented.	contained visual analogue scales (VAS), 1-5 Likert type scales and open questions. EQ-5D was also included.		VAS 0-100 mm (no problem-large problem): SH median (range) VAS=76 (0-100), mild hypoglycaemia median (range) VAS=23 (0-99); p<0.0001). There was a weak correlation between perceived problem and number of events of SH during the preceding year (r=0.24; p=0.0265). **Perceived disturbance** Number of patients indicating > 50 mm on the VAS 0-100 mm (not at all disturbing-very much disturbing): 45 patients (63%) for the risk of SH, 16 (22%) for the risk of mild hypoglycaemia, 20 (27%) for insulin injections and 15 (22%) for blood glucose tests. Adolescents responding on their own found injections less disturbing than those responding with the help of parents (p=0.026). No such difference was seen for SH. Average perceived disturbance in different life situations for SH with unconsciousness was higher than SH without unconsciousness but needing assistance, mild hypoglycaemia and diabetic ketoacidosis: 3.6 (SD±1.4), 3.3 (SD±1.2), 2.5 (SD±1.1), 1.8 (SD±1.1) respectively (p<0.001). Greater perceived disturbance in school/day-care was weakly correlated with shorter T1D duration (r=0.25, p=0.0269). **Fear** Number of patients indicating >50 mm on the VAS 0-100 mm (not afraid at all-panic): 10 patients (14%) for mild hypoglycaemia, 38 (51%) for SH without unconsciousness, 53 (72%) for SH with unconsciousness, 41 (56%) for potential late complications, 17 (24%) for ketoacidosis, 9 (12%) for insulin injections, 2 (3%) for blood glucose test. Greater fear of SH with unconsciousness was correlated with shorter T1D duration (r=0.34; p=0.0206). No correlation with T1D duration was seen with other fear readings. **"How good is life"** Number of patients indicating >50 mm on the VAS 0-100 mm (not at all-very much): 23 patients (31%) for T1D in general, 23 (31%) for the risk of SH with unconsciousness, 16 (22%) for the risk of SH without unconsciousness, 11	adolescents separately from parents.

				(15%) for the risk of mild hypoglycaemia and 8 (11%) for the risk of ketoacidosis. **Life satisfaction** Patients indicated their life satisfaction on a VAS 0-100 mm (worst possible mood-best possible mood). There was no correlation with number of incidents of SH. The median in the group with SH within the last year was 73.5 vs.81.5 in the group without SH (no significant difference). **Quality of life (EQ-5D)** There was no significant correlation with the number of incidents of SH but higher HbA1c year mean was correlated with perceived worse health (r=0.32; p=0.0227), independent of age or questionnaire responder. The EQ-5D median weight for all patients was at the maximum 1.00 (range 0.2-1.00), but lower for patients with SH within the last year compared to those without (median 0.85 vs. median 1.00; p=0.0114). Out of those indicating some limitation of their quality of life (EQ-5D<1.00, n=29), a higher proportion had reported SH within the last year.	

ANOVA, analysis of variance; ASI, anxiety sensitivity index; AUDIT, alcohol use disorders identification test; CCI, Charlson co-morbidity index; CIDS, confidence in diabetes self-care; CSII, continuous subcutaneous insulin infusion; DEMS, diabetes electronic management system; DM, diabetes mellitus; EQ-5D, EuroQoL-5D; EMR, electronic medical record; FCQ, fear of complications questionnaire; FoH, fear of hypoglycaemia; GAD, generalised anxiety disorder; HADS, hospital anxiety and depression scale; HFS, hypoglycaemia fear survey; HRQoL, health-related quality of life; HypoA-Q, Hypoglycaemia Awareness Questionnaire; IAH, impaired awareness of hypoglycaemia; ICD, international classification of diseases; MH, mild hypoglycaemia; PAID, Problem Areas in Diabetes Scale; PSS, perceived stress scale; SD, standard deviation; SH, severe hypoglycaemia; SMBG, self-monitoring of blood glucose; SPS, social phobia scale ; T1D, type 1 diabetes; VAS, visual analogue scale; W-BQ28, Wellbeing Questionnaire-28; WHO-5, World Health Organisation well-being index.

Table 12| Studies reporting fear of hypoglycaemia in parents of children with type 1 diabetes or where fear of hypoglycaemia has been reported for both children with type 1 diabetes and their parents.

Study details	Population and Setting	Study Methodology	Outcomes and methods of analysis	Results	Notes
Barnard *et al*. (2010) **Study design:** Systematic review	**Aim of study:** To systematically review studies evaluating the fear of hypoglycaemia in parents of children under 12 years of age with type 1 diabetes (T1D), assess the effect on hypoglycaemia avoidance behaviour and on glycaemic control, and identify interventions which are effective in reducing fear of hypoglycaemia (FoH) and hypoglycaemia avoidance behaviour. **Setting:** Not applicable. This systematic review incorporated a range of primary studies with various settings. **Participants:** Parents (or other primary carers) of children with T1D. **Inclusion criteria:** All study designs were eligible for inclusion. Studies with parents (or primary carers) of children under 12 years with T1D on any insulin regimen were included.	**Method of selection:** Study selection was carried out by two reviewers. Titles and abstracts were examined for inclusion by two reviewers. Full copies of papers which appeared to fulfil the inclusion criteria (or where there was doubt) were obtained and were independently selected by two reviewers for inclusion in either phase of the review. Disagreements were resolved by discussion. **Method of data collection:** The quality of each study was assessed using tools appropriate to the study design. Quality was assessed independently by two reviewers. Disagreements were resolved through discussion. Data were extracted independently by one reviewer using a standardised data extraction table and checked for accuracy by a second reviewer. Disagreements were resolved through discussion and with reference to the original article.	**Outcomes:** The extent of parental FoH, the effect of parental hypoglycaemia avoidance behaviour on child's glycaemic control as reflected in HbA1c or frequency of hypoglycaemic episodes or admissions for metabolic derangements, the effect of parental FoH on parent's quality of life, anxiety, and depression, the impact of any intervention aimed at reducing parental FoH. **Follow-up period:** No follow-up. **Method of analysis:** A meta-analysis was not possible due to the lack of data and the differences in populations and outcome measures. Studies were, therefore combined in a narrative synthesis. Possible reasons for conflicting results were also reported narratively. Differences by treatment (multiple daily injections versus insulin pump therapy versus conventional regimens) were to be explored in subgroup analysis but treatment	**Included studies:** 199/1649 studies met the initial inclusion criteria based on title and abstract only. Once investigated at full text a total of 8 papers were included from 6 studies. **Demographic results** The mean number of parent/caregiver participants taking part was 79 (range 24 to 114). The number of child participants was reported in four ranged from 32-81. One paper report results in a subset of 24 patients on continuous subcutaneous insulin infusion (CSII). The percentage of female parents/caregivers ranged from 60%-100%. One included study included only male parent/caregivers as participants. The ages of participating children ranged across studies from 2 to 11 years (means 4.45 +/- 1.5 to 5.7 +/- 1.8 years). The duration of the children's diabetes was less than 3.5 years in all studies, ranging from one month to five years. **Fear of hypoglycaemia:** One study showed mothers of young children with T1D reported greater FoH than fathers of young children (p = .006) and higher scores on the behavioural subscale, (p = .001), but there were no statistically significant differences between mothers and fathers on the worry subscale. Another study reported low levels of hypoglycaemic fear in fathers (mean = 16.7, range 0-44). Greater paternal paediatric parenting stress however, in this study, was correlated with fathers' psychological resources including lower self efficacy about diabetes management (r = -.46, p =< .01), more FoH (r = .43, p =< .01), more state anxiety (r = .67, p =< .001) and less hope (r = -.60, p =< .001). It was reported in one study that severity of hypoglycaemia was more important in causing fear than frequency, especially in parents whose child had	**Conclusions:** Parents of a child with T1D report a high level of anxiety and fear associated with managing the condition. There is some suggestion that hypoglycaemia avoidance behaviours by parents might adversely affect glycaemic control. **Limitations:** The authors identified limitations with their review which centred on a limited evidence base and argued that issues affecting parental FoH are complex and multi-faceted.

	Exclusion criteria: No exclusion criteria were presented.		regimen was not reported in most of the studies.	experienced a hypoglycaemic seizure. This was in agreement with another study which showed mothers' level of fear (as assessed by the hypoglycaemia fear survey (HFS)) did not relate to the number of hypoglycaemic episodes over the previous twelve months. Another study reported that mothers' level of fear was related to their degree of distress over hypoglycaemic episodes that occurred when their child was asleep (r = .372, p = .005) or in social situations (r = .279, p = .03); but was not related to maternal confidence in their ability to treat hypoglycaemia or to their confidence at being able to recognise hypoglycaemia. In a different study the parents of children who had experienced a hypoglycaemic seizure within the past year were shown to have significantly greater overall FoH (both behaviour and worry scales) than those whose children had not experienced a seizure. Furthermore, children who had experienced a seizure with loss of consciousness had a significantly higher percentage of self monitoring of blood glucose (SMBG) values above the desired target range than young children with no history of seizures (p = 0.03). This finding was supported in another study where mothers whose children had a history of passing out had significantly higher HFS scores than mothers whose children had never lost consciousness (79.6 +/- 13.9 versus 70.2 +/- 14.7, p = .040). One study showed no significant correlation between the parental HFS total score and parental diabetes quality of life (DQoL) general worry about their child having diabetes (r = 0.34, p =< 0.06). One study assessed the most common fears reported by parents relating to hypoglycaemia. These were feeling the child will have a low blood glucose level while asleep (63% of participants), and the child having a low blood glucose level when away from a parent (46%). Additional results from this study suggest that parents of children with higher average blood glucose levels reported greater FoH	

				(p = 0.05), with a trend between parents' worry score and children's daily blood glucose control (p = 0.06). **Hypoglycaemic avoidance behaviour:** In one study parents of children with higher than average blood glucose levels were reported to engage in frequent use of behaviours aimed at preventing hypoglycaemia as assessed by the HFS PYC behaviour score (p = 0.04). The higher scores in mothers on the behavioural subscale of the HFS indicated greater use of maladaptive coping behaviours to avoid hypoglycaemia (such as 'have my child eat large snacks at bedtime' and 'allow my child's blood glucose to be a little high to be on the safe side' items on HFS). Common strategies used by parents to prevent hypoglycaemia in another study were carrying fast-acting sugar (100%), checking blood glucose often when attending a long event (75%), avoiding being away from their child when his/her blood glucose might go low (67%), feeding the child at the first sign of hypoglycaemia (63%). A study reported that parents often engage in nocturnal blood glucose monitoring, and those who reported 'often/always' were more likely to have a child on a basal-bolus regimen and their child having significantly longer illness duration (p =< 0.05).	
Gonder-Frederick *et al*. (2006) **Study design:** Cross-sectional **Country:** USA.	**Aim of study:** This study tested the hypothesis that both trait anxiety and hypoglycaemic history contribute to FoH both in adolescents with T1D and in their parents, and relationships between FoH and other variables including metabolic control, symptom perception, and use of insulin pump therapy. **Setting:**	**Method of selection:** Participants were recruited with the approval of their physician at a university-based outpatient endocrinology clinic during the adolescents' regularly scheduled 3-month appointment. **Method of data collection:** The questionnaire pack contained a background questionnaire for parents: this focused on family demographic information, medical history, and diabetes	**Outcomes:** FoH and trait anxiety. **Follow-up period:** Not reported. **Method of analysis:** Mean replacement (individual subject mean) was used when there were missing data on questionnaire items. Additionally, we performed z-score transformations to allow comparisons of parent and adolescent trait anxiety data as the STPI and the STAIC questionnaires had	39 families (78 total participants) returned questionnaires, from both the parent and adolescent, that were adequate for data analysis (no or minimal missing data). **Participant characteristics** 17 girls and 22 boys made up the adolescent participants. The mean age was 15.36 years (SD±1.53), mean duration of diabetes was 7.03 years (SD±4) and mean HbA1C was 7.85 (SD±1.09). **Fear of hypoglycaemia (adolescents)** HFS Worry Subscale scores were significantly higher for girls than for boys (32.4 and 25.8, respectively; t = -2.43, p = 0.02). Adolescents with a history of unconsciousness due to SH had higher HFS Total scores than those with no history of unconsciousness (72.2 and 63.9, respectively; t = -2.69, p = 0.011). There were no differences in adolescents who used an insulin pump and those who did	**Conclusions:** Trait anxiety levels and recent experiences with hypoglycaemia predict FoH in adolescents with T1D. In parents, however, beliefs about their adolescents' ability to cope with hypoglycaemic episodes predicted FoH. FoH in adolescents with T1D and their parents is a complex construct influenced by multiple personality and situational and behavioural factors, and its impact on

	Questionnaires were given during a visit to an outpatient endocrinology clinic and could be completed at home and posted if necessary. **Participants:** 63 adolescents with T1D and 61 parents. **Inclusion criteria:** Adolescents between 12 and 17 years old, diagnosed with T1D for at least 1 year, and who had the ability to complete the questionnaires (e.g., no mental retardation or significant reading disability). One parent involved with the adolescent's diabetes care also needed to participate. Both adolescents and parents gave consent for the researchers to obtain the clinic results of blood drawn for HbA1c, a measure of glucose control, during the previous 6–8 weeks. **Exclusion criteria:** Significant co-morbidity in the adolescents that could affect psychosocial status, quality of life, or FoH (e.g., cystic fibrosis)	history, including recent experiences with hypoglycaemia (including number of episodes of mild and severe hypoglycaemia) and other information regarding diabetes management. A parent version of the HFS was included and a child version. The State-Trait Personality Inventory (STPI) and the State-Trait Anxiety Inventory for Children (STAIC) were also included.	different numbers of items and were rated on different scales. For group comparisons, t-tests were used. Correlations were used to examine relationships between parent and adolescent HFS and trait anxiety scores, other variables were hypothesized to predict FoH (e.g., frequency of mild hypoglycaemia (MH) and severe hypoglycaemia (SH)), and demographic/clinical variables (e.g., age of adolescent, diabetes duration, HbA1c). To identify variables that predicted HFS scores, separate stepwise regressions were conducted for parents and adolescents, as well as for the total score, worry subscale, and behaviour subscale.	not on either the HFS scales (59.8 and 57.9, respectively) or trait anxiety measures (26.6 and 28.5, respectively). **Fear of hypoglycaemia (parents)** Parents whose adolescents had experienced a hypoglycaemic episode at school had higher HFS Total scores (64.6 and 43.8, respectively; t = -2.82, p =0.007) and Worry Subscale scores (35.1 and 21.3, respectively; t = -2.7, p = 0.010) compared to those whose adolescents had not. There were also no differences in parents of adolescents who used an insulin pump and those whose child did not on either the HFS (58.3 and 60.6) or trait anxiety measures (12.9 and 15.8, respectively).	diabetes management remains unclear. **Limitations:** A total of 22 families failed to return completed questionnaires for both the adolescent and the parent, even after a telephone call reminder and request. The authors did not collect demographic questionnaires on non-participating families, the authors could not compare them to those who participated. Only one father participated in this study.

	and cognitive or learning disabilities in the child or the parent (e.g., inability to read) that would preclude their ability to complete the study protocol.				
Haugstvedt *et al*. (2010) **Study design:** Cross-sectional **Country:** Norway.	**Aim of study:** To analyse the association between parental FoH and (i) the prevalence of hypoglycaemia and diabetes treatment factors in children with T1D and (ii) emotional distress in mothers and fathers. **Setting:** Questionnaires sent to Norwegian parent's homes **Participants:** 161 parents of children with T1D. **Inclusion criteria:** Parents of children aged 0-15 years T1D. **Exclusion criteria:** No exclusion criteria were presented.	**Method of selection:** Children were identified through the Department of Paediatrics at Haukeland University Hospital (Norway). Parents of children who met the inclusion criteria were invited to participate on the study. Questionnaires and information sheets were distributed by post to their home addresses. **Method of data collection:** The sent questionnaires contained a Norwegian translation of the hypoglycaemia fear survey parent version (HFS-P). The HFS-P contains a worry and behaviour subscale. The Hopkins Symptom Checklist-25 item (HSCL-25) was used to assess parents' levels of distress.	**Outcomes:** FoH and emotional distress. **Follow-up period:** No follow-up. **Method of analysis:** Regression analyses were carried out to model variables associated with parents' HFS-P worry and behaviour subscales. Pearson correlation analysis was used to analyse the relationship between HFS-P and HSCL-25 scores.	115/161 questionnaires were returned. Either one or both the parents answered the questionnaire (103 mothers and 97 fathers). 85 of the questionnaires were answered by both parents, 18 were answered by the mother only and 12 were answered by the father only. **Demographic results:** The parents of 46 children did not respond to the questionnaire. The children of non-responders were on average 1.7 years older (p=0.04) and had an average duration of diabetes 1.3 years longer (p = 0.016) than children of respondents. No significant difference was observed in mean HbA1c levels (8.1% responders, 8.3% non-responders; p=0.26). **Variables associated with HFS-P worry score:** A significant (p=0.008) association between HFS-P worry score and higher HbA1c was observed. A higher frequency of parent-reported problematic hypoglycaemic episodes during the past year (≥7 episodes; p=0.005) and parent-reported co-morbid disease (p=0.006) were also significantly associated with a higher worry score. **Variables associated with HFS-P behaviour score:** HFS-P behaviour scores were significantly higher in the parents of children receiving insulin injections than in children using CSII (p<0.001). The frequency of blood glucose measurements and HFS-P behaviour subscale were also positively associated (p=0.027). **Differences between parents in fear of hypoglycaemia:** Mothers scored significantly higher on the worry scale than fathers (37.7 vs. 36.0; p=0.048) and significantly higher on the behaviour scale too (33.2 vs. 30.1; p<0.001). The HSCL-25 scores also differed by sex. The mean HSCL-25 scores were 1.39 ± 0.37 for mothers and 1.22 ± 0.25 for	**Conclusions:** The results suggest that future interventions should target both parental fear and appropriate ways to prevent hypoglycaemia in children with T1D. Healthcare providers need to consider both the mothers' and the fathers' level of FoH and emotional distress when designing interventions targeting at-risk parents in order to help improve their health and, by extension, their children's mental and physical health. **Limitations:** The authors state that the cross-sectional design of the study makes is impossible to explore the causal direction between variables. There are also limitations due to self-report bias and sample size. The authors also highlight that the HFS questionnaires have their own limitations including interpretation of scores.

				fathers, with 11%of the mothers and 5%of the fathers above the cut-off of ≥ 1.75, indicating considerable symptomatic emotional distress.	
Herbert *et al*. (2014) **Study design:** Cross-sectional data from a larger RCT. **Country:** USA.	**Aim of study:** To investigate the T1D-related school/day-care experiences of parents of young children and to examine the relationship among child school/day-care functioning, parent FoH and parent T1D-related quality of life. **Setting:** Information collected over the telephone from participants recruited from three tertiary endocrinology clinics in the US. **Participants:** 203 parents of children with T1D. **Inclusion criteria:** Participants needed to be the self-identified parent of a child between the ages of one and six years who had been diagnosed with T1D for at least six months. **Exclusion criteria:** Parents who lacked English fluency or whose children had been previously diagnosed with an additional chronic illness or a	**Method of selection:** Eligible parents were identified from three centres and were mailed a detailed letter explaining the purpose and procedure of the study. Approximately two weeks after the letter was mailed, families were called by a research team member to discuss their interest, describe the study in further detail, complete eligibility criteria and schedule a baseline phone call if the parent verbally agreed to participate. Written consent was obtained at the next scheduled clinic appointment and the child's medical chart was reviewed. **Method of data collection:** Questionnaires were completed over the phone by eligible parents who had consented to take part. The questionnaires contained the following questions and measures: a demographic and school/day-care questionnaire, medical questionnaire (parent reported), the HFS parents of young children version (HFS-P-YC), the Paediatric Quality of Life Inventory (PedsQL)	**Outcomes:** Medical/demographic characteristics related to school/day-care, child/parent functioning, relationship among school/day-care functioning, fear of hypoglycaemia and parents' diabetes related quality of life (QoL) **Follow-up period:** No follow-up. **Method of analysis:** Correlation and chi-square analyses were conducted to determine whether child and parent demographic and medical characteristics were related to school/day-care characteristics and parent concerns. Children's school/day-care functioning on the PedsQL and parents' psychosocial functioning on the HFS-P-YC and PDQOL were assessed, and correlation analyses among these variables were conducted. Linear regression was also carried out, controlling for child age, with parent T1D-related QOL on the PDQOL regressed on child school/day-care functioning on the PedsQL and hypoglycaemia worry	167/203 eligible parents provided verbal consent to participate. 134/167 of the consenting patients completed the assessment. Participating parents were predominantly female (90%), Caucasian (78%), married (84%), with a mean age of 36.8 years (SD = 5.93, Range = 22.2–60.1). Most parents (76%) reported an average household income of $50,000 or more. Mean child age was 5.33 years (SD = 1.34), and 49% were female. Average HbA1c was 65.4 mmol/mol (SD = 9); average length of T1D diagnosis was 2 years (SD = 124, Range = 0.54–5.95). 72% of children were on an intensive insulin regimen (basal/bolus or insulin pump). **Child/parent functioning:** School/day-care functioning scores on the PedsQL were significantly negatively correlated with parents' worry related to hypoglycaemia on the HFS-P-YC, $r(113) = -0.30$, $p < 0.01$, and parents' T1D-related QoL on the PDQOL, $r(113) = -0.43$, $p < 0.001$, indicating that parents who perceived their children as having higher school/day-care functioning had less hypoglycaemia fear and better T1D-related QoL. **Relationship among school/day-care functioning, fear of hypoglycaemia and parents' diabetes-related QoL:** Results indicated that child school/day-care functioning and hypoglycaemia worry were significantly associated with parent T1D-related QOL, $\beta = -0.36$, $p < 0.001$, $\beta = 0.33$, $p < 0.001$, yet hypoglycaemia avoidance behaviour was not, $p > 0.05$. The overall model was significant as well, $F(4,108) = 15.51$, $p < 0.001$, R^2 change = 0.36, $p < 0.001$. Parents of children with worse school/day-care functioning and who experienced greater hypoglycaemia worry also experienced poorer T1D-related QOL.	**Conclusions:** Parents' concerns about school/day-care functioning and FoH play an important role in parents' T1D-related QoL. The findings support the existing literature and, in conjunction with the rising prevalence rate of T1D among young children, further document the need for comprehensive research about school/day-care experiences among this age group. **Limitations:** The authors commented on the generalisability of the results in terms of socio-economic status and ethnicity of the participants. As this study was cross-sectional causal conclusions from correlations cannot be drawn. The authors also state that the study is based on parent self-report and may benefit from multiple informants.

	developmental disorder were excluded from participation.	general form and the Parent Diabetes Quality of Life Questionnaire (PDQOL). Medical charts were also reviewed to gather information such as: history of T1D-related hospitalisations and acute complications, such as T1D-related seizures and loss of consciousness and HbA1c.	and avoidance behaviour on the HFS-P-YC. Descriptive statistics were used to assess parent/child demographic and medical characteristics, school/day-care characteristics and parents' impressions of their child's school/day-care experiences.		
Johnson *et al*. (2013) **Study design:** Cross-sectional **Country:** Australia	**Aim of study:** To evaluate the association between FoH, episodes of hypoglycaemia and quality of life in children with T1D and their parents. **Setting:** Questionnaires were distributed to participating families at the Princess Margaret Hospital paediatric diabetes referral centre Australia between August 2009 and August 2010. **Participants:** 679 families of children with T1D were invited to participate. **Inclusion criteria:** Families were included if the patients (children) had been diagnosed with T1D for > 6 months, if they were able to	**Method of selection:** Eligible patients and their parents were approached at their routine diabetes clinic visit. Once consent was obtained, questionnaires were distributed to the families. **Method of data collection:** Parents of children aged 2–18 years were asked to complete questionnaires, appropriate to their child's age. Patients themselves who were aged 8–18 years were also given questionnaires**.** Questionnaires included the following measures and scales: the PedsQL Diabetes Module, the HFS (revised to create a parent and child version) which contained both 'worry' and 'behaviour' sub-scales and a modified version of the original Clarke questionnaire of hypoglycaemia unawareness.	**Outcomes:** FoH, quality of life of parents and children and HbA1c levels. **Follow-up period:** No follow-up. **Method of analysis:** The effect size of the potential risk factors of the parents' quality-of-life score and the children's quality-of-life score, as assessed using the PedsQL, were quantified through uni-variate linear regression. From these results, full multivariate models (controlling for child's age and duration of diabetes) were constructed. The primary variables of interest were parents' FoH score, children's FoH score and history of a SH. FoH scores were divided into quartiles to aid interpretation. The most recent HbA1c concentration was assessed using univariate and	325/679 eligible families completed and returned the questionnaire. In addition to the 325 questionnaires completed by the parents a further 196 children completed the questionnaire. **Demographic results:** There were differences between the responders (n=325) and non-responders (n=354) in terms of baseline characteristics. The mean age of those who participated was younger than those who did not (11.8 vs. 13.2 years, $p < 0.001$) and had a shorter duration of diabetes (4.8 vs. .5.6 years, $p = 0.003$) with a lower current HbA1c concentration [64 vs. 66 mmol/mol (8.0 vs. 8.2%), $p = 0$ .004]. **Parents' assessment of their children's quality of life:** There was a significant association between the parents' FoH and their report of their children's quality of life. Parents with the highest fear had a 12.4 point (or ~20%) lower quality-of-life score compared with those in the lowest fear quartile. There was no association between a history of any episode of SH and the parents' perception of their children's quality of life ($\beta = -2.17$, $p = 0.24$). A 10-mmol/mol (0.9%) reduction in the most recent HbA1c concentration was associated with a 2.6 point elevation in parents' perception of their children's quality of life ($p < 0.001$). **Children's assessment of their own quality of life:** There was a significant association between increased FoH and reduced quality of life in the children, with a 17-	**Conclusions:** FoH and not episodes of hypoglycaemia per se is associated with increased psychological burden for children with T1D. **Limitations:** The authors noted some limitations with the study. Due to the cross-sectional study design no assumption on causality can be made. The response rate was 48% and so may have inadvertently biased the results.

	answer the questionnaire and if the child did not have a significant co-morbid medical condition. **Exclusion criteria:** No exclusion criteria were presented.	Clinical data were extracted from the Western Australia Childhood Diabetes Database and included information on patient anthropometry, episodes of hypoglycaemia, HbA1c, treatment and demographic details.	multivariate analyses. FoH scores were compared between those who had experienced an episode of SH and those who had not. T-tests and χ^2 tests were used to compare baseline characteristics of responders and non-responders.	point or (22%) lower quality-of-life score in children in the highest FoH quartile compared with those in the lowest quartile. As with parents, a history of SH was not associated with quality of life in children [β = -3.1, p = 0.19]. Of the other potential influences, only HbA1c was associated with children's quality of life, with a higher HbA1c concentration of 10 mmol/mol (0.9%) corresponding to a 2.7-point lower quality-of-life score (p < 0.001). **Most recent HbA_{1c} concentration:** The most significant factor associated with the most recent HbA1c was the children's FoH. The children with the highest FoH score had a 7-mmol/mol (0.6%) higher HbA1c compared with those in the lowest quartile. In contrast, there was no association between the parents' FoH and HbA1c concentrations. Similarly, an episode of SH was not associated with a difference in HbA1c concentration. **Fear of hypoglycaemia:** There was a relationship between FoH in parents and episodes of SH. Parents whose children had experienced a SH event had a 6.3 point higher FoH score (p = 0.004); however, episodes of SH were not associated with the children's FoH score (p = 0.722). The effect sizes and significance of these associations were consistent through the sensitivity analysis, confirming that the magnitude and strength of these associations was consistent regardless of age of the child or duration of diabetes.	
Lawton *et al*. (2015) **Study design:** Qualitative, non-comparative. **Country:** UK	**Aim of study:** To explore the difficulties parents encounter in trying to achieve clinically recommended blood glucose levels and how they could be better supported to optimize their child's glycaemic control.	**Method of selection:** Participants from 4 Scottish paediatric departments were purposively sampled in an effort to obtain diversity of child's age, sex, diabetes duration, regimen, glycaemic control and parents' education, occupation employment status and marital status.	**Outcomes:** The difficulties parents encounter in trying to achieve clinically recommended blood glucose levels. **Follow-up period:** No follow-up. **Method of analysis:** Analysis was carried out by two researchers	The final sample comprised 38 mothers and 16 fathers of 41 children, with 14 mother-father dyads choosing joint interviews. **Fear of hypoglycaemia:** Parents described an ever-present concern about hypoglycaemia: "You have that underlying nervousness all the time that something might happen". Parents shared their fears about finding their child unconscious or dead in bed: "You're scared to go into her room in the morning, every morning"; "I feel physically sick". In some cases, parents' worries were precipitated by traumatic events,	**Conclusions:** It is not parents' FoH in isolation that leads to decisions to raise their child's blood glucose but, rather, parental fear in conjunction with other factors and considerations. Hence, to improve diabetes management in children, these factors may need to

	Setting: Parents were recruited from four Scottish paediatric departments using an opt-in procedure. Interviews were conducted at the parent's homes. **Participants:** Parents of 41 children with T1D. **Inclusion criteria:** Parents of children ≤ 12 years old with T1D. **Exclusion criteria:** No exclusion criteria were presented.	**Method of data collection:** The data were collected in the parent's own homes. In-depth interviews were the source of the data. A topic guide was used for the interviews which averaged 2 hours per interview. Interviews were digitally recorded and transcribed in full. The authors reported continued recruitment and interviewing until data saturation occurred.	independently before meeting to compare interpretations, reach agreements on identified themes, and findings and develop a coding framework capturing original research questions and emerging findings. Quotes from the original interviews have been included in relation to the identified themes.	such as when one parent found her son collapsed on the floor and "he couldn't use his arm and he couldn't use his leg and one side of his face had fallen and it literally looked like this 4-year-old child had had a stroke". In others, parents' worries had arisen from reading "horror stories" in magazines; or in one case, after learning that a colleague with T1D had been found dead in bed the same weekend as his child was diagnosed, "which was really horrific". **Children: unreliable reporters of hypoglycaemia:** Parents' worries about hypoglycaemia were often also driven or compounded by their child's difficulties detecting and reporting low blood glucose. This included: the inability of infants or toddlers to communicate how they are feeling, in some cases the child had never developed hypoglycaemia awareness, in others because children could become so engrossed in activities that they did not notice their blood glucose levels dropping or through worry that telling their parents will mean they have to stop an activity they are currently doing and enjoying. **Monitoring and supervision:** To address their worries about their child's safety, parents described making extensive use of blood glucose monitoring as well as looking out for behavioural and bodily changes which could signal the onset of hypoglycaemia. Parents noted, for these monitoring activities to be successful, their child needed to be under their close supervision. Hence, many (typically mothers) described giving up work or moving to part-time employment, as well as putting other aspects of their life on hold to keep a close eye on their child and accompany them to parties and on school trips. **School/nursery and other settings outside the home:** To address anxieties associated with sending their children to school/nursery, parents described going to considerable lengths to manage and monitor their child remotely. This included one parent, who would go into school every day so she could adjust the basal rate on her	be addressed; for instance, by training others in diabetes management and using new technologies. **Limitations:** The authors acknowledge that as data was collected in Scotland only, levels of glycaemic control may not be the same as other countries.

				child's pump accordingly. Parents also described requesting menus so they could work out the carbohydrate contents of their child's lunch and how both they and school staff made extensive use of phone or text communication to establish what children's blood glucose levels were, so that they could advise on the quantity of insulin needed to cover meals/snacks. Other situations which raise parents' concerns included unpredictable situations such as: changes in the weather which would affect their child's activity level, changes to food provided in the canteen and whether or not their child consumed their packed lunch which had been 'carb-counted'. Outside of school there are other sources of anxiety for parents such as: neighbours giving their children sweets which raise their child's blood sugar and also a lack of understanding about the disease from grandparents. **'Home' and 'away' targets:** Virtually all parents described using two sets of blood glucose targets. Tighter targets were used when the child was under direct parental supervision and food consumption and physical activity could be carefully monitored to inform titrated insulin doses. In contrast, looser targets were often used when parents could not directly monitor their child and predict and plan for their activities, such as when their child attended school and playgroups, or when older children went out to play unsupervised. They also explained that they elevated blood glucose levels because they lacked confidence in others (e.g. teachers), and their own child, to detect hypoglycaemia promptly. Some parents also indicated that they elevated blood glucose levels to avoid risking distressing others, such as the parents of their child's friends. Parents shared their worries that, if such people were to be exposed to hypoglycaemia, future invitations might be rescinded and their child ostracized. In some situations, parents also elevated blood glucose to address their own panic	

				reactions and distress, most typically at night when they described very poor and interrupted sleep.	
Streisand *et al*. (2005) **Study design:** Cross-sectional. **Country:** USA	**Aim of study:** To investigate the stress faced by parents and to explore the psychological and behavioural correlates of their stress. **Setting:** Participating families were recruited from two paediatric hospitals in the US. **Participants:** 134 parents of children with T1D. **Inclusion criteria:** Parents of children with T1D were included. However, no inclusion criteria have been presented. **Exclusion criteria:** No exclusion criteria were presented.	**Method of selection:** Families matching the inclusion criteria were recruited via specialty outpatient clinics from two paediatric hospitals. A letter initially informed families about the study prior to a follow-up telephone call that identified those interested in participating in the study. **Method of data collection:** An evaluation was scheduled with consenting families, usually on the day of the child's medical appointment. After parental informed consent and child assent were obtained, parents and children completed self-report questionnaires with the assistance of trained research personnel. Demographic characteristics and medical history were collected through a questionnaire. The questionnaires also collected information on diabetes self-efficacy through The Self-Efficacy for Diabetes Scale (SED), responsibility for diabetes management through The Diabetes Family Responsibility Questionnaire (DFRQ), FoH through the HFS and paediatric parenting	**Outcomes:** Effect of clinical, demographic, psychological and behavioural variables on stress frequency and difficulty. **Follow-up period:** No follow-up. **Method of analysis:** Pearson product-moment and point-bi-serial correlations were then used to determine bi-variate relationships of parent, child, and family demographics (age, gender, race, socio-economic status (SES), and marital status), children's disease characteristics (metabolic control, insulin pump use, and illness duration), and parent psychological and behavioural measures with paediatric parenting stress. Hierarchical regression analyses were then utilized to evaluate study hypotheses and specifically to determine the degree of association of SED, DFRQ, and HFS with paediatric parenting stress.	134 parents took part in the study (86% female). **Bivariate analyses:** Parents of younger children, non-Caucasian parents, those from lower SES families, from single parent families, and those with children not on the insulin pump reported more frequent paediatric parenting stress. Parents with lower self-efficacy for the diabetes regimen, greater responsibility for the diabetes regimen, and greater FoH reported more frequent paediatric parenting stress. Parents of younger children, those using injections versus the pump, and parents with greater responsibility for the diabetes regimen and greater fears of hypoglycaemia also reported more difficulty with paediatric parenting stress. **Multivariate Analyses:** Parents with lower self-efficacy, greater responsibility for the child's diabetes management, and greater FoH experienced more frequent stress related to parenting their children with diabetes. Parents with greater responsibility for the child's diabetes management and greater FoH experienced more stress difficulty related to parenting their children with diabetes.	**Conclusions:** Results suggest the importance of considering demographic and child disease characteristics in assessing parental stress. Furthermore, findings indicate that difficulties in parents' level of confidence in their ability to manage their child's diabetes, sharing much of the responsibility for their child's diabetes management, and high worry and concern about their child experiencing a severe low blood glucose level likely go hand in hand with increased frequency and difficulty of paediatric parenting stress. **Limitations:** The authors highlight that no conclusions about causality can be drawn given the cross-sectional nature of the study. Questionnaires were administered to parents of a relatively wide age range of children, and it is likely that stressors experienced by parents of younger children differed from those experienced by parents of older children. The study

		stress through the Paediatric Inventory for Parents (PIP).			relied upon self-report and did not use PIP domain scores and instead relied on total scale scores.

CSII, continuous subcutaneous insulin infusion; DFRQ, diabetes family responsibility questionnaire; DQOL, diabetes quality of life; FoH, fear of hypoglycaemia; HFS, hypoglycaemia fear survey; HFS-P, hypoglycaemia fear survey for parents; HFS-P-YC, hypoglycaemia fear survey for parents of young children; HSCL-25, Hopkins Symptom Checklist-25 item; IDDM, insulin dependent diabetes mellitus; MH, mild hypoglycaemia; PDQOL, Parent Diabetes Quality of Life Questionnaire; PedsQL, Paediatric Quality of Life Inventory; PIP, Paediatric Inventory for Parents; RCT, randomised controlled trial; SD, standard deviation; SED, self-efficacy for diabetes scale; SES, socio-economic status; SH, severe hypoglycaemia; SLC, seizures or loss of consciousness; SMBG, self monitoring of blood glucose; STAIC, State-Trait Anxiety Inventory for Children; STPI, State-Trait Personality Inventory; T1D, type 1 diabetes.

4 Discussion

Due to the multifaceted nature of this project and its results the Cedar analyst has split this discussion section into appropriate headings. Limitations of the methodologies followed to generate results for this report have also been discussed under the appropriate headings.

4.1 Hypoglycaemic episodes and cumulative incidence

4.1.1 Hypoglycaemic episodes using Welsh data

In order to determine the number of hypoglycaemic episodes recorded in Wales, linked data from the SAIL databank were used by the Cedar analyst. Data from PEDW and GP datasets were used. Unfortunately, data from the EDDS could not be used for this project due to a lack of granularity in the coding system used. Cedar initially planned to use the EDDS to determine the number of ambulance call outs for a hypoglycaemic episode in Wales as arrival method is coded in the dataset. At present there is no facility to obtain information quickly through acquisition of audit data from the Welsh Ambulance Service. Data was therefore obtained from the LAS, which is discussed in section (4.1.3). The lack of EDDS data is a limitation of our work. However, it is likely that patients requiring treatment for a hypoglycaemic episode in A&E will be admitted and will therefore be captured in the PEDW dataset.

The results generated from analysis of both PEDW and GP datasets shows a difference in the number of hypoglycaemic episodes annually. Differences in the number of hypoglycaemic episodes between males and females were also observed. Males had a higher number of hypoglycaemic episodes requiring hospital admission or a GP visits than females. For hypoglycaemic episodes requiring admission to hospital the difference between genders was not as large as that observed for the number of GP visits. Differences in the number of hypoglycaemic episodes were also observed for age groups. Patients ≥75 years old had more hypoglycaemic episodes requiring admission to hospital across the 6 years of data combined than any other age group. In addition, patients ≥75 years old had the highest number of hypoglycaemic episodes in 4/6 years when the data were analysed annually. However, the age group with the highest number of GP visits across the 6 years of data was the 45-54 year old age group. This is likely as a result of the large number of 45-54 year olds requiring a GP visit for a hypoglycaemic episode in 2013. When the data were analysed annually we see that patients ≥75 years old had the highest number of GP visits due to a hypoglycaemic episode in 3/6 years. Our results also showed that a number of patients required treatment from a GP and admission to hospital for a hypoglycaemic episode. Our results also show that a number of individuals experienced >1 hypoglycaemic episode per year which required GP visits or requiring hospital admission. This suggests that a number of individuals have trouble controlling their blood glucose levels.

The cumulative incidence of hypoglycaemia in Wales was calculated by combining linked data obtained from the SAIL databank and T1D registrations from the NDA. The cumulative incidence was calculated using data from 2015 only. In 2015-2016 the LHB participation rate across Wales was 100%. Previous years had a lower participation rate. It was decided that the number of registrations from 2015-2016 was more reliable than data from other years due to the 100% participation rate. It was also decided that a figure for the number of T1D registrations in Wales should not be used in conjunction with data obtained from the SAIL databank for 2010-2014 as this figure was for 2015-

2016 only. Cedar acknowledges that a calculation of cumulative incidence for all years would have been both useful and interesting. However, the decision was taken in order to reach a robust figure for the incidence of hypoglycaemia in Wales.

Validation of the dataset obtained from the SAIL databank was carried out by the Cedar analyst. The validation exercise showed that people with T1D were correctly diagnosed in 88.1% of instances in the PEDW dataset and 72.6% of instances in the GP dataset. Analysis of ICD-10 codes in the PEDW dataset showed that individuals from the Brecon register were diagnosed as "pre-existing T1D in pregnancy" in 9.7% of instances. The code for this diagnosis was not identified by the Cedar analyst or clinical coders at NWIS. The results suggest that the codes we used in both datasets may not have captured every person with T1D and therefore may not have captured all hypoglycaemic episodes. The results highlight a flaw in the use of real-world data, namely mistakes are made during coding diagnoses. Read codes in particular are difficult to analyse due to their being multiple versions and multiple codes for a single diagnosis. The Cedar analyst tried to negate the variability in coding for the GP dataset by labelling an individual with a diagnosis of T1D in the GP dataset if the individual was diagnosed with T1D in either the PEDW dataset or Brecon register. The use of real-world data, captured in datasets such as PEDW, allows researchers to access records for a large number of individuals simultaneously. This method of analysis is a trade-off between the quality of results and the time/resource taken to collect this type of data. The data held by the SAIL databank holds population data for the whole of Wales and it would be impossible to collect this volume of data individually.

4.1.2 Discussion on the published evidence for hypoglycaemia incidence

A study by the UK Hypoglycaemia Study group (2007) showed a mean number of severe self-reported hypoglycaemic episodes to be 1.1 (95% CI [0, 2.3]) per person year in adults with T1D for < 5 years and 3.2 (95% CI [1.6, 4.9]) in adults with T1D for >15 years. The study also reported a high number of mild self-reported hypoglycaemic episodes with a mean of 35.5 (95% CI [22.8, 48.2]) per person year in adults with T1D for <5 years and 29 (95% CI [16.4, 41.8]) in adults with T1D for >15 years. This study suggests that people with T1D suffer mild hypoglycaemic episodes which are likely to not be captured by health records as these are self-treated.

Frier and colleagues (Frier et al. 2016) have also quantified the self-reported frequency of non-severe hypoglycaemia in adults. Adults with T1D reported a mean of 129.7 non-severe hypoglycaemic events per year. The authors estimate that 3% (38/1282 non-severe hypoglycaemic episodes) resulted in contact with healthcare professionals. The results therefore suggest that a high number of mild/non-severe hypoglycaemic events occur annually and the majority would not be detectable through analysis of medical records. The results also show that a small number of non-severe hypoglycaemic episodes required contact with a healthcare professional. However, it is unclear how healthcare professionals were contacted. It is likely that diabetes specialist nurses provide advice on treatment through telephone contact. Furthermore, during discussions with a local Professor in Paediatric Endocrinology the Cedar analyst heard anecdotal evidence for consultants providing advice for hypoglycaemic episodes by phone. Resource use such as this would not have been captured by Cedar through its analysis of linked healthcare records. In addition to the occurrence of hypoglycaemic episodes requiring hospital admission, the NaDIA also shows that

around 25% of people with T1D are at risk of having a severe hypoglycaemic episode during their hospital stay.

4.1.3 Hypoglycaemic episodes requiring an ambulance

Cedar obtained data from the LAS on the number of attendances due to a hypoglycaemic episode. As previously discussed this information was not available to Cedar form the Welsh Ambulance Service and could not be determined from the EDDS due to a lack of coding granularity.

Data obtained from the LAS showed annual differences in the number of attendances due to hypoglycaemic episodes. A difference in the number of males and females requiring an ambulance for hypoglycaemic episodes was also apparent with a higher number of attendances for males than females. The data provided by the LAS were also stratified by age and differences in the number of attendances were observed across age groups. The highest number of attendances was for the 75-79 year age group. The data also presented results for the care pathway followed by the individual following an ambulance attendance. The results showed that the majority of patients were conveyed to an A&E department. However, a large proportion of patients were not conveyed by an ambulance and these patients were therefore treated by an ambulance crew.

Cedar calculated the cumulative incidence of hypoglycaemia requiring an ambulance attendance by combining data from the LAS and data on T1D registrations calculated from the NDA CCG data for 2015. The reason for calculating cumulative incidence for this year was due to a higher participation rate from the CCGs covered by the LAS during this time. It was decided that the number of registrations from 2015-2016 was more reliable than data from other years due to a higher participation rate. It was also decided that a figure for the number of T1D registrations in the CCGs covered by the LAS should not be used in conjunction with data obtained from the LAS for 2012-2014 as this figure was for 2015-2016 only. Cedar acknowledges that a calculation of cumulative incidence for all years would have been both useful and interesting. However, the decision was taken in order to reach a robust figure for the rate of hypoglycaemia requiring assistance from an ambulance. A limitation of the data obtained from the LAS is that the data are not restricted to people with T1D only. Therefore, the data are likely to include attendances for hypoglycaemia in people with T2D or even hypoglycaemic episodes that are not attributed to diabetes at all and could lead to a potential over-estimate of cumulative hypoglycaemia incidence.

4.1.4 Discussion on published evidence for ambulance attendances due to hypoglycaemia

A study by Farmer et al. (2011) presented results of an observational retrospective study of the incidence of severe hypoglycaemia requiring attendance by emergency medical services in South Central England over a 1 year period. In their analysis a total of 4,081 attendances were recorded as hypoglycaemia amongst the presenting problems. Data on the reason for the hypoglycaemic episode were not collected however the authors estimated a prevalence of 7.5% for hypoglycaemia in patients with T1D which required an ambulance. The estimate was derived from an assumption that T1D predominates in patients ≥15 years and <35 years. Therefore, the estimate of 7.5% was calculated using data from patients ≥15 years and <35 years. The results strengthened the findings from analysis of the LAS data as a large proportion of patients (24.6%) declined treatment of transport to hospital. Another study by Khunti et al. (2013) presented results from a retrospective study on SH requiring emergency medical assistance by ambulance services in the East Midlands

over a 4 month period. During the 4 months there were a total of 523 attendances for SH and this equated to an incidence rate of 2.76 per 100 patient years. 387/523 (74%) of the patients were insulin-treated and 81/387 (21.4%) of insulin-treated individuals were transported to hospital. This study once again highlights that not all patients who have a hypoglycaemic episode are transported to hospital and therefore receive treatment from ambulance personnel.

4.2 The cost of treating hypoglycaemic episodes in patients with T1D

Early on in the project Cedar researched the possibility of using Healthcare resource group (HRG) codes as a means to determine a cost for the treatment of hypoglycaemia. However, this was determined not to be feasible. Previously published studies have researched the costs associated with treating hypoglycaemia in patients with T1D. Currie et al. (2007) did not present the cost of treating hypoglycaemia. However, they presented the costs of treating T1D and T2D in Wales. The cost of treating T1D and T2D was £3,224 and £2,322 per person per year. The reason for the observed higher cost of treating a patient with T1D over a year was due to people with T1D requiring more secondary care than patients with T2D and higher prescription medicine costs.

A review by Kruger and Brennan (2013) summarised the costs of treating T1D in the UK presented in various studies. Two of the studies included by the authors estimated the cost of SH in the UK. It was estimated that the annual cost treatment for SH in the UK was ≥£13 million. The included study did not report results by diabetes type. However, Kruger and Brennan assumed that the cost of treating hypoglycaemia was the same for T1D and T2D and from this estimated that SH in patients with T1D cost the UK ≥£6 million in 1997-1998. Kruger and Brennan presented results from another study which estimated the total cost per severe hypoglycaemic episode in the UK for 2007 ranged from £37-£887.

McEwan et al. (2015) carried out a study of healthcare resource use for hypoglycaemia related hospital admissions using retrospective record-linked cohort studies in England. The study showed no significant difference in the length of stay between T1D and T2D patients who had a hypoglycaemic episode (5.46 and 5.04 days respectively). The authors calculated a mean total estimated expenditure of £1,034 per hospital admission for hypoglycaemia. The authors did not find a difference between the cost of treating a hypoglycaemic episode in patients with T1D or T2D. Furthermore, the authors carried out a matched retrospective cohort study between diabetes patients with and without hypoglycaemia. Diabetes patients with hypoglycaemia were shown to have a significantly longer length of stay than diabetes patients without hypoglycaemia (11.91 and 4.8 days respectively). Patients with T1D and hypoglycaemia were also more likely to die in hospital than patients with T1D who did not have hypoglycaemia.

4.3 Fear of hypoglycaemia

FoH can affect adults with T1D, children/adolescents with T1D and parents of children with T1D. Our systematic review shows varied results for FoH in adults. Three studies suggest that there are gender differences in FoH, with women scoring higher in the HFS worry subscales than men. However, there appears to be some evidence to show that the items with the highest scores in the HFS worry subscale are the same for men and women. The impact of a previous hypoglycaemic episode on FoH has also been researched with 2 studies showing that both severe and mild/moderate hypoglycaemic episodes can increase FoH. It was also shown that adult patients modify their behaviour following a hypoglycaemic episode in order to avoid future hypoglycaemic episodes.

The results from the single study of FoH in children and adolescents show that hypoglycaemia can have a negative impact on their lives. SH appears to be a perceived problem, is disturbing and negatively affects life satisfaction and quality of life of children and adolescents with T1D. The study suggested that perceived disturbance in school/day-care and greater fear of SH with unconsciousness were weakly correlated with a shorter duration of T1D.

Two studies presented results for both children and their parents. The results highlighted differences in parents' and a child's perceived FoH. Previous severe hypoglycaemic events were shown to lead to higher FoH for parents in both studies and children in one of the studies. In addition, one study showed FoH was higher in parents whose adolescents had experienced a hypoglycaemic episode in school. Gender differences in children's FoH were also observed with girls showing a higher level of FoH than boys. One study reported on quality of life and showed no impact of FoH on quality of life neither in parents nor in children.

A total of 5 studies presented results for parents of children/adolescents with T1D only. A previous systematic review researching FoH in parents of children with T1D had been carried out. Therefore, the Cedar analyst did not present the 6 primary studies used in the review but summarised the review instead. The evidence showed FoH in parents of children with T1D and that there are many factors which contribute to parents' fear. The included studies suggested differences between parents with mothers showing a higher level of FoH than fathers. Previous hypoglycaemic episodes were shown to play a role in a parent's fear. However, it appears that the severity and not the frequency of hypoglycaemic episodes leads to higher FoH in parents. Results from the included studies also showed that stress over hypoglycaemic episodes which occur when a parent is away (e.g. when the child is asleep, at school or in social situation) leads to an increase in a parent's FoH. In a qualitative study parents expressed an ever present concern about hypoglycaemia and that they feared finding their child unconscious or dead in bed. Parents also expressed making changes to their lives in order to be able to directly monitor their children and they acknowledged elevating their child's blood glucose levels as they did not trust school/day care staff or their own children to recognise hypoglycaemia. Analysis in two studies showed the type of treatment used by a child can have an impact on a parent's FoH with parents of children not using an insulin pump showing higher HFS behaviour scores and higher parenting stress.

The FoH observed in parents of children with T1D is likely to have emerged from a feeling of wanting to protect their child. In the qualitative study included by Cedar, parents described making use of blood glucose monitoring devices as an approach to monitor their child's blood glucose levels. The need for parents to monitor their child's blood glucose levels is illustrated by the Nightscout project (www.nightscout.info). The project was developed by parents of children with T1D for the remote monitoring of Dexcom's G4 continuous glucose monitor by using open-source software. However, the developers have since developed solutions for the Dexcom G5, Medtronic devices (including 530g/Veo, MiniMed connect and 640g) and the FressStyle Libre. The Nightscout system allows parents to pair a receiver to the device to transmit glucose reading to the Internet. Parents can then view their child's readings using a computer, an iOS/Android device or a smart watch. The developers of the Nightscout project have used #wewillnotwait as their slogan. This was borne out of their frustration at the pace of technological developments and reflects the strength of feeling people with T1D and the parents of children with T1D have towards the need for better control of

blood glucose. This story of technology “hacking” has been covered in many outlets including the Wall Street Journal which ran a story titled “citizen hackers tinker with medical devices” (available at: https://www.wsj.com/articles/citizen-hackers-concoct-upgrades-for-medical-devices-1411762843?tesla=y).

5 Conclusions

The aims of the HERO project were to determine healthcare resource use of hypoglycaemia in people with T1D and to present the impact of FoH to inform DG21 (Integrated sensor-augmented pump therapy systems for managing blood glucose levels in type 1 diabetes (the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system). This report has presented our findings.

We sought to determine healthcare resource use through the analysis of linked health records from the SAIL databank and data obtained from the LAS. We sought to determine the impact of FoH by carrying out a systematic review. The main results from this project are as follows:

- The number of hypoglycaemic episodes in individuals with T1D differs annually.
- The number of hypoglycaemic episodes in people with T1D differs by age group and gender.
- By combining linked health data with registration data from the NDA we have shown that the cumulative incidence of hypoglycaemia in patients with T1D was 4.33% in 2015.
- The results also show that ambulance services attend a number of hypoglycaemic episodes per year. Furthermore, in a large percentage of their attendances patients were not conveyed and were therefore treated by ambulance personnel.
- The NaDIA highlighted that hypoglycaemia is a problem in T1D inpatients, with over a quarter having one or more hypoglycaemic episode during their hospital stay in 2016.
- FoH affects children, adults and the parents of children with T1D.
    - In adults the severity of hypoglycaemia leads to an increase in FoH, changes in behaviour to avoid future hypoglycaemic episodes were observed and women scored higher in tools designed to measure FoH.
    - In children the severity of hypoglycaemia leads to an increase of FoH, a greater fear of hypoglycaemia with unconsciousness was correlated with a shorter T1D duration and girls scored higher in tools designed to measure FoH.
    - Parents of children with T1D described a constant concern about hypoglycaemia, were shown to have higher scores in tools designed to measure FoH if their child experienced a hypoglycaemic episode whilst at school, mothers of young children expressed a higher FoH than fathers, FoH was related to the severity of a hypoglycaemic episode in their child and not the frequency, parents made changes to their lives including taking part-time employment in order to directly monitor their child and purposely elevated their child's blood glucose due to a lack of confidence in their own child and school staff to recognise a hypoglycaemic episode.
    - Parents also noted making use of blood glucose monitoring devices. This has relevance to an open-source initiative called the Nightscout project. This project enables parents to access real time CGM data through a website, smartphone or smartwatch.

This project which has some limitations which have previously been discussed (see Discussion section). However, we have presented results from analysis of real-world data in addition to previously published evidence.

6 References

Anderbro, T., Amsberg, S., Adamson, U., Bolinder, J., Lins, P.E., Wredling, R., Moberg, E., Lisspers, J., & Johansson, U.B. 2010. Fear of hypoglycaemia in adults with Type-1 diabetes. *Diabetic Medicine*, 27, (10): 1151-1158

Anderbro, T., Gonder-Frederick, L., Bolinder, J., Lins, P.E., Wredling, R., Moberg, E., Lisspers, J., & Johansson, U.B. 2015. Fear of hypoglycemia: relationship to hypoglycemic risk and psychological factors. *Acta Diabetologica*, 52, (3): 581-589

Anderson, B. J., Auslander, W. F., Jung, K. C., Miller, J. P., & Santiago, J. V. 1990. Assessing family sharing of diabetes responsibilities. *Journal of Pediatric Psychology*, 15, 477–492.

Barnard, K., Thomas, S., Royle, P., Noyes, K., & Waugh, N. 2010. Fear of hypoglycaemia in parents of young children with type 1 diabetes: a systematic review. *BMC Pediatrics*, 10, 50

Cohen, S., Kamarck, T., & Mermelstein, R. 1983. A global measure of perceived stress. *Journal of Health and Social Behavior*, 24, (4):385–396.

Cox, D.J., Irvine, A., Gonder-Frederick, L., Nowacek, G., & Butterfield, J. 1987. Fear of hypoglycemia: Quantification, validation, and utilization. *Diabetes Care*, 10, (5) 617-621.

Currie, C. J., Poole, C. D., Woehl, A., Morgan, C. Ll., Cawley, S., Rousculp, M. D., Covington, M. T., & Peters, J. R. 2007. The financial costs of healthcare treatment for people with Type 1 or Type 2 diabetes in the UK with particular reference to differing severity of peripheral neuropathy. *Diabetic Medicine*, 24, 187–194.

Farmer, A.J., Brockbank, K.J., Keech, M.L., England, E.J., & Deakin, C.D. 2012. Incidence and costs of severe hypoglycaemia requiring attendance by the emergency medical services in South Central England. *Diabetic Medicine*, 29, (11): 1447-1450

Frier, B.M., Jensen, M.M., & Chubb, B.D. 2016. Hypoglycaemia in adults with insulin-treated diabetes in the UK: self-reported frequency and effects. *Diabetic Medicine*, 33, (8) 1125-1132

Gjerlow, E., Bjorgaas, M.R., Nielsen, E.W., Olsen, S.E., & Asvold, B.O. 2014. Fear of Hypoglycemia in Women and Men With Type 1 Diabetes. *Nursing Research*, 63, (2): 143-149

Gonder-Frederick, L. A., Fisher, C. D., Ritterband, L. M., Cox, D. J., Hou, L., DasGupta, A. A. & Clarke, W. L. 2006. Predictors of fear of hypoglycemia in adolescents with type 1 diabetes and their parents. *Pediatric Diabetes*, 7, 215–222.

Gonder-Frederick, L.A., Schmidt, K.M., Vajda, K.A., Greear, M.L., Singh, H., Shepard, J.A., & Cox, D.J. 2011. Psychometric properties of the hypoglycemia fear survey-ii for adults with type 1 diabetes. *Diabetes Care,* 34, (4): 801-806

Haugstvedt, A., Wentzel-Larsen, T., Graue, M., Sovik, O., & Roknet,B. 2010. Fear of hypoglycaemia in mothers and fathers of children with Type 1 diabetes is associated with poor glycaemic control and parental emotional distress: a population-based study. *Diabetic Medicine*, 27, (1): 72-78

Hendrieckx, C., Halliday, J.A., Bowden, J.P., Colman, P.G., Cohen, N., Jenkins, A., & Speight, J. 2014. Severe hypoglycaemia and its association with psychological well-being in Australian adults with type

1 diabetes attending specialist tertiary clinics. *Diabetes Research & Clinical Practice*, 103, (3): 430-436

Herbert, L.J., Clary, L., Owen, V., Monaghan, M., Alvarez, V., & Streisand, R. 2015. Relations among school/daycare functioning, fear of hypoglycaemia and quality of life in parents of young children with type 1 diabetes. *Journal of Clinical Nursing*, 24, (9-10): 1199-1209

Johnson, S.R., Cooper, M.N., Davis, E.A., & Jones, T.W. 2013. Hypoglycaemia, fear of hypoglycaemia and quality of life in children with Type 1 diabetes and their parents. *Diabetic Medicine*, 30, (9): 1126-1131

Khunti, K., Fisher, H., Sanjoy, P., Iqbal, M., Davies, M.J., & Siriwardena, A.N. 2013. Severe hypoglycaemia requiring emergency medical assistance by ambulance services in the East Midlands: A retrospective study. *Primary care diabetes*, 7, (2): 159-165

Khunti, K., Davies, M., Majeed, A., Thorsted, B.L., Wolden, M.L., & Paul, S.K. 2015. Hypoglycemia and Risk of Cardiovascular Disease and All-Cause Mortality in Insulin-Treated People With Type 1 and Type 2 Diabetes: A Cohort Study. *Diabetes Care*, 38, (2): 316.

Kruger, J., & Brennan, A. 2013. The cost of Type 1 diabetes mellitus in the United Kingdom: A review of cost-of-illness studies. *European Journal of Health Economics*, 14, (6): 887-899

Lawton, J., Waugh, N., Barnard, K.D., Noyes, K., Harden, J., Stephen, J., McDowell, J., & Rankin, D. 2015. Challenges of optimizing glycaemic control in children with Type 1 diabetes: a qualitative study of parents' experiences and views. *Diabetic Medicine*, 32, (8): 1063-1070

Leiter, L.A., Yale, J., Chiasson, J., Harris, S.B., Kleinstiver, P., & Sauriol, L. 2005. Assessment of the impact of fear of hypoglycemic episodes on glycemic and hypoglycemia management. *Canadian Journal of Diabetes*, 29, (3): 186-192

Mattick, R.P., & Clarke, J.C. 1998. Development and validation of measures of social phobia scrutiny fear and social interaction anxiety. *Behaviour Research and Therapy*, 36, (4):455–470

McCoy, R.G., van Houten, H.K., Ziegenfuss, J.Y., Shah, N.D., Wermers, R.A., & Smith, S.A. 2013. Self-report of hypoglycemia and health-related quality of life in patients with type 1 and type 2 diabetes. *Endocrine Practice*, 19, (5): 792-799

McEwan, P., Larsen Thorsted, B., Wolden, M., Jacobsen, J., & Evans, M. 2015. Healthcare resource implications of hypoglycemia-related hospital admissions and inpatient hypoglycemia: retrospective record-linked cohort studies in England. *BMJ Open Diabetes Research Care*, 3, (1): e000057

Nordfeldt, S., & Ludvigsson, J. 2005. Fear and other disturbances of severe hypoglycaemia in children and adolescents with type 1 diabetes mellitus. *Journal of Pediatric Endocrinology*, 18, (1): 83-91

Olokoba, A.B., Obateru, O.A., & Olokoba, L.B. 2012. Type 2 Diabetes Mellitus: A Review of Current Trends. *Oman Medical Journal*, 27, (4): 269-273.

R Core Team. 2015. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

Reiss, S., Peterson, R.A., Gursky, D.M., & McNally, R.J. 1986. Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. *Behaviour Research and Therapy,* 24, (1):1–8

Spielberger, C.D. 1973. State-Trait Anxiety Inventory for Children: Preliminary Manual. Palo Alto, CA: Consulting Psychologists Press.

Spielberger, C.D. 1979. The preliminary manual for the State-Trait Personality Inventory. Unpublished manual. University of South Florida, Tampa, FL.

Strachan, M.W.J. 2005. Fear of diabetes complications. *Diabetes/Metabolism Research and Reviews*, 21, (3): 262-263.

Streisand, R., Swift, E., Wickmark, T., Chen, R., & Holmes, C.S. 2005. Pediatric parenting stress among parents of children with type 1 diabetes: The role of self-efficacy, responsibility, and fear. *Journal of Pediatric Psychology*, 30, (6): 513-521

Taylor, E.P., Crawford, J.R., & Gold, A.E. 2005. Design and development of a scale measuring fear of complications in type 1 diabetes. *Diabetes/Metabolism Research and Reviews*, 23, (3):264–270

UK Hypoglycaemia Study Group. 2007. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia*, 50, (6): 1140-1147

van Belle, T.L., Coppieters, K.T., & Von Herrath, M.G. 2011. Type 1 Diabetes: Etiology, Immunology, and Therapeutic Strategies. *Physiological Reviews*, 91, (1): 79-118.

Vandagriff, J.L., Marrero, D.G., Ingersoll, G.M., & Fineberg, N.S. 1992. Parents of children with diabetes: what are they worried about? *Diabetes Educator*, 18, 299–302.

Varni, J.W., Seid, M., & Rode, C.A. 1999. The PedsQL: measurement model for the pediatric quality of life inventory. *Medical Care*, 37, 126–139.

Wickham, H. 2009. ggplot2: Elegant Graphics for Data Analysis. Springer-Verlag New York.

Zhong, V.W., Juhaeri, J., Cole, S.R., Shay, C.M., Gordon-Larsen, P., Kontopantelis, E., & Mayer-Davis, E.J. 2018. HbA1C variability and hypoglycemia hospitalization in adults with type 1 and type 2 diabetes: a nested case-control study. *Journal of Diabetes and its Complications*, 32, (2): 203-209.

Zigmond, A. S., & Snaith, R.P. 1983. The Hospital Anxiety And Depression Scale, *Acta Psychiatrica Scandinavica*, 67, 361-370.

Appendix 1 – Accident and Emergency Diagnosis Type used in the EDDS

Value	Meaning	Valid From
	Wound	
01A	Laceration	1st July 2010
01B	Contusion	1st July 2010
01C	Abrasion	1st July 2010
01D	Soft tissue inflammation	1st July 2010
01Z	Wound, other or unspecified	1st July 2010
	Head Injury	
02A	Glasgow Coma Score 15	1st July 2010
02B	Glasgow Coma Score <15	1st July 2010
02C	Dental Injury	1st July 2010
02Z	Head Injury, other or unspecified	1st July 2010
	Fracture	
03A	Open Fracture	1st July 2010
03B	Closed Fracture	1st July 2010
03C	Fracture Dislocation	1st July 2010
03Z	Fracture, other or unspecified	1st July 2010
	Joint Injury	
04A	Sprain	1st July 2010
04B	Dislocation	1st July 2010
04C	Subluxation	1st July 2010
04Z	Joint Injury, other or unspecified	1st July 2010
	Amputation	
05Z	Amputation, other or unspecified	1st July 2010
	Soft Tissue Injury	
06A	Muscle Injury	1st July 2010
06B	Tendon Injury	1st July 2010
06C	Nerve Injury	1st July 2010
06D	Visceral Injury	1st July 2010
06E	Vascular Injury	1st July 2010
06Z	Soft Tissue Injury, other or unspecified	1st July 2010
	Burns, Scalds and Thermal Conditions	
07A	Electric	1st July 2010
07B	Chemical	1st July 2010
07C	Radiation	1st July 2010
07D	Scald	1st July 2010
07E	Sunburn	1st July 2010
07F	Hyperthermia	1st July 2010
07G	Hypothermia	1st July 2010
07H	Frostbite	1st July 2010
07Z	Burns, Scalds and Thermal Conditions, other or unspecified	1st July 2010
	Foreign Body	
08A	Ingested Foreign Body	1st July 2010
08Z	Foreign Body, other or unspecified	1st July 2010
	Puncture Wounds	

09A	Needle Stick Injury	1st July 2010
09B	Human Bite	1st July 2010
09C	Animal Bite	1st July 2010
09D	Insect Bite or Sting	1st July 2010
09Z	Puncture Wounds, other or unspecified	1st July 2010
	Poisoning or Overdose	
10A	Alcohol	1st July 2010
10B	Prescribed Drug	1st July 2010
10C	Non-prescribed/purchased drug	1st July 2010
10D	Illicit Drug	1st July 2010
10Z	Poisoning or Overdose, other or unspecified	1st July 2010
	Drowning	
11A	Near Drowning	1st July 2010
11Z	Drowning, other or unspecified	1st July 2010
	Infectious Disease	
12A	Notifiable Disease	1st July 2010
12B	Non-notifiable Disease	1st July 2010
	Local Infection	
13A	Septicaemia	1st July 2010
13Z	Infection, other or unspecified	1st July 2010
	Respiratory Conditions	
14A	Asthma	1st July 2010
14B	Chronic Obstructive Pulmonary disease	1st July 2010
14Z	Respiratory Conditions, other or unspecified	1st July 2010
	Endocrinological Conditions	
15A	Diabetes	1st July 2010
15Z	Endocrinological Conditions, other or unspecified	1st July 2010
	Cardiovascular Conditions	
16A	Myocardial Infarction	1st July 2010
16B	Vascular Condition	1st July 2010
16Z	Cardiovascular Conditions, other or unspecified	1st July 2010
	Neurological Conditions	
17A	Seizure/Convulsion	1st July 2010
17B	Cerebrovascular Event	1st July 2010
17Z	Neurological Conditions, other or unspecified	1st July 2010
	Gastrointestinal Conditions	
18Z	Gastrointestinal Conditions, other or unspecified	1st July 2010
	Urological Conditions	
19Z	Urological Conditions, other or unspecified	1st July 2010
	Dermatological Conditions	
20Z	Dermatological Conditions, other or unspecified	1st July 2010

	Psychological/Psychiatric Conditions	
21Z	Psychological/Psychiatric Conditions, other or unspecified	1st July 2010
	Obstetric Conditions	
22Z	Obstetric Conditions, other or unspecified	1st July 2010
	Gynaecological Conditions	
23Z	Gynaecological Conditions, other or unspecified	1st July 2010
	Haematological Conditions	
24Z	Haematological Conditions, other or unspecified	1st July 2010
	Ophthalmic Conditions	
25Z	Ophthalmic Conditions, other or unspecified	1st July 2010
	Rheumatological Conditions	
26Z	Rheumatological Conditions, other or unspecified	1st July 2010
	Genito-Urinary Medicine	
27Z	Genito-urinary Medicine, other or unspecified	1st July 2010
	Ear, Nose and Throat Conditions	
28Z	Ear, Nose and Throat Conditions, other or unspecified	1st July 2010
	Pain	
29A	Chest Pain, non cardiac	1st July 2010
29B	Abdominal Pain	1st July 2010
29Z	Pain, other or unspecified	1st July 2010
	Allergy (including Anaphylaxis)	
30Z	Allergy (including Anaphylaxis), other or unspecified	1st July 2010
	Social Problems/Homelessness	
31A	Chronic Alcohol Abuse	1st July 2010
31B	Chronic Drug Abuse	1st July 2010
31Z	Social Problems/Homelessness, other or unspecified	1st July 2010
97Z	**Nothing Abnormal Detected**	1st July 2010
98Z	**Diagnosis Type Not Otherwise Specified**	1st July 2010
99Z	**Diagnosis Not Recorded**	1st July 2010

Appendix 2 – ICD-10 codes used by Cedar and the SAIL analyst for the PEDW

Relevant ICD-10 codes

NWIS identified the following ICD-10 codes which are relevant to the HERO project:

Codes used to identify hypoglycaemia:

- E16.0 Drug induced hypoglycaemia without coma
- E16.1 Other hypoglycaemia – which includes :
    - Functional non-hyper-insulinamic hypoglycaemia
    - Hyper-insulinism
    - Hyperplasia of pancreatic islet beta cells
    - Post-hypoglycaemic coma encephalopathy
- E16.2 Hypoglycaemia, unspecified

Codes used to identify type 1 diabetes:

- E10.0 with coma
- E10.1 ketoacidosis – without mention of coma
- E10.2 with renal complications
- E10.3 with ophthalmic complications
- E10.4 with neurological complications
- E10.5 with peripheral complications
- E10.6 other specified complications
- E10.9 without complications – includes hyperglycaemia

Other potentially useful codes:

- T38.3 Insulin and oral hypoglycaemic drug
- X44.9 Accidental poisoning by and exposure to other and unspecified drugs, medicaments and biological substances, unspecified place

ICD-10 code combinations used by the SAIL analyst for the HERO project

Hypoglycaemic coma in patient with type 1 diabetes mellitus

E10.0 AND (E16.2 OR E16.1)

Hypoglycaemia (without coma) in patient with type 1 diabetes

E10.1 AND (E16.0 OR E16.1 OR E16.2)

E10.2 AND (E16.0 OR E16.1 OR E16.2)

E10.3 AND (E16.0 OR E16.1 OR E16.2)

E10.4 AND (E16.0 OR E16.1 OR E16.2)

E10.5 AND (E16.0 OR E16.1 OR E16.2)

E10.6 AND (E16.0 OR E16.1 OR E16.2)

E10.7 AND (E16.0 OR E16.1 OR E16.2)

E10.8 AND (E16.0 OR E16.1 OR E16.2)

E10.9 AND (E16.0 OR E16.1 OR E16.2)

Hypoglycaemic coma in patient with type 1 diabetes mellitus following accidental overdose of insulin

E10.0 AND E16.2 AND T38.3 AND X44.9

Hypoglycaemia (without coma) in patient with type 1 diabetes mellitus following accidental overdose of insulin

E10.1 AND T38.3 AND X44.9 AND (E16.0 OR E16.1 OR E16.2)

E10.2 AND T38.3 AND X44.9 AND (E16.0 OR E16.1 OR E16.2)

E10.3 AND T38.3 AND X44.9 AND (E16.0 OR E16.1 OR E16.2)

E10.4 AND T38.3 AND X44.9 AND (E16.0 OR E16.1 OR E16.2)

E10.5 AND T38.3 AND X44.9 AND (E16.0 OR E16.1 OR E16.2)

E10.6 AND T38.3 AND X44.9 AND (E16.0 OR E16.1 OR E16.2)

E10.7 AND T38.3 AND X44.9 AND (E16.0 OR E16.1 OR E16.2)

E10.8 AND T38.3 AND X44.9 AND (E16.0 OR E16.1 OR E16.2)

E10.9 AND T38.3 AND X44.9 AND (E16.0 OR E16.1 OR E16.2)

Appendix 3 – Read codes used by Cedar and the SAIL analyst for the GP dataset

Version 2 and 3 Read codes identified by Cedar with relevance to the project

Type 1 diabetes Read codes

"C100000", "C100011", "C104000", "C105000", "C106000", "C107000", "C107300", "C108.00", "C108000", "C108011", "C108012", "C108100", "C108.11", "C108112", "C108.12", "C108.13", "C108200", "C108211", "C108212", "C108300", "C108311", "C108400", "C108411", "C108412", "C108500", "C108511", "C108512", "C108600", "C108611", "C108612", "C108700", "C108711", "C108712", "C108800", "C108811", "C108812", "C108A00", "C108A11", "C108A12", "C108B00", "C108B11", "C108B12", "C108C00", "C108C11", "C108C12", "C108D00", "C108D11", "C108D12", "C108F00", "C108F11", "C108F12", "C108G00", "C108G11", "C108G12", "C108H00", "C108H11", "C108H12", "C108J00", "C108J11", "C108J12", "C10E.00", "C10E000", "C10E011", "C10E012", "C10E100", "C10E.11", "C10E111", "C10E112", "C10E.12", "C10E200", "C10E211", "C10E212", "C10E300", "C10E311", "C10E312", "C10E400", "C10E411", "C10E412", "C10E500", "C10E511", "C10E512", "C10E600", "C10E611", "C10E612", "C10E700", "C10E711", "C10E712", "C10E800", "C10E811", "C10E812", "C10EA00", "C10EA11", "C10EA12", "C10EB00", "C10EB11", "C10EB12", "C10EC00", "C10EC11", "C10EC12", "C10ED00", "C10ED11", "C10ED12", "C10EF00", "C10EF11", "C10EF12", "C10EG00", "C10EG11", "C10EG12", "C10EH00", "C10EH11", "C10EH12", "C10EJ00", "C10EK00", "C10EK11", "C10EL00", "C10EL11", "C10EP00", "C10EP11", "C10EQ00", "C10EQ11", "C10P000", "C10P011", "C10z000", "L180500", "C1000", "C1040", "C1050", "C1060", "C1070", "C1073", "C108.", "C1080", "C1081", "C1082", "C1083", "C1084", "C1085", "C1086", "C1087", "C1088", "C108A", "C108B", "C108C", "C108D", "C108F", "C108G", "C108H", "C108J", "C10E.", "C10E0", "C10E1", "C10E2", "C10E3", "C10E4", "C10E5", "C10E6", "C10E7", "C10E8", "C10EA", "C10EB", "C10EC", "C10ED", "C10EF", "C10EG", "C10EH", "C10EJ", "C10EK", "C10EL", "C10EP", "C10EQ", "C10P0", "C10z0", "L1805", "XE10E", "X40J4", "Xa4g7", "XaELP", "XaEnn", "XaEno", "XaF04", "XaFm8", "XaFmK", "XaFmL", "XaFMm", "XaIzM", "XaIzN", "XaJSr", "XaKyW", "Xaage"

Hypoglycaemia Read codes

"C112.00", "C112z00", "C11y10", "C112.", "C112z", "C11y1", "X40K3"

Hypoglycaemia with coma Read codes

"C110.00", "XE10J", "C110.", "X40Jo", "C110z00", "C110z"

Other hypoglycaemia Read codes

"Cyu3000", "Cyu30"

Type 1 diabetes with hypoglycaemic coma Read codes (specific Read code for this)

"C108E00", "C108E11", "C108E12", "C10EE00", "C10EE11", "C10EE12", "XaFWG"

Read codes combinations used by the SAIL analyst for the HERO project

Type 1 diabetes

"C100000" OR "C100011" OR "C104000" OR "C105000" OR "C106000" OR "C107000" OR "C107300" OR "C108.00" OR "C108000" OR "C108011" OR "C108012" OR "C108100" OR "C108.11" OR "C108112" OR "C108.12" OR "C108.13" OR "C108200" OR "C108211" OR "C108212" OR "C108300" OR "C108311" OR "C108400" OR "C108411" OR "C108412" OR "C108500" OR "C108511" OR "C108512" OR "C108600" OR "C108611" OR "C108612" OR "C108700" OR "C108711" OR "C108712" OR "C108800" OR "C108811" OR "C108812" OR "C108A00" OR "C108A11" OR "C108A12" OR "C108B00" OR "C108B11" OR "C108B12" OR "C108C00" OR "C108C11" OR "C108C12" OR "C108D00" OR "C108D11" OR "C108D12" OR "C108F00" OR "C108F11" OR "C108F12" OR "C108G00" OR "C108G11" OR "C108G12" OR "C108H00" OR "C108H11" OR "C108H12" OR "C108J00" OR "C108J11" OR "C108J12" OR "C10E.00" OR "C10E000" OR "C10E011" OR "C10E012" OR "C10E100" OR "C10E.11" OR "C10E111" OR "C10E112" OR "C10E.12" OR "C10E200" OR "C10E211" OR "C10E212" OR "C10E300" OR "C10E311" OR "C10E312" OR "C10E400" OR "C10E411" OR "C10E412" OR "C10E500" OR "C10E511" OR "C10E512" OR "C10E600" OR "C10E611" OR "C10E612" OR "C10E700" OR "C10E711" OR "C10E712" OR "C10E800" OR "C10E811" OR "C10E812" OR "C10EA00" OR "C10EA11" OR "C10EA12" OR "C10EB00" OR "C10EB11" OR "C10EB12" OR "C10EC00" OR "C10EC11" OR "C10EC12" OR "C10ED00" OR "C10ED11" OR "C10ED12" OR "C10EF00" OR "C10EF11" OR "C10EF12" OR "C10EG00" OR "C10EG11" OR "C10EG12" OR "C10EH00" OR "C10EH11" OR "C10EH12" OR "C10EJ00" OR "C10EK00" OR "C10EK11" OR "C10EL00" OR "C10EL11" OR "C10EP00" OR "C10EP11" OR "C10EQ00" OR "C10EQ11" OR "C10P000" OR "C10P011" OR "C10z000" OR "L180500" OR "C1000" OR "C1040" OR "C1050" OR "C1060" OR "C1070" OR "C1073" OR "C108." OR "C1080" OR "C1081" OR "C1082" OR "C1083" OR "C1084" OR "C1085" OR "C1086" OR "C1087" OR "C1088" OR "C108A" OR "C108B" OR "C108C" OR "C108D" OR "C108F" OR "C108G" OR "C108H" OR "C108J" OR "C10E." OR "C10E0" OR "C10E1" OR "C10E2" OR "C10E3" OR "C10E4" OR "C10E5" OR "C10E6" OR "C10E7" OR "C10E8" OR "C10EA" OR "C10EB" OR "C10EC" OR "C10ED" OR "C10EF" OR "C10EG" OR "C10EH" OR "C10EJ" OR "C10EK" OR "C10EL" OR "C10EP" OR "C10EQ" OR "C10P0" OR "C10z0" OR "L1805" OR "XE10E" OR "X40J4" OR "Xa4g7" OR "XaELP" OR "XaEnn" OR "XaEno" OR "XaF04" OR "XaFm8" OR "XaFmK" OR "XaFmL" OR "XaFMm" OR "XaIzM" OR "XaIzN" OR "XaJSr" OR "XaKyW" OR "Xaage"

Hypoglycaemia

"C112.00" OR "C112z00" OR "C11y10" OR "C112." OR "C112z" OR "C11y1" OR "X40K3"

Hypoglycaemia with coma

"C110.00" OR "XE10J" OR "C110." OR "X40Jo" OR "C110z00" OR "C110z"

Other hypoglycaemia

"Cyu3000" OR "Cyu30"

Type 1 diabetes with hypoglycaemic coma_SRC (specific Read code)

"C108E00" OR "C108E11" OR "C108E12" OR "C10EE00" OR "C10EE11" OR "C10EE12" OR "XaFWG"

Appendix 4 – Data tables for the number of hypoglycaemic episodes identified in data obtained from the SAIL databank

Table 13| The number of hypoglycaemic episodes identified in the PEDW dataset by year and gender

PEDW				
Year	Number of hypoglycaemic episodes	Number of hypoglycaemic episodes (female)	Number of hypoglycaemic episodes (male)	Number of hypoglycaemic episodes (unknown)
2010	581	308	269	4
2011	619	305	301	13
2012	559	241	303	15
2013	692	344	339	9
2014	705	303	394	8
2015	505	245	250	10
	Total	Total	Total	Total
	3661	1746	1856	59

Table 14| The number of hypoglycaemic episodes identified in the GP dataset by year and gender

GP				
Year	Number of hypoglycaemic episodes	Number of hypoglycaemic episodes (female)	Number of hypoglycaemic episodes (male)	Number of hypoglycaemic episodes (unknown)
2010	177	83	94	0
2011	197	91	105	1
2012	206	85	121	0
2013	281	118	162	1
2014	230	108	122	0
2015	119	39	80	0
	Total	Total	Total	Total
	1210	524	684	2

Table 15| The number of hypoglycaemic episodes identified in the PEDW dataset by age and gender

	PEDW					
	Hypoglycaemic episodes per year					
Age group (years)	2010	2011	2012	2013	2014	2015
Unknown	4	13	15	9	8	10
0-15	73	67	57	87	65	56
16-24	66	96	74	66	67	42
25-34	77	65	62	68	76	66
35-44	80	83	82	83	73	53
45-54	62	80	84	91	120	61
55-64	55	74	50	106	82	72
65-74	62	63	59	70	81	47
75+	102	78	76	112	133	98
Total	**581**	**619**	**559**	**692**	**705**	**505**

Table 16| The number of hypoglycaemic episodes identified in the GP dataset by age and gender

	GP					
	GP visits due to a hypoglycaemic episode per year					
Age group (years)	2010	2011	2012	2013	2014	2015
Unknown	0	1	0	1	0	0
0-15	14	17	18	35	16	11
16-24	18	25	25	27	29	17
25-34	40	23	25	39	24	19
35-44	17	26	29	25	33	5
45-54	28	27	29	58	32	25
55-64	15	25	25	34	27	18
65-74	17	18	26	24	26	10
75+	28	35	29	38	43	14
Total	**177**	**197**	**206**	**281**	**230**	**119**

Appendix 5 – Search strategy for Cedar's systematic review

Search strategy for databases

ASSIA AND BNI

(TI,AB,SU("Type 1 diabetes")) AND (TI,AB,SU(hypoglycemi* OR hypoglycaemi*)) AND (TI,AB,SU(incidence or prevalence or "quality of life" or wellbeing or well being))

CINAHL

(TI "Type 1 diabetes" OR AB "Type 1 diabetes" OR SU "Type 1 diabetes") AND ((hypoglycemi* OR hypoglycaemi*) N10 (episod* or event* or incident* or outcome* or occurrence* or complication* or rate or rates)) AND (TI (incidence or prevalence or "quality of life" or wellbeing or "well being") OR AB (incidence or prevalence or "quality of life" or wellbeing or "well being") OR SU (incidence or prevalence or "quality of life" or wellbeing or "well being"))) Limiters - English Language

---

Cochrane Library – NHS EED and HTA only

#1 MeSH descriptor: [Diabetes Mellitus, Type 1] this term only

#2 "Type 1" near/10 diabetes:ti,ab,kw (Word variations have been searched)

#3 #1 or #2

#4 (hypoglyc*mi*) near/10 (episod* or event* or incident* or outcome* or occurrence* or complication* or rate or rates):ti,ab,kw (Word variations have been searched)

#5 MeSH descriptor: [Hypoglycemia] this term only

#6 (episod* or event* or incident* or outcome* or occurrence* or complication* or rate or rates*):ti,ab,kw (Word variations have been searched)

#7 #5 and #6

#8 #4 or #7

#9 MeSH descriptor: [Prevalence] this term only

#10 MeSH descriptor: [Incidence] this term only

#11 prevalence or incidence:ti,ab,kw (Word variations have been searched)

#12 MeSH descriptor: [Quality of Life] this term only

#13 "quality of life":ti,ab,kw (Word variations have been searched)

#14 wellbeing or well being:ti,ab,kw (Word variations have been searched)

#15 #9 or #10 or #11 or #12 or #13 or #14

#16 #3 and #8 and #15

ECONLit

TI "Type 1 diabetes" OR AB "Type 1 diabetes" OR SU "Type 1 diabetes"

EMBASE

EMBASE <1947-Present>

1 insulin dependent diabetes mellitus/ (95460)

2 Type 1 diabetes.tw. (44949)

3 1 or 2 (101644)

4 (hypoglyc?emi* adj10 (episod* or event* or incident* or outcome* or occurrence* or complication* or rate or rates)).tw. (16010)

5 Hypoglycemia/ and (episod* or event* or incident* or outcome* or occurrence* or complication* or rate or rates*).tw. (27641)

6 4 or 5 (30531)

7 prevalence/ (621568)

8 incidence/ (270765)

9 (prevalence or incidence).tw. (1463388)

10 "quality of life"/ (365759)

11 "quality of life".tw. (298375)

12 (wellbeing or well being).tw. (77957)

13 or/7-12 (2078923)

14 3 and 6 and 13 (2044)

15 limit 14 to english language (1862)

HMIC

HMIC Health Management Information Consortium

1 Type 1 diabetes.tw. (156)

2 hypoglyc?emi*.tw. (137)

3 hypoglycemia/ (36)

4 2 or 3 (146)

5 (prevalence or incidence).tw. (12079)

6 "quality of life"/ (2609)

7 "quality of life".tw. (4589)

8 (wellbeing or well being).tw. (4350)

9 "prevalence of disease"/ (1090)

10 5 or 6 or 7 or 8 or 9 (21344)

11 1 and 4 and 10 (15)

Ovid MEDLINE(R)

Ovid MEDLINE(R) <1946 to October Week 4 2016>

1 Diabetes Mellitus, Type 1/ (67600)

2 ("Type 1" adj10 diabetes).tw. (31323)

3 1 or 2 (74439)

4 (hypoglyc?emi* adj10 (episod* or event* or incident* or outcome* or occurrence* or complication* or rate or rates)).tw. (7898)

5 Hypoglycemia/ and (episod* or event* or incident* or outcome* or occurrence* or complication* or rate or rates*).tw. (6682)

6 or/4-5 (10516)

7 Prevalence/ (230718)

8 Incidence/ (214404)

9 (prevalence or incidence).tw. (927393)

10 "Quality of Life"/ (144795)

11 "quality of life".tw. (169839)

12 (wellbeing or well being).tw. (51322)

13 or/7-12 (1302524)

14 3 and 6 and 13 (921)

15 limit 14 to english language (845)

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <November 07, 2016>

1 ("Type 1" adj10 diabetes).tw. (3668)

2 (hypoglyc?emi* adj10 (episod* or event* or incident* or outcome* or occurrence* or complication* or rate or rates)).tw. (1145)

3 (prevalence or incidence).tw. (97894)

4 "quality of life".tw. (24674)

5 (wellbeing or well being).tw. (7483)

6 3 or 4 or 5 (125295)

7 1 and 2 and 6 (66)

8 limit 7 to english language (59)

PsycINFO

PsycINFO <1806 to October Week 4 2016>

1 Type 1 diabetes.tw. (1507)

2 hypoglyc?emi*.tw. (1785)

3 hypoglycemia/ (585)

4 2 or 3 (1800)

5 (prevalence or incidence).tw. (130239)

6 "quality of life"/ (32900)

7 "quality of life".tw. (52926)

8 (wellbeing or well being).tw. (68069)

9 EPIDEMIOLOGY/(43983)

10 5 or 6 or 7 or 8 or 9 (255259)

11 1 and 4 and 10 (39)

Scopus

(TITLE-ABS-KEY ("type 1" W/10 diabetes) AND TITLE-ABS-KEY (hypoglyc*emi* W/10 (episod* OR event* OR incident* OR outcome* OR occurrence*)) AND TITLE-ABS-KEY (prevalence OR incidence OR "quality of life" OR well*being OR "well being")) AND (LIMIT-TO (LANGUAGE , "English"))

Web of Science

(TS=("Type 1 diabetes") AND TS=((hypoglycemi* OR hypoglycaemi*) NEAR/10 (episod* or event* or incident* or outcome* or occurrence* or complication* or rate or rates)) AND TS=(prevalence OR incidence OR "quality of life" OR wellbeing OR "well being")) AND LANGUAGE: (English)

Pubmed ('epub ahead of press' search for 'pubstatusaheadofprint AND key subject term')

pubstatusaheadofprint AND "type 1 diabetes" AND hypoglyc* AND (episod* or event* or incident* or outcome* or occurrence* or complication* or rate or rates)

CEA registry

Type 1 diabetes

EconPapers

"type 1" AND diabetes AND (hypoglycaemia or hypoglycaemia)

IDEAS https://ideas.repec.org/

"type 1" + diabetes + hypoglycaemia or "type 1" + diabetes + hypoglycemia

PRISMA diagram

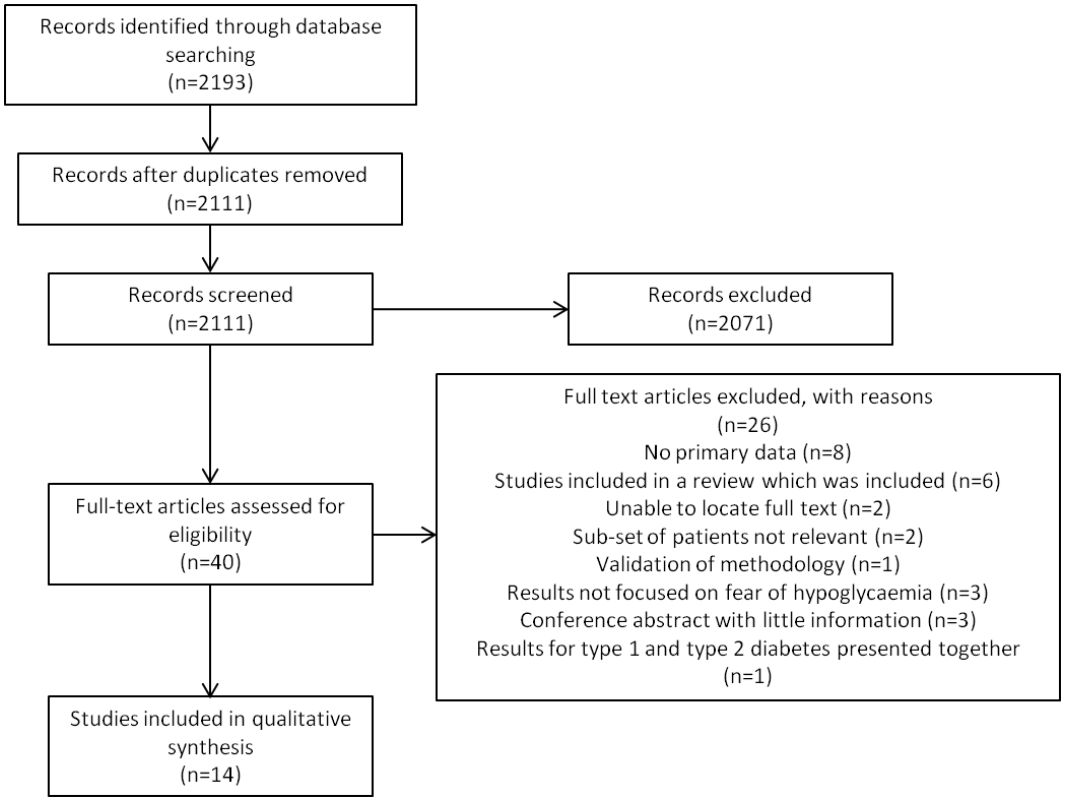

Figure 21| PRISMA diagram of studies included in a systematic review of fear of hypoglycaemia

Appendix 5 – FoH systematic review quality checklists

The following checklists are produced by the Specialist Unit for Review Evidence (SURE) and were used by Cedar for it systematic review of fear of hypoglycaemia. The following checklists were used:

- Specialist Unit for Review Evidence (SURE) 2015. Questions to assist with the critical appraisal of qualitative studies available at: http://www.cardiff.ac.uk/insrv/libraries/sure/checklists.html
- Specialist Unit for Review Evidence (SURE) 2016. Questions to assist with the critical appraisal of cross-sectional studies. Available at: http://www.cardiff.ac.uk/insrv/libraries/sure/checklists.html
- Specialist Unit for Review Evidence (SURE) 2013. Questions to assist with the critical appraisal of systematic reviews available at: http://www.cardiff.ac.uk/insrv/libraries/sure/checklists.html

Citation: Anderbro *et al*. (2010) *Are there other companion papers from the same study?* Yes. See Anderbro *et al*. (2015)	
	Yes/ Can't tell/ No
1. Is the study design clearly stated?	No
2. Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Outcomes.	Yes Population – patients with type 1 diabetes Exposure – Hypoglycaemia Outcomes – severe hypoglycaemic episode history, nocturnal hypoglycaemia and hypoglycaemia fear survey (HFS) results.
3. Are the setting, locations and relevant dates provided? Consider: recruitment period; exposure; data collection.	Yes Setting described as was how the data were collected. Dates were not included.
4. Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants.	Yes. Eligibility criteria were listed and all participants that returned the sent questionnaire were included.
5. Are participant characteristics provided? Consider if: sufficient details; a table is included.	Yes. Participant characteristics have been included in a table. The table presents all eligible patients, responders and non-responders.
6. Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable.	Yes. Measures of exposure assessment seem appropriate.
7. Is there a description of how the study size was arrived at?	Yes. The authors have described how final study size was arrived at.

8. Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) considered/controlled for.	Yes. Statistical methods are described in detail. Demographic data includes statistical analysis in addition to presentation of means, standard deviation, medians, 25th and 75th percentiles. Regression analysis has been carried out on the HFS results. Differences between groups were analysed through unpaired t-tests or χ^2 tests.
9. Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; numbers of outcome events.	Yes. No flow diagram has been included. However, details on how the final number of participants was arrived at have been included. In addition, the authors have given details on how missing values were dealt with.
10. Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the abstract and the full text.	Yes. Results have been described well. Result statistics and p-values have been presented where appropriate. Demographic data also includes means, standard deviation, medians, 25th and 75th percentiles.
11. Is any sponsorship/conflict of interest reported?	No. The authors have declared no conflicts of interest.
12. Finally…Did the authors identify any limitations and, if so, are they captured above?	Yes. The authors identify that there was a significant difference between responders and non-responders in terms of demographic characteristics. The authors also highlight that their models are of little predictive value as the adjusted R^2 values were not high.

Citation: Anderbro *et al*. (2015) *Are there other companion papers from the same study?*	
	Yes See Anderbro *et al*. (2010)
1. Is the study design clearly stated?	No
2. Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Outcomes.	Yes Population – patients with type 1 diabetes Exposure – Hypoglycaemia Outcomes – severe hypoglycaemic episode history, nocturnal hypoglycaemia and hypoglycaemia fear survey (HFS) results.
3. Are the setting, locations and relevant dates provided? Consider: recruitment period; exposure; data collection.	Setting described as was how the data were collected. Dates were not included.

4. Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants.	Yes. Eligibility criteria were listed and all participants that returned the sent questionnaire were included.
5. Are participant characteristics provided? Consider if: sufficient details; a table is included.	Participant characteristics have been included in a table. The table presents all eligible patients, responders and non-responders.
6. Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable.	Measures of exposure seem appropriate.
7. Is there a description of how the study size was arrived at?	The authors have described how final study size was arrived at.
8. Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) considered/controlled for.	Statistical methods are described in detail. Demographic data includes statistical analysis in addition to presentation of means, standard deviation, medians, 25th and 75th percentiles. Regression analysis has been carried out on the HFS results in addition to ANOVA and χ^2 analysis of author derived subgroups.
9. Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; numbers of outcome events.	No flow diagram has been included. However, details on how the final number of participants was arrived at have been included. In addition, the authors have given details on how missing values were dealt with.
10. Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the abstract and the full text.	Results have been described well. Result statistics and p-values have been presented where appropriate. Demographic data also includes means, standard deviation, medians, 25th and 75th percentiles.
11. Is any sponsorship/conflict of interest reported?	The authors have declared no conflicts of interest.
12. Finally…Did the authors identify any limitations and, if so, are they captured above?	The authors identify that there was a moderate response rate and that by their definition the majority of patients were at low risk for severe hypoglycaemia.

Citation: Barnard *et al*. (2010)
Study Design: Systematic review

Questions ** relate to whether the methodology used is described – e.g. independently in duplicate

1. Does the review address a clearly focused question/hypothesis	Yes	~~Can't tell~~	~~No~~
Population/Problem?	Parents (or primary carers) of children < 12 years with type 1 diabetes.		

	Intervention?	Hypoglycaemia
	Comparator/control?	None
	Outcomes? Can you identify the primary outcome?	The extent of parental fear of hypoglycaemia (primary); the effect of parental hypoglycaemia avoidance behaviour on child's glycaemic control as reflected in HbA1c or frequency of hypoglycaemic episodes or admissions for metabolic derangements; the effect of parental fear of hypoglycaemia on parent's quality of life, anxiety, and depression; the impact of any intervention aimed at reducing parental fear of hypoglycaemia and hypoglycaemia avoidance behaviour.
2.	Did the authors look for the appropriate types of paper? Did the studies address the review's question and have an appropriate design?	All study designs were eligible for inclusion. All included studies were cross-sectional. The studies answered the review's primary outcome. However, there was limited evidence on behaviour to avoid hypoglycaemia and no studies reported interventions aimed at reducing parental fear of hypoglycaemia.
3.	Is the search likely to have identified all the relevant evidence?	Yes A sufficient range of databases were searched and conference proceedings were also searched. There were no restrictions on date.
	Sufficient range of databases searched? Date range appropriate?	
	Good range of search terms (indexed terms and keywords)	Yes – indexed terms included.
	Reference list/bibliography checking?	Yes
	Hand search (journals)	No
	Grey literature searched (unpublished work) Websites? Contacting experts/manufacturers?	Experts in the field were contacted.
	Search terms/ strategy provided? Were they comprehensive?	Search terms for Medline were included. Adapted searches for other databases were not included. Search terms for Medline appeared quite comprehensive and used indexed terms.

	Search results provided (no of hits and final studies)? Flow diagram?	A flow diagram was included for the number of records identified and how the final number of included studies was reached.
	All languages included?	All languages were included.
4.	Are all relevant studies likely to have been included?	Yes
	Are the inclusion and exclusion criteria stated?	Inclusion criteria were stated but no exclusion criteria.
	Is the study selection process described? **	The study selection process was described. Study selection was carried out by two reviewers. Disagreements were resolved through discussion.
	Multiple papers relating to same study identified?	Yes. 8 articles from 6 studies.
	Is the data extraction process described? **	Yes. Data extraction was checked for accuracy by a second reviewer. Disagreements were resolved through discussion.
5.	Did the authors assess the quality (rigour) of the included studies?	Yes
	Is the assessment process described? **	The assessment process is described and was assessed by two reviewers. Disagreements were resolved through discussion.
6.	Information about included studies Is key information provided (e.g. study design, population, interventions, comparators, outcomes, areas of potential bias)?	Key information on studies has been presented in an appendix in addition to quality assessments of each study.
7.	If the results of the review have been combined (meta-analysis), was this appropriate?	Results have not been combined into a meta-analysis. This would not have been appropriate due to the different results presented and methodologies in each paper.
	Were the studies sufficiently similar in design and results?	All studies were cross-sectional in design. Outcome measures in the included studies were different.
	Are the reasons for any variations discussed?	Variations in results have been discussed in the review.
8.	Are results provided for all included studies? Do the conclusions reflect all results? Is the quality assessment of individual studies reflected	Yes Yes

in the results?	All studies were of decent quality. Quality of the individual studies was not mentioned in the body of the review.
9. Were all the important outcomes considered?	Important outcomes related to this topic area were considered.
10. Is any sponsorship/conflict of interest reported?	The authors state there are no conflicting interests.
11. Finally…consider: Did the authors identify any limitations? Date of review – is it likely to be out of date? Are the conclusions the same in the abstract and the full text?	The authors identified limitations with their review which centred on a limited evidence base and argued that issues affecting parental fear of hypoglycaemia are complex and multi-faceted. Yes.

Citation: Gjerlow *et al.* (2014) *Are there other companion papers from the same study?* No	
	Yes/ Can't tell/ No
1. Is the study design clearly stated?	No. However, it is a cross-sectional (observational), prospective study.
2. Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Outcomes.	Yes – the aim of the study was, in a large and unselected sample of Norwegian adults with type 1 diabetes, to investigate different aspects of fear of hypoglycaemia and to examine gender differences in these aspects of fear. Population – Adults (18-75 years) with type 1 diabetes. Exposure – hypoglycaemia. Outcomes – history of severe hypoglycaemia, HFS-II-Worry.
3. Are the setting, locations and relevant dates provided? Consider: recruitment period; exposure; data collection.	Yes. Study start date (but not study end date), exposure and method of data collection have been presented.
4. Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants.	Yes. Inclusion criteria have been listed but no exclusion criteria have been presented. All patients with type 1 diabetes attending an outpatient clinic at St Olavs Hospital, Norway, were

	invited to participate.
5. Are participant characteristics provided? Consider if: sufficient details; a table is included.	Yes. A table has been included and another table comparing age, diabetes duration and HbA1c of responders and non-responders has been included.
6. Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable.	Yes. A Norwegian version of the HFS-II-Worry scale was sent to patients. A non-validated set of questions were also included to gather information on clinical characteristics including history of severe hypoglycaemia. Awareness of hypoglycaemia was assessed using a previously published question. Information from the questionnaire was supplemented with data from hospital records including the last recorded measurement of HbA1c.
7. Is there a description of how the study size was arrived at?	Yes.
8. Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) considered/controlled for.	Yes. When a participant did not respond to all items, the average score was calculated by dividing the sum of scores for individual items by the number of items that the participant had replied to.
9. Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; numbers of outcome events.	Yes. No flow diagram was included presented. However, the authors explain how the final number of study participants was reached.
10. Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the abstract and the full text.	Yes. Main results have been presented in tables and include: means, standard deviation of the mean and p values. Conclusions in the abstract match those in the full text.
11. Is any sponsorship/conflict of interest reported?	The authors report no conflict of interests.
12. Finally…Did the authors identify any limitations and, if so, are they captured above?	The authors identified one limitation: responders had no opportunity to express specific concerns about hypoglycaemia other than those included in the HFS-II-Worry. Yes.

Citation: Gonder-Frederick et al. (2006) *Are there other companion papers from the same study?* No	
	Yes/ Can't tell/ No

1. Is the study design clearly stated?	No. However, the study is a cross-sectional study.
2. Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Outcomes.	Yes. Population – adolescents with T1D and their parents. Exposure – Hypoglycaemia Outcomes – number of episodes of mild hypoglycaemia (MH) and severe hypoglycaemia (SH) experienced by the adolescent over the past year, whether the parent had confidence that their child carries fast-acting glucose at all times for hypoglycaemia treatment, the extent parents and adolescents believed they could recognise low blood glucose and HFS (HFS-C (children) and HFS-P (parents).
3. Are the setting, locations and relevant dates provided? Consider: recruitment period; exposure; data collection.	The setting has been provided but no dates for the recruitment period have been provided.
4. Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants.	Yes. Participants were recruited from a university-based outpatient endocrinology clinic during the adolescents' regularly scheduled 3-month appointment. Inclusion and exclusion criteria have been presented. One parent involved in the adolescent's diabetes care also needed to participate.
5. Are participant characteristics provided? Consider if: sufficient details; a table is included.	Yes. A basic demographic table for the adolescents has been presented. Some demographic information on the parents has been presented within the paper's text.
6. Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable.	Yes. The measures of exposures and outcomes seem appropriate. The authors have used the HFS questionnaire which has been previously published.
7. Is there a description of how the study size was arrived at?	Yes. The authors have described how final study size was arrived at.
8. Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) considered/controlled for.	Yes. The authors have described how missing data were handled. T-tests were used where appropriate and correlations were calculated to examine relationships between parent and adolescent HFS and trait anxiety scores, other variables were hypothesized to predict FoH (e.g., frequency of MH and SH), and demographic/clinical variables (e.g., age of adolescent, diabetes duration, HbA1c).

9. Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; numbers of outcome events.	Yes. No flow diagram has been included. However, details on how the final number of participants was arrived at have been included. In addition, the authors have given details on how missing values were dealt with.
10. Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the abstract and the full text.	Yes. Ranges for mean scores have been presented where appropriate. T-test statistics have been presented alongside p-values for t-tests. The conclusions in the abstract were the same in the abstract and the full text.
11. Is any sponsorship/conflict of interest reported?	The authors have not stated if there are any sponsorship/conflicts of interest.
12. Finally…Did the authors identify any limitations and, if so, are they captured above?	Yes. Limitations identified by the authors included: A total of 22 families failed to return completed questionnaires for both the adolescent and the parent, even after a telephone call reminder and request. The authors did not collect demographic questionnaires on non-participating families, the authors could not compare them to those who participated. Only one father participated in this study. The limitations listed here were not captured above.

Citation: Haugstvedt *et al*. (2010) *Are there other companion papers from the same study? Can't tell.*	
	Yes/ Can't tell/ No
1. Is the study design clearly stated?	Yes. Population-based study (cross-sectional).
2. Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Outcomes.	Yes: to analyse the association between parental fear of hypoglycaemia and the prevalence of hypoglycaemia and diabetes treatment factors in children with type 1 diabetes and the emotional distress in mothers and fathers. Population - Parents of children with type 1 diabetes Exposure – hypoglycaemic event Outcomes – fear of hypoglycaemia and emotional distress.
3. Are the setting, locations and relevant dates provided? Consider: recruitment period; exposure; data collection.	Yes. The setting, location and recruitment period has been reported. Information on how data were

	collected has been presented too.
4. Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants.	Yes. All parents of children with type 1 diabetes were invited to participate. Inclusion criteria have been presented and some limited exclusion reasons too.
5. Are participant characteristics provided? Consider if: sufficient details; a table is included.	Yes A table of characteristics of the included children as reported by the parents.
6. Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable.	Yes. The measures used have been previously published.
7. Is there a description of how the study size was arrived at?	Yes. The authors didn't include a flow diagram and there isn't a power calculation. However, the authors describe how the final participant numbers were reached.
8. Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) considered/controlled for.	Yes. The statistical analyses followed are described in detail. Analyses included regression and Pearson correlation. The authors described how they dealt with missing data.
9. Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; numbers of outcome events.	Yes. The authors didn't include a flow diagram. However, the authors describe how the final participant numbers were reached.
10. Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the abstract and the full text.	Yes. Results are presented as means where appropriate with ranges and standard deviations also presented. For regression analyses regression coefficients, lower and upper confidence intervals and p-values are presented.
11. Is any sponsorship/conflict of interest reported?	No. The authors declare no competing interests.
12. Finally…Did the authors identify any limitations and, if so, are they captured above?	Yes. The authors state that the cross-sectional design of the study makes is impossible to explore the causal direction between variables. There are also limitations due to self-report bias and sample size. The authors also highlight that the HFS questionnaires have their own limitations including interpretation of scores.

Citation: Hendrieckx *et al*. (2014) *Are there other companion papers from the same study? No*	
	Yes/ Can't tell/ No
1. Is the study design clearly stated?	No. However, the study is cross-sectional in design.
2. Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Outcomes.	Yes: to examine self-reported prevalence of hypoglycaemia in a population of Australian adults with type 1 diabetes attending one of three specialist diabetes clinics; and to explore its associations with IAH, clinical, psychological and socio-demographic factors. Population – adults with type 1 diabetes Exposure – hypoglycaemia Outcomes – prevalence of self-reported severe hypoglycaemia, impaired awareness of hypoglycaemia and psychological measures (including general emotional well-being), diabetes-related distress, diabetes-specific positive well-being, fear of hypoglycaemia).
3. Are the setting, locations and relevant dates provided? Consider: recruitment period; exposure; data collection.	Yes. Setting, recruitment dates and how data were collected has been presented.
4. Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants.	Yes. Adults with type 1 diabetes were recruited when they attended clinic across 3 sites. Inclusion criteria have been presented.
5. Are participant characteristics provided? Consider if: sufficient details; a table is included.	Yes. A comprehensive table has been provided.
6. Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable.	Yes. The methods of assessment have been previously published.
7. Is there a description of how the study size was arrived at?	Yes.
8. Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) considered/controlled for.	Yes. Means, standard deviations, medians and ranges have been used. χ^2 tests, t-tests and Mann-Whitney U-test have been used were appropriate in addition to logistic regression. Questionnaires with missing data were removed from analysis.
9. Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; numbers of outcome events.	Yes. No flow diagram is presented. However, the authors have explained how the final participant numbers have been reached. The authors have also explained

	how missing data was dealt with.
10. Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the abstract and the full text.	Yes. P-values and confidence intervals have been presented where appropriate. Results and conclusions appear to be the same in the abstract as those in the full text.
11. Is any sponsorship/conflict of interest reported?	No. The authors have declared no conflict of interest.
12. Finally…Did the authors identify any limitations and, if so, are they captured above?	Yes. The self-reported nature of the questionnaires has not been validated against objectively collected data on patient hypoglycaemic episodes.

Citation: Herbert *et* al. (2014) *Are there other companion papers from the same study? No*	
	Yes/ Can't tell/ No
1. Is the study design clearly stated?	Yes – cross-sectional
2. Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Outcomes.	Yes - to investigate the type 1 diabetes-related school/day-care experiences of parents of young children and to examine the relationship among child school/day-care functioning, parent fear of hypoglycaemia and parent type 1 diabetes-related quality of life. Outcomes - medical/demographic characteristics related to school/day-care, child/parent functioning, relationship among school/day-care functioning, fear of hypoglycaemia and parents' diabetes-related QOL.
3. Are the setting, locations and relevant dates provided? Consider: recruitment period; exposure; data collection.	Yes. The setting, locations and how data were collected has been presented. No dates for recruitment have been presented.
4. Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants.	Yes. Both inclusion and exclusion criteria have been presented for the participants. Participants were recruited from three tertiary clinics.
5. Are participant characteristics provided? Consider if: sufficient details; a table is included.	Yes. No table has been provided, instead participant characteristics have been presented in a single paragraph.

6. Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable.	Yes. Assessments used have been previously published.
7. Is there a description of how the study size was arrived at?	Yes.
8. Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) considered/controlled for.	Yes. The statistical methods used include χ^2analyses, and correlation analyses. Methods aren't' described in great detail however. The authors have not discussed how missing data were dealt with.
9. Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; numbers of outcome events.	Yes. No flow diagram has been provided. However, the authors have described how the final participant number was reached. No information on how missing data was dealt with has been presented.
10. Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the abstract and the full text.	Yes. The results are adequately described. P-values are presented where necessary. However, no confidence intervals have been presented.
11. Is any sponsorship/conflict of interest reported?	No. The authors did not declare any conflicts of interest.
12. Finally…Did the authors identify any limitations and, if so, are they captured above?	Yes. The authors commented on the generalisability of the results in terms of socio-economic status and ethnicity of the participants. As this study was cross-sectional causal conclusions from correlations cannot be drawn. The authors also state that the study is based on parent self-report and may benefit from multiple informants.

Citation: Johnson *et al.* (2013) *Are there other companion papers from the same study? No*	
	Yes/ Can't tell/ No
1. Is the study design clearly stated?	Yes – cross-sectional
2. Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Outcomes.	Yes - to evaluate the association between fear of hypoglycaemia, episodes of hypoglycaemia and quality of life in children with Type 1 diabetes and their parents. Population – Parents of children with type 1 diabetes and children with type 1 diabetes. Exposure – hypoglycaemia Outcomes – fear of hypoglycaemia, quality of life and HbA1c levels.

3. Are the setting, locations and relevant dates provided? Consider: recruitment period; exposure; data collection.	Yes. Recruitment period, exposure and how data were collected has been presented.
4. Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants.	Yes. Inclusion criteria were presented but no exclusion criteria. Parents of children with type 1 diabetes were approached in clinic.
5. Are participant characteristics provided? Consider if: sufficient details; a table is included.	Yes. A table has been presented and is comprehensive.
6. Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable.	Yes. The quality of life questionnaires and hypoglycaemia fear survey used have previously been published.
7. Is there a description of how the study size was arrived at?	Yes.
8. Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) considered/controlled for.	Yes. Regression analyses, t-tests and χ^2 tests were used to analyse the data. Information on how missing data were handled has not been provided.
9. Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; numbers of outcome events.	Yes. No flow diagram has been presented. However, the authors have explained how the final participant number was reached. There is no information on how missing participant data were addressed.
10. Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the abstract and the full text.	Yes. However, the majority of the results are discussed in paragraphs and not in tables. In the patient demographic table means, standard deviation and p-values are presented. However, the majority of the data is presented in charts. The charts have large scales and so make differences between bars difficult to gauge.
11. Is any sponsorship/conflict of interest reported?	No. The authors have no competing interests to declare.
12. Finally…Did the authors identify any limitations and, if so, are they captured above?	Yes. Due to the cross-sectional study design no assumption on causality can be made. The response rate was 48% and so may have inadvertently biased the results.

Citation: Lawton *et al.* (2014)
Study Design: Qualitative, non-comparative.

1. Does the study address a clearly focused question/hypothesis	Yes - to explore the difficulties parents encounter in trying to achieve clinically recommended blood glucose levels and how they could be better supported to optimize their child's glycaemic control.
Setting?	Difficulties trying to achieve clinically recommended blood glucose levels.
Perspective?	Parents of children with type 1 diabetes.
Intervention or Phenomena	Optimising glycaemic control.
Comparator/control (if any)?	None
Evaluation/Exploration?	Evaluation of difficulties faced by parents, including fear of a hypoglycaemic episode, through in-depth interviews.
2. Is the choice of qualitative method appropriate? Is it an exploration of e.g. behaviour/reasoning/ beliefs)? Do the authors discuss how they decided which method to use?	Yes The choice of qualitative method was an in-depth review with an average time of two hours per interview. The interviews are an exploration of behaviour and reasoning. Yes The authors decided to conduct a qualitative study following the recommendation from a systematic review.
3. Is the sampling strategy clearly described and justified? Is it clear how participants were selected? Do the authors explain why they selected these particular participants? Is detailed information provided about participant characteristics and about those who chose not to participate?	Yes. Participants were recruited from 4 Scottish paediatric departments using an opt-in procedure. Participants were purposively sampled in an effort to obtain diversity of child's age, sex, diabetes duration, regimen, glycaemic control and parents' education, occupation employment status and marital status. Detailed information is provided on participant characteristics but not those who chose not to participate. This is likely to be due to the purposively sampling that was carried out.
4. Is the method of data collection well described? Was the setting appropriate for data collection? Is it clear what methods were used to collect data? Type of method (e.g., focus groups, interviews, open questionnaire etc) and tools (e.g. notes, audio, audio visual recording). Is there sufficient detail of the methods used (e.g. how any topics/questions were generated and whether they were piloted; if observation was used, whether the context described and were observations made in a variety of circumstances? Were the methods modified during the study? If YES, is this explained?	Yes. The data was collected out in the parent's own homes. The methods used to collect data are described in detail. In-depth interviews were the source of the data. A topic guide was used for the interviews which averaged 2 hours per interview. Interviews were digitally recorded and transcribed in full. The authors have included the topic guide used during the interviews and have presented this in a table. Methods were not modified during the study.

Is there triangulation of data (i.e. more than one source of data collection)? Do the authors report achieving data saturation?	There was no triangulation of data. The authors reported data saturation and continued recruitment and interviewing until this occurred.
5. Is the relationship between the researcher(s) and participants explored? Did the researcher report critically examining/reflecting on their role and any relationship with participants particularly in relation to formulating research questions and collecting data). Were any potential power relationships involved (i.e. relationships that could influence in the way in which participants respond)?	Yes. The authors have stated that the researcher is not a healthcare worker and the interviews were conducted in the parents' home.
6. Are ethical issues explicitly discussed? Is there sufficient information on how the research was explained to participants? Was ethical approval sought? Are there any potential confidentiality issues in relation to data collection?	Yes. Ethical approval was sought and granted by the South East Scotland Research Ethics Committee. There are no apparent confidentiality issues. Participants have been designated unique identifiers with 'M' and 'F' signifying a child's mother or father respectively.
7. Is the data analysis/interpretation process described and justified? Is it clear how the themes and concepts were identified in the data? Was the analysis performed by more than one researcher? are negative/discrepant results taken into account?	Yes. The authors have described how themes were identified. Analysis was carried out by two researchers independently before meeting to compare interpretations, reach agreements on identified themes, and findings and develop a coding framework capturing original research questions and emerging findings.
8. Are the findings credible? Are there sufficient data to support the findings? Are sequences from the original data presented (e.g. quotations) and were these fairly selected? Are the data rich (i.e. are the participants' voices foregrounded)? Are the explanations for the results plausible and coherent? Are the results of the study compared with those from other studies?	Yes. Quotes from the original interviews have been included in relation to the identified themes. The participants' voices are at the foreground. Each identified theme has its own section which is structured using quotes from parents. Yes. The results of the study are compared with other studies in the paper's discussion section.
9. Is any sponsorship/conflict of interest reported?	No. The authors have not declared any competing interests.
10. Finally…consider: Did the authors identify any limitations? Are the conclusions the same in the abstract and the full text?	Yes. The authors acknowledge that as data was collected in Scotland only levels of glycaemic control may not be the same as other countries.

Citation: Leiter *et al.* (2005) *Are there other companion papers from the same study? No*	
	Yes/ Can't tell/ No
1. Is the study design clearly stated?	Yes – cross-sectional (observational), retrospective.
2. Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Outcomes.	Yes – to assess the impact of mild, moderate and severe hypoglycaemia and fear of future hypoglycaemic episodes on patients with type 1 or insulin-treated type 2 diabetes. Population – Adults with type 1 or insulin treated type 2 diabetes. Exposure – hypoglycaemia. Outcomes – number of hypoglycaemic episodes (mild, moderate and severe), glucose monitoring, changes to insulin regimen following a hypoglycaemic episode and changes to lifestyle following a hypoglycaemic episode.
3. Are the setting, locations and relevant dates provided? Consider: recruitment period; exposure; data collection.	Yes. Recruitment period, exposure and method of data collection have been presented.
4. Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants.	Yes. Inclusion criteria have been listed but no exclusion criteria have been presented. Participants were recruited from 4 centres.
5. Are participant characteristics provided? Consider if: sufficient details; a table is included.	Yes. No table has been included but participant characteristics are discussed in the text of the paper.
6. Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable.	Yes. The questionnaire administered was not validated in its entirety. However, the questionnaire was pretested using a focus group of people with type 1 or 2 diabetes. But the questionnaire did contain a validated hypoglycaemia fear survey (results not presented). Details on HbA1c were collected from the patient's doctor.
7. Is there a description of how the study size was arrived at?	Yes.
8. Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) considered/controlled for.	No. Limited statistical methods were required for this study. The authors have not described how missing data were handled.

9. Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; numbers of outcome events.	Yes. No flow diagram was included presented. However, the authors explain how the final number of study participants was reached.
10. Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the abstract and the full text.	No. Reading the results is difficult. Most results are discussed in the text and are difficult to read. Tables do not state clearly what is presented and it is difficult to determine how the presented percentages have been calculated.
11. Is any sponsorship/conflict of interest reported?	None presented.
12. Finally…Did the authors identify any limitations and, if so, are they captured above?	The authors identified the following limitations: we may have inadvertently excluded participants who were not able to speak either English or French, potentially introducing biases related to cultural diversity, isolation, age and inability to access healthcare. Additionally, the majority of the patients were recruited from diabetes specialist clinics and were likely aware of the value of regular visits to their physician. Furthermore, a participation bias may exist as those who volunteered to participate may have been more concerned and knowledgeable about their disease and its management than the general population. Yes.

Citation: Nordfeldt and Ludvigsson (2005) *Are there other companion papers from the same study? No*	
	Yes/ Can't tell/ No
1. Is the study design clearly stated?	Yes. It is a cross-sectional (observational), prospective study.
2. Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Outcomes.	Yes – to establish the prevalence of self-reported hypoglycaemia among ambulatory patients with diabetes and assess its impact on health-related quality of life. Population – Adults (≥18 years) with type 1 or type 2 diabetes. Exposure – hypoglycaemia. Outcomes – anxiety, health-related quality of life and fear of hypoglycaemia.
3. Are the setting, locations and relevant dates provided? Consider: recruitment period; exposure; data collection.	Yes. Study dates, exposure and method of data collection have been presented.

4. Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants.	Yes. Inclusion criteria have been listed but no exclusion criteria have been presented. Patients with type 1 or type 2 diabetes identified in a Diabetes Electronic Management System (DEMS) at the Mayo Clinic were randomly selected to receive a postal questionnaire. It is unclear how these patients were randomly selected.
5. Are participant characteristics provided? Consider if: sufficient details; a table is included.	Yes. A table has been included on clinical characteristics for responders, non-responders, patients with type1 diabetes and patients with type 2 diabetes. P-values have been included to highlight significant differences between groups.
6. Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable.	Yes. The authors used the EuroQol EQ-5D to gauge quality of life, the GAD-7 to gauge levels of general anxiety and HFS to gauge fear of hypoglycaemia. Prevalence of hypoglycaemia was self-reported by the patients.
7. Is there a description of how the study size was arrived at?	Yes.
8. Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) considered/controlled for.	To a certain a degree. The statistical tests used have been described and include: the two-sample *t* test ant χ^2 test. Multivariable analysis was used to adjust for factors potentially contributing to hypoglycaemia. However, there is no mention of how missing data were handled. The authors have compared responders and non-responders to determine if there was a difference or not.
9. Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; numbers of outcome events.	Yes. No flow diagram was included presented. However, the authors explain how the final number of study participants was reached.
10. Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the abstract and the full text.	Yes. Some results have been presented in tables and include descriptions of what has been presented. Other results have been presented in the text under appropriate sub-headings. Conclusions in the abstract match those in the full text.
11. Is any sponsorship/conflict of interest reported?	The authors have no interests to declare.
12. Finally…Did the authors identify any limitations and, if so, are they captured above?	The authors identified the following limitations: by focusing on self-report of hypoglycaemia, we could not detect all hypoglycaemic events experienced by patients with little or no hypoglycaemia awareness;

	the study relied on voluntary mailed questionnaires and therefore has the potential for response bias. Yes.

Citation: Nordfeldt and Ludvigsson (2005) *Are there other companion papers from the same study? No*	
	Yes/ Can't tell/ No
1. Is the study design clearly stated?	No. However, it is a cross-sectional (observational), prospective study.
2. Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Outcomes.	Yes – the aims of the study were to explore the occurrence of fear and other disturbances of severe hypoglycaemia, and their average perceived magnitude in comparison to other aspects of type 1 diabetes, in children and adolescents with modern intensive treatment including active education and psychological support. Population – Children and adolescents (<19 years) with type 1 diabetes. Exposure – hypoglycaemia. Outcomes – severe hypoglycaemia, perceived disturbance, fear, life satisfaction, quality of life and responses to open questions.
3. Are the setting, locations and relevant dates provided? Consider: recruitment period; exposure; data collection.	No. No study dates have been reported. However, exposure and method of data collection have been presented.
4. Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants.	Yes. Inclusion criteria have been listed but no exclusion criteria have been presented. All patients with type 1 diabetes diagnosed in the catchment area belonging to the University Hospital of Linköping, Sweden, were invited to participate.
5. Are participant characteristics provided? Consider if: sufficient details; a table is included.	Yes. A table has been included on clinical characteristics. Differences and similarities between responders and non-responders have been described in the text.
6. Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable.	To a certain degree. Visual analogue scales (VASs) were used to gauge perceived disturbance, fear, “how good is life” and life satisfaction. However, it is unclear if the questions asked in combination with the VASs were validated. The authors used the EuroQol EQ-5D to gauge

	quality of life.
7. Is there a description of how the study size was arrived at?	Yes.
8. Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) considered/controlled for.	To a certain a degree. The statistical tests used have been described and include: the Friedman, Wilcoxon signed rank, Mann Whitney *U* tests and Spearman rank correlation. The χ^2 test was used for proportions. However, there is no mention of how missing data were handled. The authors have compared responders and non-responders to determine if there was a difference or not.
9. Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; numbers of outcome events.	Yes. No flow diagram was included presented. However, the authors explain how the final number of study participants was reached.
10. Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the abstract and the full text.	Yes. Some results have been presented in tables and include: means, standard deviation of the mean and p values. Other results have been presented in the text under appropriate sub-headings. Conclusions in the abstract match those in the full text.
11. Is any sponsorship/conflict of interest reported?	Not presented in the paper.
12. Finally…Did the authors identify any limitations and, if so, are they captured above?	The authors identified the following limitations: the study population was too small for stratification of age, insulin types and regimens or other factors; it might be valuable to study adolescents separately from patents; future studies might also include psychosocial factors. Yes.

Citation: Streisand et al. (2005) *Are there other companion papers from the same study?* No.	
	Yes/ Can't tell/ No
1. Is the study design clearly stated?	Yes. To investigate the stress faced by parents and to explore the psychological and behavioural correlates of their stress.
2. Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Outcomes.	Yes. Population: Parents of children with type 1 diabetes. Exposure: Hypoglycaemia

	Outcomes: Effect of clinical, demographic, psychological and behavioural variables on stress frequency and difficulty.
3. Are the setting, locations and relevant dates provided? Consider: recruitment period; exposure; data collection.	Yes. Participating families were recruited from two paediatric hospitals in the US.
4. Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants.	Uncertain. No inclusion and exclusion criteria were presented by the authors.
5. Are participant characteristics provided? Consider if: sufficient details; a table is included.	Yes. No table has been presented. However, a narrative description of participant characteristics has been discussed by the authors.
6. Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable.	Yes. The study utilised the Self-Efficacy for Diabetes Scale (SED) and determined responsibility for diabetes management through The Diabetes Family Responsibility Questionnaire (DFRQ), fear of hypoglycaemia through the Hypoglycaemia Fear Survey (HFS) and paediatric parenting stress through the Paediatric Inventory for Parents (PIP). All of the tools utilised have been previously published.
7. Is there a description of how the study size was arrived at?	No. However, the final study numbers have been presented.
8. Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) considered/controlled for.	Yes. Missing data was imputed. Descriptions of the statistical methods have been detailed by the authors under a “data analysis plan” heading.
9. Is information provided on participant flow? Consider if following provided: flow diagram; numbers of participants at each stage; details of drop-outs; details of missing participant data; numbers of outcome events.	No. However, the final study numbers have been presented. Missing data was imputed.
10. Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the abstract and the full text.	Yes. Standard deviations have been presented when means have been presented. In addition, statistical results have been presented in APA style with p values, a test statistic and the degrees of freedom.
11. Is any sponsorship/conflict of interest reported?	Unknown. The authors have not stated whether or not there are any sponsorship/conflicts of interest.
12. Finally…Did the authors identify any limitations and, if so, are they captured above?	Yes. The authors identified the following limitations: No conclusions about causality can be drawn given

	the cross-sectional nature of this work. Specifically, whether paediatric parenting stress is a cause or consequence of parent psychological and behavioural functioning in other areas. Additionally, questionnaires were administered to parents of a relatively wide age range of children, and it is likely that stressors experienced by parents of younger children differed from those experienced by parents of older children, as those who had reached adolescence. The study relied upon self-report, and data were not validated by other methods. The majority of our sample was comprised of mothers, and it is likely that fathers also experience considerable paediatric parenting stress, although that stress may differ in quality and quantity. The limitations listed by the authors were not captured above.