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A systematic review of the effect of prior hypoglycaemia on cognitive function in type 1 diabetes

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Abstract

Background: The effect of prior hypoglycaemia on cognitive function in type 1 diabetes is an important unresolved clinical question. In this systematic review, we aimed to summarize the studies exploring the impact of prior hypoglycaemia on any aspect of cognitive function in type 1 diabetes.

Methods: We used a multidatabase search platform Healthcare Database Advanced Search to search Medline, PubMed, EMBASE, EMCARE, CINAHL, PsycINFO, BNI, HMIC, and AMED from inception until 1 May 2019. We included studies on type 1 diabetes of any age. The outcome measure was any aspect of cognitive function.

Results: The 62 studies identified were grouped as severe hypoglycaemia (SH) in childhood (⩽18 years) and adult-onset (>18 years) diabetes, nonsevere hypoglycaemia (NSH) and nocturnal hypoglycaemia (NH). SH in early childhood-onset diabetes, especially seizures and coma, was associated with poorer memory (verbal and visuospatial), as well as verbal intelligence. Among adult-onset diabetes, SH was associated with poorer cognitive performance in the older age (>55 years) group only. Early *versus* late exposure to SH had a significant association with cognitive dysfunction (CD). NSH and NH did not have any significant association with CD, while impaired awareness of hypoglycaemia was associated with poorer memory and cognitive-processing speeds.

Conclusion: The effect of SH on cognitive function is age dependent. Exposure to SH in early childhood (<10 years) and older age groups (>55 years) was associated with a moderate effect on the decrease in cognitive function in type 1 diabetes [PROSPERO ID: CRD42019141321].

Keywords: cognitive function, hypoglycaemia, severe hypoglycaemia, type 1 diabetes

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Introduction

Type 1 diabetes incidence is increasing worldwide, with estimates suggesting almost a doubling of the incidence in Europe.[1,2] While complications such as retinopathy and nephropathy, as well as mortality have reduced significantly over decades due to improvements in management, achieving day-to-day euglycaemia remains a challenge for most people with type 1 diabetes.[3]

Hypoglycaemia, hyperglycaemia and increased glucose variability remain the three major glycaemic pathologies of diabetes.[4] The goal of therapy in type 1 diabetes is to maximize time in euglycaemia and minimize both hypo- and hyperglycaemia. However, hypoglycaemia, both mild and severe is not uncommon among people with type 1 diabetes. A survey of 1076 people with type 1 diabetes reported rates of severe hypoglycaemia (SH) of 1.3 episodes per person-year (PY), with a third experiencing at least one episode of SH a year and each person, on average, self-treating at least two hypoglycaemia episodes per week.[5]

Acute effects of hypoglycaemia on cognitive function (CF) are well described.[6,7] Evidence suggests that CF returns to baseline 40–90 min after the restoration of euglycaemia.[6] However, there is concern about the long-term effects of SH on cognition among both people with type 1 diabetes and the healthcare professionals.

Prior meta-analyses have described the impact of type 1 diabetes on cognition. Most studies have examined the effect of type 1 diabetes on CF in comparison with people without type 1 diabetes. Multiple disease-related factors like the age of onset, duration of diabetes, hypoglycaemia, hyperglycaemia, retinopathy and neuropathy status are associated with CF.[8,9] However, the effect of hypoglycaemia on cognition reported in these studies are varied. Brands and colleagues[10] found no association between severe hypoglycaemia and CF, while He and colleagues[9] and Naguib and colleagues[11] found that SH was associated with a decline in overall CF and memory. Gaudieri and colleagues[12] found early-onset type 1 diabetes in children to have a more significant impact on learning and memory while seizures had a negligible effect on cognition. Broadley and colleagues[13] found that early SH was associated with lower executive function, while Tonoli and colleagues[14] found that SH had an impact on CF only in adults. To our knowledge, the only meta-analysis, which focused on the effect of recurrent SH on cognition in children with type 1 diabetes found impaired memory, learning, intelligence and verbal fluency in those with recurrent SH.[15]

Currently, there is a lack of literature focusing on the effect of prior hypoglycaemia on cognitive dysfunction (CD) in type 1 diabetes across all age groups. Available studies on the impact of type 1 diabetes report varied effects of hypoglycaemia on cognition. We conducted a systematic review to address this important clinical question.

Methodology

We formulated a research question using the modified PI(E)CO format (Population, Intervention, Exposure, Comparator, Outcome). Is prior exposure to hypoglycaemia associated with CD in type 1 diabetes compared with those without exposure to hypoglycaemia? Hypoglycaemia was defined as blood glucose <3.9 mmol/l, with or without symptoms. Participants with no self-reported or documented hypoglycaemia were assumed to have had no prior exposure.

A search strategy with three key concepts, 'hypoglycaemia', 'type 1 diabetes' and 'cognitive function' and their synonyms were drawn out (Table 1). The search strategy was intentionally broad to include all potential studies. We used the search platform Healthcare Databases Advanced Search by National Institute of Clinical Excellence (NICE), UK[16] to search Medline, Pubmed, EMBASE, EMCARE, CINAHL, PsycINFO, BNI, HMIC, and AMED from inception until 1st May 2019, and identified a total of 7799 articles (Figure 1). After de-duplication, we screened the studies for eligibility.

Inclusion criteria: studies on type 1 diabetes with at least one aspect of CF assessed as an outcome measure.

Exclusion criteria: studies on type 2 diabetes, case reports and studies with less than five participants, non-English articles, studies not investigating the effect of hypoglycaemia separately and studies not clarifying the type of diabetes.

SR assessed the abstracts and undertook data extraction and risk-of-bias assessment, with input from PJ. We screened the reference lists of included studies for any relevant articles. Any difference of interpretation was resolved after discussion with PC and achieving consensus. Data were extracted using a standardized table using Excel software (version 2007, by Microsoft, Washington, United States) from full-text articles. Risk of bias was assessed using the Newcastle–Ottawa scoring system[16] for case-control and cohort studies and the modified version for cross-sectional studies.[78,79] We interpreted the study methodology with exposure of interest (hypoglycaemia) for risk-of-bias assessment. These scoring systems assess for selection, exposure, comparability and outcome biases. SH rate was computed as mean SH episodes per 100 PY. Where two groups existed with no combined data provided, the highest SH rate was extracted. The effect size of significant cognitive outcomes between groups with and without SH was calculated where possible, using Hedges' *g* for individual studies. No pooling of effect sizes or meta-analysis was done. Data synthesis for narrative review was done after grouping the studies into the five clinically relevant subtopic categories prespecified in the protocol (Table 2).

(1) Association of SH with CD:
   (a) childhood onset (mean age of diabetes onset $\leqslant 18$ years)

Table 1. Search strategy used for multidatabase search on HDAS.

1	Hypoglycemia
2	Hypoglyc?emi* OR (low adj3 glucose)
3	1 OR 2
4	Diabetes mellitus, Type 1
5	"insulin* depend*" OR "insulin?depend*"
6	"typ? 1 diabet*" OR "typ? I diabet*" OR "typ?1 diabet*" OR "typ?I diabet*"
7	(("auto-immun*" OR "autoimmune*" OR "sudden onset") ADJ2 diabet*)
8	insulin* defic* ADJ2 absolut*
9	IDDM or T1DM or T1D
10	4 OR 5 OR 6 OR 7 OR 8 OR 9
11	Cognition
12	Memory
13	Cogniti* OR memory OR ((brain OR cortical OR executive OR mental OR cerebral) ADJ2 function) OR neuro?psycholog* OR academic* OR psycho?metric OR language OR neuro?cognit* OR psycholog* OR cerebral OR amnesia OR motivation* OR attention* OR recall OR psycho?motor OR neuro?behavio?r*
14	11 OR 12 OR 13
15	3 AND 10 AND 14

HDAS, Healthcare Databases Advanced Search; IDDM, insulin-dependent diabetes mellitus; T1DM, type 1 diabetes mellitus.

  - (i) prospective cohort studies, cross-sectional studies, case-control studies
- (b) adult onset (mean age of diabetes onset >18 years)
  - (i) prospective cohort studies, cross-sectional studies, case-control studies

(2) Effect of early *versus* late exposure to SH
(3) Effect of nonsevere hypoglycaemia (NSH) on CF
(4) Effect of nocturnal NSH on CF
(5) Effect of impaired awareness of hypoglycaemia (IAH) on CF

We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines for systematic reviews and the protocol is registered with the international prospective register of systematic reviews, PROSPERO [ID: CRD42019141321].

Results

We found 7799 abstracts from a multidatabase search and identified 61 studies that met our eligibility criteria, with publication year ranging from 1987 to 2019. An additional study was included, based on reference searches of included studies. The majority of studies were undertaken using the White population, with only two studies from Egypt,[44,68] and one each from Indian, Chinese and Turkish populations. The definition of SH varied across studies and this is discussed where relevant. The majority of studies excluded people with neuropsychiatric conditions and those taking drugs that may interfere with the cognitive assessment. A narrative synthesis of the findings is given. The calculated effect sizes for individual studies are quoted in this narrative synthesis where relevant; however, no pooling of effect sizes or metanalysis was done.

Effect of prior SH on CF in type 1 diabetes with childhood-onset (⩽18 years) diabetes

We found 28 studies in this group; 14 cross-sectional, 11 prospective cohorts and 3 case-control studies. The mean age of diabetes onset

Table 2. Summary of all included studies in the systematic review.

First author	Association of hypo-glycaemia with CD	Study type	Bias score*	Participants (*n*)	Mean age of recruitment (years)	Mean diabetes duration (years)	Mean age of onset (years)	Hypoglycaemia definition	Estimated SH rate	Cognitive domain affected	Direction of association#
Effect of SH on childhood (⩽18 years) on CF											
Reichard *et al.*[17]	No	Prospective cohort	60%	97	30.5	17	13.5	SH: third-party help, LOC	12.7/100 PY	Nil	–
Northam *et al.*[18]	No	Cross-sectional	70%	85	15.5	6.8	8.5	SH: third-party help	16.9/100 PY	Nil	–
Ryan *et al.*[19]	No	Cross-sectional	70%	142	33.5	24.8	8.7	SH: medical help (ER or doctor)	1.36/100 PY	Nil	–
Hershey *et al.*[20]	Yes	Cross-sectional	70%	38	22.8–26.2	12.3–18.5	7.5/7.7	SH: medical attention	29/100 PY	Verbal memory	Negative
Rovet *et al.*[21]	Yes	Cross-sectional	70%	103	13.5	6.8	6.4	SH: seizure	42/100 PY	Selective attention and focus	Negative
Rovet *et al.*[22]	Yes	Prospective cohort	67%	16	12.1	7.6	4.5	SH: seizure	13/100 PY	Verbal IQ, visual memory and attention	Negative
Northam *et al.*[23]	Yes	Prospective cohort	89%	116	7.5	–	7.5	SH: altered conscious state, seizures or LOC	6.8/100 PY	Attention and short-term memory, learning and consolidation, long-term memory	Negative
Northam *et al.*[24]	Yes	Prospective cohort	89%	80	12.1	6	3–11	SH: seizures or LOC	4.6/100 PY	Verbal IQ and full-scale IQ	Negative
Schoenle *et al.*[25]	No	Prospective cohort	78%	64	7–16	4–12	3–4	SH: LOC	10.1SH/100 PY	Nil	–
Wysocki *et al.*[26]	No	Prospective cohort	60%	142	11.6	5	6.6	SH: seizure, coma, third-party help, glucagon	15.6/100 PY	Nil	–
Ferguson *et al.*[27]	No	Cross-sectional	60%	74	26.4/31.5	17/26	9.4/5.5	SH: third-party help	35/100 PY	Nil	—
Hershey *et al.*[28]	Yes	Cross-sectional	60%	51	11.7	4.7	7.0	SH: seizure, LOC or inability to arouse, third-party help	41.7/100 PY	Long delay spatial delayed response performance	Negative

(Continued)

Table 2. (Continued)

First author	Association of hypo-glycaemia with CD	Study type	Bias score*	Participants (*n*)	Mean age of recruitment (years)	Mean diabetes duration (years)	Mean age of onset (years)	Hypoglycaemia definition	Estimated SH rate	Cognitive domain affected	Direction of association#
McCarthy *et al.*[29]	Yes	Cross-sectional	60%	244	14.8	7.1	7.7	SH: hospitalization	–	Academic achievement	Negative
Hannonen *et al.*[30]	Yes	Case control	50%	21	9.5/9.1	6.2/3.7	3.3/4.8	SH: seizures or LOC	20/100 PY	Attention and executive function	Negative
Hershey *et al.*[31]	Yes	Prospective cohort	60%	42	11.3/11.7	4.9/4.7	6.5	SH: seizure, LOC or inability to arouse, third-party help	86/100 PY	Spatial long-term memory	Negative
Tupola *et al.*[32]	No	Case control	30%	20	5.6–11.9	1.8–9.6	2–4	SH: seizure or LOC	–	Nil	–
Hershey *et al.*[33]	Yes	Prospective cohort	70%	103	12–13.4	3.3–6.3	7.5	SH: seizure, LOC or inability to arouse, third-party help	42/100 PY	Spatial delayed response, long-delay spatial memory, long-term memory	Negative
Brismar *et al.*[34]	No	Cross-sectional	70%	150	43.3	26.6	16.7	SH: third-party help, hospital admission	11.3/100 PY	Nil	–
Musen *et al.*[35]	No	Prospective cohort	100%	249	16.0	25	11.0	SH: LOC, seizure, third-party help, symptomatic BG < 2.78	6.8/100 PY	Nil	–
Perantie *et al.*[36]	Yes	Cross-sectional	70%	117	12.1	5.3	6.8	SH: seizure, LOC, inability to arouse, third-party help	16.9/100 PY	Delayed recall of explicitly learned information and spatial analysis skills	Negative
Northam *et al.*[37]	Yes	Prospective cohort	100%	106	20.5	12.7	7.8	SH: seizure or LOC	3.2/100 PY	Verbal IQ	Negative
Lin *et al.*[38]	Yes	Prospective cohort	100%	106	20.5	13	7.5	SH: seizure or LOC	3.69/100 PY	Verbal memory, working memory and nonverbal-processing speeds	Negative
Osipoff *et al.*[39]	No	Cross-sectional	70%	94	12.5	4.9	7.6	SH: LOC, seizure	4.1/100 PY	Nil	–

(Continued)

Table 2. (Continued)

First author	Association of hypo-glycaemia with CD	Study type	Bias score*	Participants (*n*)	Mean age of recruitment (years)	Mean diabetes duration (years)	Mean age of onset (years)	Hypoglycaemia definition	Estimated SH rate	Cognitive domain affected	Direction of association#
Hannonen *et al.*[40]	No	Case control	80%	63	9.0	6	3.0	SH: LOC or third-party help	8.3/100 PY	Nil	–
Lin *et al.*[41]	Yes	Prospective cohort	89%	95	21.8	13.24	8.6	SH: seizure or LOC	0.11/100 PY	Verbal IQ	Negative
Semenkovich *et al.*[42]	No	Cross-sectional	60%	61	16.2	9.4	6.8	SH: seizure or LOC	8.5/100 PY	Nil	–
Ryan *et al.*[43]	Yes	Cross-sectional	60%	244	55.0	41	14.0	SH: LOC, hospitalization	9.8/100 PY	SH (1 year): mental efficiency, executive functioning	Negative
Abo-El-Asrar *et al.*[44]	Yes	Cross-sectional	20%	50	12.0	6.42	5.6	–	–	Verbal IQ	Negative
Effect of SH on adult onset (>18 years) on CF											
Langan *et al.*[45]	Yes	Cross-sectional	60%	100	40.2	13.4	26.8	SH: third-party help	120/100 PY	IQ (performance > verbal), information-processing speed	Negative
Deary *et al.*[46]	Yes	Cross-sectional	70%	100	40.2	13.4	26.8	SH: third-party help or LOC	–	Performance IQ	Negative
DCCT group[47]	No	Prospective cohort	100%	1144	26.5	5.5	21	SH: third-party help and BG < 2.78 mmol/l	61/100 PY	Nil	–
Lincoln *et al.*[48]	Yes	Cross-sectional	70%	70	38.9		>18	SH: third-party help	–	IQ, memory, information-processing speed	Negative
Kramer *et al.*[49]	No	Case control	70%	108	38	17.6	20.4	SH: LOC or seizures or third-party help	Not stated	Nil	–
Snoek *et al.*[50]	No	Case control	50%	19	36.9	not stated	>17	–	–	Nil	–
Austin *et al.*[51]	No	Prospective cohort	100%	11441	27.0	6	21.0	SH: seizure, LOC or inability to arouse, third-party help	61/100 PY	Nil	–

(Continued)

Table 2. (Continued)

First author	Association of hypo-glycaemia with CD	Study type	Bias score*	Participants (*n*)	Mean age of recruitment (years)	Mean diabetes duration (years)	Mean age of onset (years)	Hypoglycaemia definition	Estimated SH rate	Cognitive domain affected	Direction of association#
Strachan *et al.*[52]	No	Case control	50%	40	36.4	15.5	20.9	SH: third-party help	18/100 PY	Nil	–
DCCT group[53]	No	Prospective cohort	100%	1144	27.0	6	21.0	SH: LOC or seizure	61/100 PY	Nil	–
Duinkerken *et al.*[54]	Yes	Prospective cohort	89%	36	60.4	38	22.4	SH: LOC or third-party help	8.1/100 PY	Overall cognitive function, information-processing speed	Negative
Perzynski *et al.*[55]	Yes	Cross-sectional	20%	59	32.5	12.8	19.7	–	–	Executive function, speed and motor control	Negative
Bortolotti *et al.*[56]**	Yes	Cross-sectional	60%	26	45.8	18	27.8	SH: LOC	1.05/100 PY	Cognitive-processing speed	Negative
Chaytor *et al.*[57]	Yes	Case control	60%	201	68.3	39	29.3	SH: third-party help	105/100 PY	SH (1 year): memory and executive function	Negative
Effect of early *versus* late exposure to SH on CF											
Rovet *et al.*[58]	Yes	Cross-sectional	50%	51	9.8	5.5	–	SH: seizures	41/100 PY	SH (<4 years): visuospatial and visuo-memory, arithmetic skills	Negative
Bjørgaas *et al.*[59]	Yes	Case control	50%	28	11.9–13.4	2.9–8.3	6.3–9.7	SH: seizure or LOC	27/100 PY	SH (<5 years): psychomotor efficiency and attention	Negative
Ferguson *et al.*[60]	Yes	Cross-sectional	70%	71	5.2/29.9	20.1/17	5/12.2	SH: seizure, LOC, third-party help	28/100 PY	SH (<7 years): nonverbal intelligence performance IQ, slower psychomotor speed	Negative
Strudwick *et al.*[61]	No	Case control	70%	84	10.0	7.1	2.9	SH: seizure or LOC	40/100 PY	SH (<6 years): nil	–

(Continued)

Table 2. (Continued)

First author	Association of hypo-glycaemia with CD	Study type	Bias score*	Participants (*n*)	Mean age of recruitment (years)	Mean diabetes duration (years)	Mean age of onset (years)	Hypoglycaemia definition	Estimated SH rate	Cognitive domain affected	Direction of association#
Asvold *et al.*[62]	Yes	Prospective cohort	89%	28	28.0	20	8.0	SH: LOC or third-party help	50/100 PY	SH (<10 years): overall CF	Negative
Tolu-Kendir *et al.*[63]	Yes	Case control	60%	60	10.9	5.1/7.9	4.4	SH: third-party help, admission, LOC	0.4/100 PY	SH (<5 years): visual motor perception and visual motor integration	Negative
He *et al.*[9]	Yes	Cross-sectional	80%	105	12.2	2.56	9.6	SH: third-party help for seizure, LOC, disorientation	0.37/100 PY	Visual memory (immediate and delayed)	Negative
Effect of nonsevere hypoglycaemia on CF											
Golden *et al.*[64]	Yes	Cross-sectional	50%	23	6.0	3	3	SH: LOC NSH: <2.8 mmol/l	96/100 PY	NSH: abstract reasoning	Negative
Rovet *et al.*[65]	Yes	Cross-sectional	78%	63	7.3	1	7.3	SH: LOC or seizures NSH: <3.9 mmol/l	3.17/100 PY	Overall IQ, verbal IQ, vocabulary	Positive
Puczynski *et al.*[66]	Yes	Cross-sectional	50%	24	12.2	6	4.3	NSH: <3.3 mmol/l	–	Memory and concentration	Negative
Kaufman *et al.*[67]	Yes	Cross-sectional	70%	55	7.9	2.6	5.3	SH: LOC or IV treatment or seizures NSH: <3.9 mmol/l	21.6/100 PY	SH: memory; NSH: memory, verbal comprehension, broad cognition and academic achievement	Positive
Shehata *et al.*[68]	No	Cross-sectional	60%	40	11.7	>6 months		NSH: <3.3 mmol/l	–	Nil	–
Jain *et al.*[69]	No	Cross-sectional	40%	49	11.7	4.25	7.5	NSH: <3.3 mmol/l	–	Nil	–
Mauras *et al.*[70]	No	Prospective cohort	78%	144	7.0	2.5	4.5	SH: LOC or third-party help, NSH: <3.9 mmol/l	3.7/100 PY	Nil	–

(Continued)

Table 2. (Continued)

First author	Association of hypo-glycaemia with CD	Study type	Bias score*	Participants (*n*)	Mean age of recruitment (years)	Mean diabetes duration (years)	Mean age of onset (years)	Hypoglycaemia definition	Estimated SH rate	Cognitive domain affected	Direction of association#
Effect of nocturnal nonsevere hypoglycaemia on CD											
Bendtson *et al.*[71]	No	Case control	60%	8	31.0	11	20	NH: 1.5 mmol/l for 101 min	–	Nil	–
King *et al.*[72]	No	Case control	70%	10	28.0	7	21.0	NH: 2.3–2.7 mmol/l for 60 min	–	Nil	–
Matkya *et al.*[73]	No	Case control	60%	29	8.7	3.9	4.8	NH: <3.5 mmol/l for 30 min	–	Nil	–
Jauch-Chara *et al.*[74]	Yes	Case control	70%	16	31.3	9.1	22.2	NH: 2.2 mmol/l for 60 min	–	Declarative memory	Negative
Sharifi *et al.*[75]	No	Case control	60%	28	42.1/15.2	26.9/6.6	15.2/8.6	NH: <3.9 mmol/l and <3 mmol/l on CGM	–	Nil	–
Effect of hypoglycaemia unawareness on CD											
Sachon *et al.*[76]	Yes	Cross-sectional	10%	55	37.5	16.5	13.5	SH: third-party help or LOC	6.6/100 PY	Memory	Negative
Hansen *et al.*[77]	Yes	Cross-sectional	80%	68	47.0	30	17.0	SH: third-party help	14.6/100 PY	In verbal memory and pattern separation	Negative
Bortolotti *et al.*[56]**	Yes	Cross-sectional	60%	26	45.8	18	27.8	SH: LOC	1.05/100 PY	Cognitive-processing speed	Negative

*Bias score: Newcastle–Ottawa risk-of-bias scoring system was used. As the total score differed across scoring systems, a percentage of maximum score achievable is calculated and expressed as a percentage for ready comparison. At 100% = full score = low risk of bias. The lower the percentage score, the higher the risk of bias. A percentage score less than 30% was considered as a study with a high risk of bias. Data that were not reported or could not be reliably calculated from full-text articles are not reported and appear as missing values.

**This study appears under two categories. #Direction of association- Negative: higher hypoglycaemia rates associated with worse cognitive function; Positive: higher hypoglycaemia rates associated with better cognitive function.

BG, blood glucose; CD, cognitive dysfunction; CGM, continuous glucose monitoring; DCCT, Diabetes Control and Complications Trial; ER, Emergency Room; IQ, Intelligence Quotient; IV, intravenous; LOC, loss of consciousness; NH, nocturnal hypoglycaemia; NSH, nonsevere hypoglycaemia; PY, person-years; SH, severe hypoglycaemia.

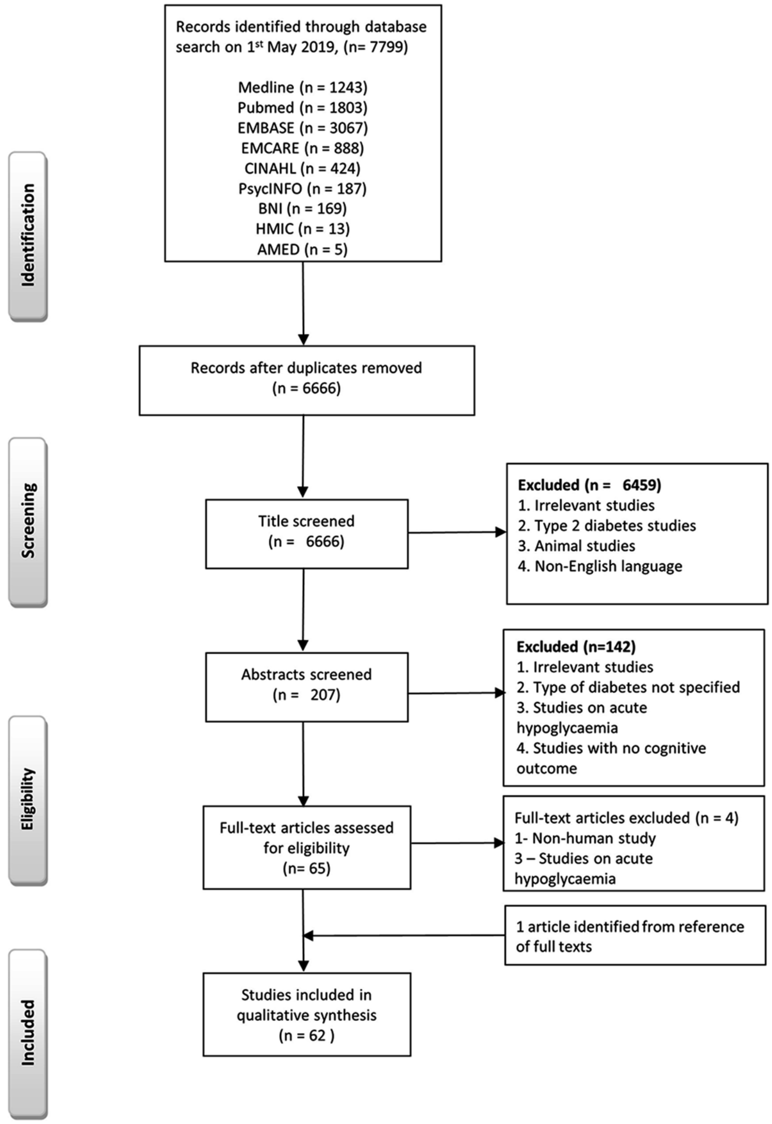

Figure 1. Flowchart of study screening and inclusion in the systematic review.

ranged from 3 to 16.7 years, and participant numbers ranged from 20 to 249.

Prospective cohort studies

Of the prospective cohort studies, 7/11 found a significant association between SH and CD. All seven studies had a mean age of onset of 4.5–7.5 years. Five of the seven cohort studies[23,24,37,38,41] are from a single representative cohort. This prospective cohort study recruited 116 children aged 3–14 years (mean age of diabetes onset 7.5 years) with normal baseline neuropsychology, and undertook neuropsychological assessments within 3 months of diagnosis and at 2, 6 and 12 years after diagnosis. SH was defined as seizures or coma. SH had a dominant effect on memory (short and long term) in early childhood (2 years)[23] followed by an effect on verbal and full-scale Intelligence Quotient (IQ)[24] in later childhood (6 and 12 years).[37] At 12 years, the verbal IQ (VIQ) in the SH subgroup was 0.33 standard deviation (SD) lower than type 1 diabetes with no SH. Regression analysis showed that each additional seizure reduced the VIQ score by 1.19 points.[41] A similar association of SH with deterioration in verbal memory[22] and spatial delayed long-term memory (effect size 1.0 SD)[31] in early childhood (mean ages of onset 4.5 and 6.5 years, respectively) was also found in other prospective studies.

Interestingly, three of the four studies that did not find an association between SH and CF randomized participants with type 1 diabetes to intensive *versus* conventional therapy and studied the association of incident SH during the trial period only with CF. The relatively short study durations (1.5 and 3 years)[17,26] and older mean age of diabetes onset (11 and 13.5 years) might explain the negative findings. The largest study in terms of participant numbers (n = 249) and duration of follow up was the adolescent subgroup of the Diabetes Control and Complications Trial (DCCT)–Epidemiology of Diabetes Interventions and Complications trial (EDIC) cohort, which studied participants in the 13–19-year age group at recruitment and did not find any association between SH and CF up to 18 years after recruitment.[35] The fourth study, a prospective cohort from Switzerland, enrolled children diagnosed before age 10 years and conducted neurocognitive tests at least four times at prespecified ages until age 16 years. No association between SH and CF was found in this study. However, interestingly, there was no SH reported before the age of 6 years, despite the study including 27 children aged less than 6 years with an age range of 1.1–5.8 years.[25]

Cross-sectional studies

Of the 14 cross-sectional studies, 8 found a significant association between SH and CD. Six of these eight studies recruited participants aged less than 18 years, while half of the studies not finding a significant association recruited those aged ⩾18 years. The eight studies with an association of SH and CD had an estimated lifetime SH rate of ⩾15/100 PY, while it was lower (<15/100 PY) in four of the six studies not finding a significant association between SH and CD. There were also other important methodological differences between the studies, especially in terms of defining SH and the tests used for measuring cognitive outcomes. Studies not finding a significant association defined SH as the need for external assistance or an altered state of consciousness, except for one that required an emergency room (ER) visit or medical attention.[19] On the other hand, four of the eight studies finding a positive association between SH and CD had a higher threshold to qualify as SH, requiring a seizure, loss of consciousness (LOC), need for medical attention, or hospitalization,[20,21,29,43] and found a significant association of SH with lower scores of attention and focus,[21] delayed recall of verbal information[20] and academic achievement.[29] However, another study that defined SH as an ER visit or medical attention, with an older mean age at recruitment of 33.5 years did not find any significant association between SH and CD.[19] All three studies that used the DCCT definition[53] of SH without modification, with mean ages at recruitment of 12–13 years and 23–26 years, found a significant association between SH and spatial delayed memory response[28,33] (effect size 0.6 SD), and spatial analysis skills[36] (effect size 0.7 SD) while one found deficits in long-term memory[36] (effect size 1 SD). Other studies found SH associated with deficits in long-term[20,36] (effect size 0.3 SD in comparison with healthy controls) and short-term memory[67] (effect size 0.8 SD). Recent SH (<1 year) reduced mental efficiency and executive functioning in older people (mean age 55 years) with a long duration of childhood-onset disease.[43]

Of the 14 cross-sectional studies, 6 did not find an association between SH and CD but recruited at an older mean age (3/6 recruited at ⩾25 years) and had in general lower thresholds for defining hypoglycaemia as discussed earlier.[19,18,27,34,39,42] Thus, studies that recruited younger participants and defined SH as more severe manifestations of hypoglycaemia were more likely to find a significant association with CD

Case-control studies

None of the three case-control studies[30,32,40] comparing people with SH with those without, all by the same group from Finland, found any significant association of SH with CD.

Effect of prior hypoglycaemia on CF of adult-onset (>18 years) type 1 diabetes

We found five cross-sectional studies, two prospective cohorts (four studies) and four case-control studies of adult-onset type 1 diabetes with mean ages of onset ranging from 19.7 to 27.8 years, and participant numbers ranging from 26 to 1144.

Prospective cohorts

Studies based on the DCCT cohort are included here, as the mean age of diabetes onset of the DCCT cohort was 21 years. DCCT recruited type 1 diabetes participants aged 13–39 years (mean age of recruitment 27 years), excluded those with previous SH in the past 2 years and randomized them to intensive *versus* conventional therapy. The cohort underwent neuropsychological testing at baseline, 2, 5 and 7, and 9 years. No new development of CD occurred after the fifth year of testing; however, there was a 57% dropout in the participants who attended neurocognitive testing after 5 years.[51] Despite a relatively high incidence of SH in the intensive arm (61 SH/100 PY), the study did not find any association between SH and the risk of worsening CF. While there was no difference in the cumulative glycated haemoglobin (HbA1c) at 5 years, by 18 years, those with higher HbA1c (>8.8%) had a significant slowing of psychomotor efficiency.[47,53] A subsequent analysis of 85% of the DCCT–EDIC cohort with neurocognitive testing, only at baseline and 18 years after recruitment, also did not find any association of SH with CD.[53]

Interestingly, a shorter duration prospective cohort of older type 1 diabetes participants, with a mean age at recruitment of 60.4 years, with cognitive assessment done at baseline and 4 years later, found a significant association between incident SH and reduced overall CF and information-processing speed.[54]

Cross-sectional studies

We identified five studies with a similar mean age at recruitment (32.5–45 years) with adult-onset diabetes. Excluding one study[55] with a high degree of selection bias, the rest described SH as an event requiring a third person's help or LOC and found lifetime frequency of SH to be associated with reduced IQ (effect size 0.5 SD);[45] performance IQ was affected more than VIQ.[45,46,48,56] Another study comparing those with and without SH found a significantly reduced cognitive-processing speed (effect size 6.6 SD)[56] in those with SH, with a mean age of 58 years.

Case-control studies

Two case-control studies compared subjects with a mean age of 36.9 and 38 years with and without SH and found no differences in mini-mental state exam (MMSE), attention, and cognitive-processing speed.[49,50] Another study compared subjects with a recent SH (DCCT definition, mean age of 36.4 years) and tested their CF up to a month after the event and found no significant differences.[52] Interestingly, a study in older adults (mean age at recruitment 68.3 years) comparing those with clinically significant cognitive impairment (memory and executive function) with those without found that recent SH (<1 year) was significantly higher in the group with cognitive impairment, while lifetime frequency of SH was the same.[57]

Effect of early *versus* late exposure to SH on cognitive function in type 1 diabetes

We identified seven studies; three cross-sectional, three case-control and one prospective cohort that specifically explored the effect of early exposure to SH (EE-SH) on CF. The cut-off age defining early exposure ranged from 4 to 10 years. Four of these seven studies, used third-party assistance as the lowest threshold criterion for SH, while two used LOC and one used seizure. Except for one study with a mean age of recruitment of 28 years, the mean age of subjects ranged from 5.2 to 13.4 years. Six of the seven studies found a significant association between EE-SH and CD, all of which controlled for diabetes duration. EE-SH was associated with decrements in visual memory (effect size 0.9 SD),[80] visuomotor perception and visual integration,[58,63] as well as verbal memory[80] (effect size 0.8 SD) and full-scale IQ[80] (effect size 0.6 SD), psychomotor efficiency (effect size 2 SD) and attention.[59] Early-onset diabetes (<7 years) predicted CD[60] independent of retinopathy status and diabetes duration, suggesting the potential role of SH. The only study[61] that did not find any significant effect of EE-SH on CF was a cross-sectional study of early (<6 years) diabetes onset, with those at any age (inclusive of those with early-onset seizure).

Effect of nonsevere hypoglycaemia (NSH) on CF in type 1 diabetes

We found six cross-sectional studies and two prospective cohorts studying the effect of NSH on CF. Four of these six studies found a significant association between NSH and CF; however, the effect on CF was varied. Three cross-sectional studies,[64,66,67] with 23–55 participants, aged 6–12.2 years, and NSH defined as <2.8 to <3.9 mmol/l found a significant association with CD. Two of them excluded conditions that may affect CF, while one[64] did not, and, hence, could be biased. Another study found poorer attention and concentration immediately after symptomatic recovery from NSH in a diabetes camp setting but did not verify biochemical recovery from hypoglycaemia and, hence, ongoing hypoglycaemia during cognitive testing could not be excluded.[66] Interestingly, a well-conducted study with low risk of bias found improved scores on memory, comprehension, broad cognition and academic achievement in those with ⩾10 NSH per month.[67] A similar positive correlation of NSH with improved overall IQ, VIQ and vocabulary were found in a prospective cohort tested at diagnosis and 1 year later.[65] Another prospective continuous-glucose-monitoring-based study, as well as two other cross-sectional studies defining NSH as <3.9 or <3.3 mmol/l did not find any significant associations of NSH with CD.[68–70]

Effect of nocturnal NSH on subsequent daytime cognitive function in type 1 diabetes

Of the five studies we identified, three induced nocturnal hypoglycaemia (NH) ranging from <2 to <3 mmol/l for an hour or longer and two others were observational. A euglycaemic night in the same subject served as the control in all studies. The only study finding a significant effect dropped overnight glucose to a nadir of <2 mmol/l for 60 min and found a decrease in the consolidation of declarative memory the next day (effect size 0.3 SD).[74] However, all three studies found significant noncognitive effects like lower mood,[74] more fatigue (effect size 4.7 SD),[72] reduced deep sleep (effect size 1.2 SD) and higher arousals[71] during/after nights with NH. A home-based observational study[73] of children tested after NH (median hypoglycaemia: 1.9 mmol/l for 270 min) also did not find any effect on CF but a lower mood was evident. A recent study[75] comparing 8 nights of sensor-augmented pump therapy *versus* hybrid closed loop, with significant differences in overnight symptomatic hypoglycaemia (23 *versus* 6, $p < 0.0016$) also did not find any significant effect on subsequent daytime CF. However, the mean overnight time < 3 mmol/l was 0% in both groups.

Effect of impaired awareness of hypoglycaemia (IAH) on cognitive dysfunction

We found only three studies comparing people with IAH with those without. The frequency of hypoglycaemia was significantly higher in the IAH group in all studies. Lower scores for predominantly memory[76,77] and slowing of cognitive-processing speed[56] were found in the IAH group.

Discussion

This systematic review summarizes data from 62 studies exploring the effect of prior hypoglycaemia on subsequent CD in people with type 1 diabetes with exposure to hypoglycaemia from 3 years to 68 years. Many of the studies had only a low–moderate risk of bias. We classified studies into those with childhood-onset (⩽18 years) and those with adult-onset (>18 years) type 1 diabetes, as the neurodevelopment and maturity of the brain extends until early adulthood and insults occurring during the developmental stages have a greater impact on later cognition.[81] While a single, consistent effect of hypoglycaemia on cognitive outcomes across this age range was not evident, various patterns have emerged.

The age at exposure to SH

The effect of exposure to SH on CF is age dependent. Younger age of onset of type 1 diabetes and early exposure to hypoglycaemia before the age of 10 years is associated with a significant decrease in CF.[23,28,31,33,36,60,62,63,80] Exposure to SH at a young age had a moderate-to-large effect (effect sizes of individual studies ranging from 0.6 to 2 SD) on the decrease of intelligence and memory.[31,80] Exposure to SH during late childhood (>10–13 years) did not have a significant effect on CF.[17,35,34]

The DCCT adolescent and adult cohort was an excellent design for exploring the effect of incident SH. In excluding people with SH in the previous 2 years and randomizing those included into two treatment arms with different hypoglycaemia risks (19 *versus* 62 SH/100 PY), any carry-on effect of prior exposure to SH before recruitment was negated. During adulthood, specifically the third and fourth decades of life, there was no evidence of incident SH affecting CF.[53] Interestingly, the association of SH with CF returns in the older age group (>55 years), although there is a paucity of studies in this age group. In this group, both incident SH (1–4 years)[43,54] and frequency of lifetime SH coma was associated with deficits in overall cognition and cognitive-processing speed.[56]

This bimodal distribution of risk of CD from SH exposure is interesting. While it is plausible that the developing brain and the ageing brain are more sensitive to the effects of prior hypoglycaemia, other potential confounders must be considered. A young child with type 1 diabetes is fully dependent on its parents for diabetes care. Hence, the parents' cognitive abilities and skills in managing their child's diabetes will have an impact on the risk of hypoglycaemia. Similarly, in the older age groups, a bidirectional effect of SH on cognition and of poor self-management skills due to cognitive impairment, leading to SH, is likely. Undoubtedly, the association of SH with CF is highest in two crucial periods, under 10 years of age and over 55 years of age. Our findings are similar to the observations made a decade earlier.[82]

The severity of hypoglycaemia

There was wide variation in the estimated SH rate across the studies due to the varying definitions of SH, the different methods of data capture, retrospective recall *versus* prospective periodic reporting and the lack of a standardized reporting format for SH rate. This made any direct comparison between studies and pooling of results difficult.

During acute hypoglycaemia, lower blood glucose is associated with more severe manifestations. Neuroglycopenic symptoms start at 2.9–3.2 mmol/l, progressing to CD at 2.7–2.9 mmol/l and culminating in reduced or LOC, coma and seizures at glucose levels <1.5 mmol/l.[7] Hence, we recognize that a lower glucose for a longer period is more likely to produce a more serious effect on the person with diabetes. For this reason, we assume that events leading to seizure or coma are more likely to represent more profound hypoglycaemia (lower glucose for longer) than those just requiring third-party assistance. Exposure to SH manifesting as seizure, coma or hospitalization was highly associated with CD.[20–22,29,30,38,43,56,58,59] However, NH, even with glucose concentrations as low as <2 mmol/l for an hour or longer was not associated with any significant CD the subsequent day.[71–75] Similarly, nonsevere mild episodes of hypoglycaemia did not have any significant effect on CF. On the contrary, NSH was associated with an improvement in the CF scores.[65,67] This is likely a confounding effect of the association of higher frequency of NSH in those with better glycaemic control.

Cognitive domains affected by prior exposure to SH

Cognitive domains assessed by the majority of studies included intelligence, memory, concentration, visuomotor function, executive function and language skills. Exposure to SH at an age less than 7 years predominantly affected visual memory, visuospatial ability and visuomotor integration, with a moderate effect size of 0.9 SD.[22,58,63,80] Spatial memory, spatial analysis skills, verbal memory and VIQ were predominantly affected in those with exposure to SH beginning between 5 years and 10 years of age.[20,23,24,28,31,33,36–38,41,44,76] The effect size for spatial analysis and VIQ were moderate (effect size 0.7 SD and 0.6 SD, respectively) while that for memory was large at 1.0 SD.[36,41] In adulthood, SH had a small effect on performance IQ (effect size 0.5 SD)[45,46] in the few studies that showed a significant association. SH in the older age group was associated with larger deficits in overall cognition and cognitive-processing speed (effect size 6.6 SD).[43,54,56,57]

Strengths and limitations

The strengths of this study include the use of a multidatabase search culminating in the summary of 62 relevant articles. To the best of our knowledge, this is the first systematic review focusing specifically on the relation between hypoglycaemia and CF in type 1 diabetes across all age groups and thus providing an in-depth review of this topic. Limitations include the considerable heterogeneity of the studies included in terms of the definition of SH, as well as the use of different measures of cognitive outcomes. Many studies did not report the cumulative burden of SH in an accepted metric such as SH/100 PY. Although we attempted to compute this, variability in the reporting styles made this an estimation, at best. The majority of studies included were retrospective studies, and recall bias about lifetime frequency of SH, especially when the age at recruitment was older, is a significant concern. Prospective cohort studies, on the other hand, capture SH prospectively and periodically, and document a baseline neurocognitive function before exposure to SH. In the younger age groups, reporting biases of parents might explain very-low-to-absent SH rates in some studies on young children.[25,65] Prospective cohorts that were randomized to intensive *versus* conventional therapy stringently adhere to the trial guidelines and, hence, findings from these studies may not be translatable to real-world settings. In these studies, the incidence of SH is skewed, with a small proportion experiencing a high number of SH, which limits the applicability of average scores across the group. Another limitation was that most studies classified groups into those with and without SH, which does not account for the potential incremental impact of exposure to higher frequencies of SH. In trying to tease out the effect of SH from the effects of other disease-related factors on CF, recognizing and adjusting for these confounding factors is of utmost relevance. While most studies considered diabetes duration, age of onset, parental intelligence and socioeconomic factors, a significant confounder, the chronic exposure to hyperglycaemia, was not considered in most studies. Measurement of chronic exposure to hyperglycaemia is limited by the lack of a well-recognized measure, as well as a lack of continuous data in retrospective and cross-sectional studies. Some studies tried to use surrogates, like retinopathy[60] and novel hyperglycaemia indices.[80]

Suggestions for future research

Future studies in this field should try to overcome some of the limitations discussed. The use and reporting of standardized cognitive outcome measures, use of a standard definition of SH and reporting the burden of SH will make comparisons and compilations of research data more meaningful. Future studies should also aim to compute and adjust for chronic exposure to hyperglycaemia as a confounder for the effect of hypoglycaemia on CF. There is a paucity of data in the older age groups and more studies in this group will be valuable.

Conclusion

SH is associated with CD in type 1 diabetes in an age-dependent manner. Exposure to prior SH has a mild-to-moderate effect on CF in early childhood and the older age group. More severe manifestations of SH like seizures and coma have a larger impact on CD. It is reassuring that exposure to SH during most of adolescence and adulthood is not associated with deficits in CF. SH remains a complication of insulin therapy, which we should strive to avoid at all ages, but most importantly at the two crucial periods: the early childhood and the older age groups.

Authors' note

SR and PC conceptualized this systematic review. SR and PJ developed the search strategy. SR conducted the database search, and extracted the relevant studies. SR and PJ retrieved data from the studies, verified it and created a narrative review in discussion with PC. SR wrote up the first draft of the manuscript. All authors reviewed the manuscript and were involved in revisions to the manuscript.

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Conflict of interest statement

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Supplemental material

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