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DIABETIC Medicine

SYSTEMATIC REVIEW OR META-ANALYSIS

Changes in quality of life following hypoglycaemia in adults with type 2 diabetes: A systematic review of longitudinal studies

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Abstract

Aim: To conduct a systematic review of published studies reporting on the longitudinal impacts of hypoglycaemia on quality of life (QoL) in adults with type 2 diabetes.

Method: Database searches with no restrictions by language or date were conducted in MEDLINE, Cochrane Library, CINAHL and PsycINFO. Studies were included for review if they used a longitudinal design (e.g. cohort studies, randomised controlled trials) and reported on the association between hypoglycaemia and changes over time in patient-reported outcomes related to QoL.

Results: In all, 20 longitudinal studies published between 1998 and 2020, representing 50,429 adults with type 2 diabetes, were selected for review. A descriptive synthesis following Synthesis Without Meta-analysis guidelines indicated that self-treated symptomatic hypoglycaemia was followed by impairments in daily functioning along with elevated symptoms of generalised anxiety, diabetes distress and fear of hypoglycaemia. Severe hypoglycaemic events were associated with reduced confidence in diabetes self-management and lower ratings of perceived health over time. Frequent hypoglycaemia was followed by reduced energy levels and diminished emotional well-being. There was insufficient evidence, however, to conclude that hypoglycaemia impacted sleep quality, depressive symptoms, general mood, social support or overall diabetes-specific QoL.

Conclusions: Longitudinal evidence in this review suggests hypoglycaemia is a common occurrence among adults with type 2 diabetes that impacts key facets in the physical and psychological domains of QoL. Nonetheless, additional longitudinal research is needed—in particular, studies targeting diverse forms of hypoglycaemia, more varied facets of QoL and outcomes assessed using hypoglycaemia-specific measures.

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KEYWORDS

adult, blood glucose, health-related quality of life, hypoglycaemia, quality of life, systematic review, type 2 diabetes

1 | INTRODUCTION

For adults with type 2 diabetes, hypoglycaemia is a common side effect of glucose-lowering medication. An estimated 83% of insulin and 59% of sulfonylurea users experience symptoms of hypoglycaemia annually.[1] Hypoglycaemia can be distressing[2] and may interfere with diabetes self-management, resulting in greater glucose variability and suboptimal HbA_{1c}.[3] Hypoglycaemia is also associated with heightened risks for long-term neurological and cardiovascular complications,[4] and poorer quality of life (QoL).[5]

Disagreements remain regarding the suitability of specific instruments,[6] but most agree QoL is best conceptualised as a subjective appraisal spanning multiple dimensions of life, particularly facets in the physical, psychological and social domains.[7] Hypoglycaemia has been linked primarily to detriments in the physical domain, including diminished work capacity and sleep quality,[8] and the psychological domain, including elevated anxiety[9] and depression[10] symptoms.

Previous systematic reviews reinforce these findings but present two major limitations. First, evidence linking hypoglycaemia and QoL comes predominantly from cross-sectional studies.[11,12] The lack of longitudinal research makes it difficult to determine whether hypoglycaemia impacts QoL or merely shares an independent association. Second, outcomes in longitudinal studies have typically been assessed using a handful of domain-specific measures which fall short of capturing the full breadth of QoL (e.g. a single mood questionnaire). In fact, no systematic review to date has investigated the longitudinal impacts of hypoglycaemia on multiple facets of QoL; a single review from 2010 examined longitudinal data from randomised controlled trials (RCTs) but targeted measures related exclusively to emotional well-being—a single facet of psychological QoL—and health status.[13]

Novelty statement

What is already known?

- Cross-sectional studies report negative associations between hypoglycaemia and numerous facets of quality of life, but systematic reviews of longitudinal evidence have focused exclusively on health status and emotional well-being.

What has the study found?

- Severe hypoglycaemia is associated with reduced diabetes self-efficacy and perceived health.
- Self-treated hypoglycaemia is followed by impaired daily functioning and elevated symptoms of anxiety, diabetes distress and fear of hypoglycaemia.
- Frequent hypoglycaemia is followed by diminished energy and emotional well-being.

What are the implications of the study?

- Understanding which specific facets of quality of life are impacted by hypoglycaemia may enable targeted interventions to improve quality of life on an outcome-by-outcome basis.

This systematic review aimed to summarise evidence from longitudinal studies reporting on the association between hypoglycaemia and changes in QoL among adults with type 2 diabetes. QoL was characterised using a wide scope, with measures considered for inclusion if they were subjective evaluations of (a) generic QoL; (b) facets in the physical, psychological or social domains of generic QoL; or (c) diabetes-specific

or hypoglycaemia-specific QoL (and constituent domains).

2 | METHOD

This systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14] The protocol is registered on Prospective Register of Systematic Reviews (PROPSERO) under record no. CRD42020154023.

2.1 | Search strategy

A database search strategy was developed to identify published studies reporting on the relationship between hypoglycaemia and patient-reported outcomes (PROs) related to QoL (Table S1). This approach employed a comprehensive set of search terms in four categories: population (e.g. 'type 2 diabetes'), exposure (e.g. 'hypoglycaemia'), generic and specific outcomes (e.g. 'quality of life', 'well-being') and study design (e.g. 'randomised controlled trial', 'cohort study'). No restrictions were placed on language or date of publication. Searches of MEDLINE, Cochrane Library, CINAHL and PsycINFO were completed on 5 November 2020.

2.2 | Screening process

Studies were eligible for inclusion if they (a) sampled adults (18+ years old) with type 2 diabetes; (b) had a longitudinal quantitative design; (c) assessed the occurrence of hypoglycaemia; (d) included PRO(s) related to generic, diabetes-specific or hypoglycaemia-specific QoL; and (e) reported on the statistical relationship between hypoglycaemia and changes in PROs over time. Mixed-population studies (e.g. combined samples of adults with type 1 and type 2 diabetes) were eligible for inclusion if results for adults with type 2 diabetes were reported separately. Outcomes were restricted to standardised PROs to maintain a person-centred, subjective appraisal of QoL and to maximise validity and reliability of findings, reducing heterogeneity and enabling comparisons across studies.

Records identified through database searches were split between five assessors (AC, AS, KM, MB and MC) who screened titles and abstracts; 15% were double-screened to ensure consistent application of inclusion criteria. Short-listed records were full text screened independently by two reviewers (KM and MVJ) as dual screening produces fewer errors than single screening.[15] Studies meeting inclusion criteria were subjected to forward citation searches on Web of Science and backward citation searches. To address publishing and database indexing bias, hand searches were conducted on ClinicalTrials.gov and references from excluded studies deemed to be of interest. As an additional safeguard, 10% of excluded records, chosen at random, were double-screened by a third reviewer (MCJC). Inconsistencies were discussed between reviewers until consensus was reached.

2.3 | Study quality

Quality of included studies was rated by a reviewer (KM) using critical appraisal tools from the Joanna Briggs Institute (JBI) specific to RCTs and cohort studies,[16] and ratings were checked by a second reviewer (MVJ). To provide a concise metric for quantitative comparisons across designs, an overall quality proportion (α_q) was calculated for each study using a count score[17] whereby the number of 'yes' items was divided by the total number of items on the appraisal tool ('unclear' items were counted as half, while 'not applicable' items were excluded). Proportions ranged from 0 to 1 and were interpreted in a manner similar to Cronbach's α[18]: $\alpha_q \geq 0.9$ (*excellent*), $\alpha_q \geq 0.8$ (*good*), $\alpha_q \geq 0.7$ (*acceptable*) and $\alpha_q < 0.7$ (*poor*).

2.4 | Extraction and synthesis

One reviewer (KM) extracted data pertaining to study authors, publication year, country, sample size, study design, intervention type, hypoglycaemia measures and frequency, PROs related to QoL, and findings regarding the relationship between hypoglycaemia and changes in PROs. Extractions for measures and results were verified independently by another reviewer (MVJ) and disagreements were resolved by consensus. Due to the diversity of PROs and inconsistent reporting of statistical values, meta-analysis and subgroup analysis were not possible. Consequently, following Synthesis Without Meta-analysis (SWiM) guidelines,[19] descriptive synthesis of hypoglycaemic impacts was performed with PROs grouped by QoL domain[7] and specificity to better demarcate the degree of generalisability.

3 | RESULTS

3.1 | Study selection and characteristics

Database searches identified 12,571 records. Abstract and title screening excluded 12,096 records, and full-text

screening eliminated 460 records, leaving 15 studies[20–34] that satisfied inclusion criteria. Backward and forward citation searches of these studies identified 3 additional studies,[35–37] and hand searches identified 2 studies,[38,39] resulting in 20 total studies selected for extraction and synthesis (Figure 1).

These 20 studies, published between 1998 and 2020, sampled adults with type 2 diabetes ($N = 50{,}429$) from more than 20 countries (Table 1). Studies were conducted in Europe ($n = 9$), North America ($n = 5$), Asia ($n = 3$) and other regions worldwide ($n = 3$). Participants were generally older adults, with a mean age of 60 across studies (range: 55–71). Gender ratios varied greatly between studies (range: 32%–74% female), but overall representation was roughly balanced ($M = 45\%$ female). Studies used either cohort (60%) or RCT (40%) designs, and most examined the effectiveness of oral or injectable glucose-lowering medications ($n = 10$) or self-management interventions ($n = 6$). The remainder had no stated intervention ($n = 4$).

3.2 | Study quality

Quality proportions (Table 1) revealed that study quality was excellent ($n = 9$) or good ($n = 3$) for cohort studies ($0.80 \leq \alpha_q \leq 1.00$). Quality was more diverse for RCTs ($0.58 \leq \alpha_q \leq 0.88$), with studies rating as good ($n = 3$), acceptable ($n = 3$), or poor ($n = 2$). Apart from two studies,[29,35] however, quality was acceptable or better for both cohort studies ($M\alpha_q = 0.92$) and RCTs ($M\alpha_q = 0.75$), and differences in quality were largely attributable to omissions in reporting as few RCTs provided information about blinding (20%) or reliability statistics for measures (25%). These criteria were deemed less relevant as hypoglycaemia was not a component of study interventions,

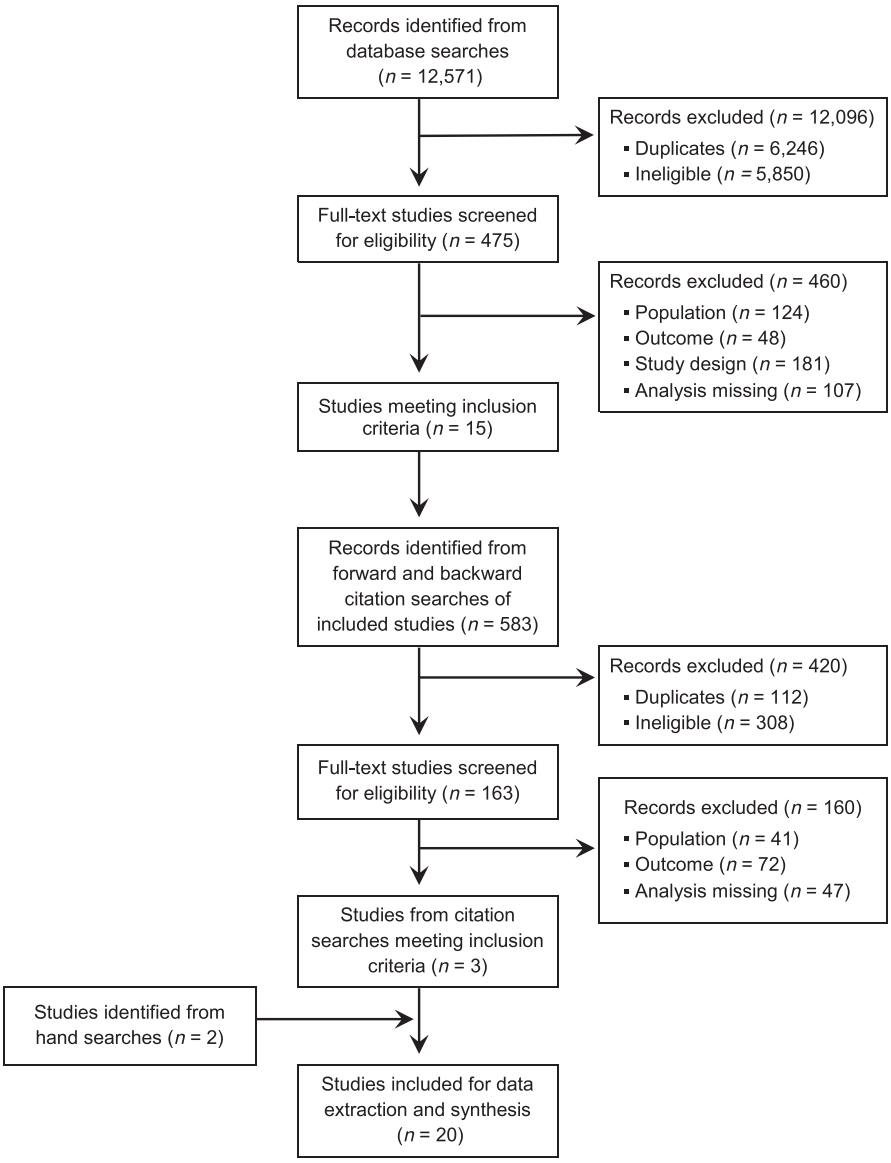

FIGURE 1 PRISMA flow diagram of the search and screening process

TABLE 1 Characteristics and findings of included studies

Authors (year)	Reference	Design	Country	Sample *N* (baseline)	Study intervention	Study quality (α_q)	Quality of life assessment		Impact of self-treated symptomatic hypoglycaemia	
							Measure	Outcome	Direction[a]	Sig.
Ali et al. (2012)	[35]	RCT	US	2053	Intensive versus standard glucose control	0.58	SF-36	General health		
								Physical health	▲	NS
								Mental health	▼	NS
Briggs et al. (2017)	[20]	RCT	Worldwide	16,492	Saxagliptin versus placebo	0.77	EQ-5D	General health	▼[b]	<0.05
de Sonnaville et al. (1998)	[36]	Cohort	Netherlands	237	Insulin versus oral medication	1.00	POMS	Negative mood	—[c]	NS
Genovese et al. (2013)	[21]	Cohort	Italy	1046	Vildagliptin + metformin	0.90	WPAI	Work/school impairment		
								Activity impairment	▲	0.001
Goddijn et al. (1999)	[22]	Cohort	Netherlands	99	Insulin versus oral medication	1.00	RAND-36	General health		
								Mental health	▼	NR
Haluzik et al. (2018)	[23]	Cohort	Eastern Europe	6369	None	0.93	Targeted question	Work impairment	▲	NA
Jódar et al. (2020)	[24]	RCT	Worldwide	3297	Semaglutide versus placebo	0.77	SF-36	General health		
								Physical health	▲	<0.01
								Mental health	▼	0.08
Malanda et al. (2011)	[25]	Cohort	UK	453	G-Meter versus standard monitoring	1.00	EQ-5D	General health	▼	0.23
							W-BQ12	Emotional well-being	▲	0.82
								Positive mood	▲	0.47
								Negative mood	▼	0.92
								Energy level	▲	0.46
							IPQ-R	Illness perceptions		
								Illness control	▼	NS
								Emotional distress	▼	0.24
Menard et al. (2007)	[26]	RCT	Canada	72	Intensive versus standard care	0.88	DQOL	DQOL	—	NS
Mitchell et al. (2013)	[27]	Cohort	UK	1329	None	0.85	HFS-II	Fear of hypoglycaemia	▲[d]	<0.001
Nauck et al. (2019)	[28]	RCT	Worldwide	3014	Liraglutide versus placebo	0.85	EQ-5D	General health	▼[b]	<0.001
							EQ-VAS	General health	▼[b]	0.98

(Continues)

TABLE 1 (Continued)

Authors (year)	Reference	Design	Country	Sample *N* (baseline)	Study intervention	Study quality (α_q)	Quality of life assessment		Impact of self-treated symptomatic hypoglycaemia	
							Measure	Outcome	Direction[a]	Sig.
Nicolucci et al. (2011)	29	RCT	Italy	238	Telephone versus standard care	0.58	W-BQ22	Emotional well-being	▼	0.002
								Positive mood	—	NS
								Depressive symptoms	—	NS
								Anxiety symptoms	▼	0.007
								Energy level	▼	0.003
							SF-36	General health		
								Physical health	—	NS
								Mental health	▼	0.004
Pathan et al. (2018)	38	Cohort	Southeast Asia	2594	None	0.93	Targeted question	Work impairment	▲	NA
Peyrot et al. (2008)	30	RCT	US	211	Pramlintide versus placebo	0.85	DDS	Diabetes distress	—	NS
Pichayapinyo et al. (2018)	31	Cohort	Thailand	35	Telephone assistance	0.85	DDS	Diabetes distress	▼	NS
							SEDS	Diabetes self-efficacy	▼	NS
							PHQ-8	Depressive symptoms	▲	NS
							SSQ	Social support	▲	NS
							PROMIS	General health		
								Sleep disturbance	▼	NS
Polonsky et al. (2018)	39	Cohort	US	424	None	0.90	WHO-5	Emotional well-being	▲	NS
							GAD	Anxiety symptoms	▲	<0.01
							PHQ-8	Depressive symptoms	▲	NS
							DDS	Diabetes distress	▲	<0.05
							HFS-II	Fear of hypoglycaemia		
								Hypoglycaemia worry	▲	<0.01
Ritter et al. (2016)	37	RCT	US	1674	Efficacy care versus placebo	0.77	DSES	Diabetes self-efficacy	▼	0.026
Torre et al. (2018)	32	Cohort	Portugal	1303	DPP-4 versus GLP-1 vs.SGLT2	0.90	EQ-5D	General health	▲	NS
							EQ-VAS	General health	▲	NS

(Continues)

TABLE 1 (Continued)

Authors (year)	Reference	Design	Country	Sample *N* (baseline)	Study intervention	Study quality (α_q)	Quality of life assessment		Impact of self-treated symptomatic hypoglycaemia	
							Measure	Outcome	Direction[a]	Sig.
Wieringa et al. (2018)	[33]	Cohort	Netherlands	911	Insulin glargine	1.00	WHO-5	Emotional well-being	▼[c]	0.30
							HFS-II	Fear of hypoglycaemia		
								Hypoglycaemia worry	▲[e]	<0.001
Yang et al. (2014)	[34]	Cohort	China	8578	Biphasic insulin aspart 30/70	0.80	EQ-VAS	General health	▼[b]	<0.001

Abbreviations: DDS, Diabetes Distress Scale; DQOL, Diabetes Quality of Life measure; DSES, Diabetes Self-Efficacy Scale; EQ-5D, EuroQol 5-Dimension health status instrument; EQ-VAS, EuroQol Visual Analogue Scale; GAD, General Anxiety Disorder scale; HFS-II, Hypoglycaemia Fear Survey version II; IPQ-R, Illness Perception Questionnaire Revised; NA, not applicable; NR, not reported; NS, not significant (no *p*-value reported); PHQ-8, Patient Health Questionnaire 8-item; POMS, Profile of Mood States; PROMIS, Patient-Reported Outcomes Measurement Information System; RAND-36, RAND Corporation 36-item health survey; RCT, randomised controlled trial; SEDS, Self-Efficacy for Diabetes Scale; SF-36, Medical Outcomes Study Short Form 36-item health survey; SSQ, Social Support Questionnaire; W-BQ12 and W-BQ22, Well-Being Questionnaire 12-item and 22-item; WHO-5, World Health Organisation 5-item well-being index; WPAI, Work Productivity and Activity Impairment.

[a] Increases and decreases in outcomes are depicted with upward (▲) and downward arrows (▼), respectively; associations of unknown direction are depicted with a dash (—); black and grey symbols indicate significant and non-significant or untested effects, respectively.

[b] Reflects impact of severe hypoglycaemic events only.

[c] Direction and significance of impact was similar for severe hypoglycaemic events.

[d] Reflects impact of any hypoglycaemic event.

[e] Direction of impact for severe hypoglycaemic events was similar but not significant, $p = 0.23$

and thus was unaffected by blinding, and nearly all studies relied on PROs with established validity and reliability. Consequently, included studies were interpreted as having good quality given the quasi-experimental nature of the variables under review (see Tables S2 and S3 for item-by-item appraisals).

Regarding hypoglycaemic impacts on QoL, evidence across studies was limited by the narrow scope of QoL instruments and the lack of hypoglycaemia-specific measures. Furthermore, only three studies explicitly controlled for the intervention[25,28,29] and none controlled for diabetes education. Reporting of statistical values also varied widely, with most studies lacking standardised effect sizes and other values necessary for clear interpretation and meta-analysis.

3.3 | Frequency and severity of hypoglycaemia

All studies assessed hypoglycaemia using self report, except for one RCT that used clinical records.[20] Recall periods for hypoglycaemia ranged from 1 to 36 months, though recall in most studies (70%) was 6 months or longer. Reporting on hypoglycaemic severity was absent in four studies.[21,24,29,37] Remaining studies described the severity of hypoglycaemia using classifications comparable to those given by Malanda et al.[25]: *Grade 1*, asymptomatic episodes accompanied by glucose measurements below 4.0 mmol/L (72 mg/dl); *Grade 2*, self-treated symptomatic episodes; *Grade 3*, severe events requiring assistance; and *Grade 4*, severe events requiring hospitalisation.

Nearly, all studies (90%) reported on the occurrence of hypoglycaemia during the study period (Table 2). A few studies provided episode frequencies, but most (75%) categorised participants based on whether or not they had experienced hypoglycaemia. In studies where asymptomatic and symptomatic episodes were considered together, hypoglycaemia was common, affecting 28%–54% of participants over a 1-month period.[23,27] Symptomatic self-treated and severe hypoglycaemia were less common. Over a 2-year period, studies reported 23%–86% of participants experienced at least one self-treated episode[32,39] and 1%–23% experienced at least one severe event.[32,39]

3.4 | Impact of hypoglycaemia on generic QoL

Studies examined hypoglycaemic impacts using 11 PROs related to generic QoL. Relevant PROs almost exclusively targeted facets within the physical and psychological domains. Impacts on each PRO are summarised in Table 1, and detailed statistical results are provided in Table 3.

3.4.1 | Health status

The most common outcome, perceived health, was assessed in 45% of studies. Although frequently interpreted as a global assessment of generic or health-related QoL, PROs assessing health status measured facets exclusively in the physical and psychological domains.

The EuroQol 5-Dimension (EQ-5D) health instrument was the most frequently adopted PRO in studies targeting health status ($n = 5$). While the full EQ-5D includes four physical health items and one mental health item, all studies save one[25] used the EQ-5D utility index, a summed total of all items rated against a normed sample,[20,28,32] or the EuroQoL Visual Analogue Scale (EQ-VAS), a single item rating general health on a scale from 1 to 100.[32,34]

Three studies focusing on severe events found EQ-5D utility index[20,28] and EQ-VAS scores[34] were negatively associated with hypoglycaemia; compared to those reporting no events, those experiencing at least one severe event had lower ratings of perceived health. In contrast, two cohort studies showed that self-treated hypoglycaemia was not associated with EQ-5D totals[25] or EQ-VAS scores.[27]

The Medical Outcomes Study Short Form 36-item (SF-36) survey, a broad health status measure comprised of Mental and Physical Component scales, was adopted solely by RCTs ($n = 3$). A 12-month study examining the impact of severe hypoglycaemia revealed no significant declines in either physical or mental health among those experiencing severe events.[35] Two studies which did not specify hypoglycaemic severity likewise reported no decline in physical health among those experiencing hypoglycaemia over a 1-month[29] or 26-month[24] period. One of these studies did find that treatment-related improvements in mental health were blunted among those experiencing three or more hypoglycaemic episodes,[29] but the other reported no change in Mental Component scores.[24] Moreover, the latter was consistent with a study examining mental health using a subscale of the RAND Corporation 36-item (RAND-36) survey—a measure that parallels the SF-36—which found no change in mental health following self-treated hypoglycaemia.[22]

Taken as a whole, findings from health status studies ($n = 9$) indicated perceptions of health worsened among those experiencing hypoglycaemic over a period of 6–36 months, but only for events severe enough to require assistance. Furthermore, this impact was only evident when health status was assessed using the EQ-5D. Findings regarding self-treated hypoglycaemia were less

TABLE 2 Hypoglycaemic episodes reported in included studies

Authors (year)	Reference	Measure characteristics			Occurrence of hypoglycaemia[a]
		Type of record	Recall period (months)	Severity classification	
Ali et al. (2012)	[35]	Yes/no	12	Grade 3	2.8% reported 1+ episodes
Briggs et al. (2017)	[20]	Yes/no	12	Grade 4	0.5% hospitalised for 1+ events
de Sonnaville et al. (1998)	[36]	Frequency	1	Grade 3	4.4 events per person-year
Genovese et al. (2013)	[21]	Frequency	12	NR	NR
Goddijn et al. (1999)	[22]	Yes/no	1	Grade 2	6.4% and 19.1% reported 1+ episodes (at baseline and 1 year, respectively)
Haluzik et al. (2018)	[23]	Yes/no	1	Grades 1–2	57.0% and 53.7% reported 1+ episodes (at baseline and 1 month, respectively)
				Grade 3	6.7% and 7.6% reported 1+ events (at baseline and 1 month, respectively)
Jódar et al. (2020)	[24]	Yes/no	26	NR	22.1% reported 1+ episodes
Malanda et al. (2011)	[25]	Yes/no	12	Grade 1	25.2% reported 1+ episodes
				Grade 2	17.7% reported 1+ episodes
Menard et al. (2007)	[26]	Yes//no	12	Grade 2	20.8% reported 1+ episodes
		Frequency		Grade 2	21.6 episodes per person-year
Mitchell et al. (2013)	[27]	Yes/no	1	Grades 1–3	27.5% reported 1+ episodes
Nauck et al. (2019)	[28]	Yes/no	36	Grade 3	42.3% reported 1+ events
Nicolucci et al. (2011)	[29]	Frequency	1	NR	7.2, 19.2 and 21.6 episodes per person-year (at 1, 5 and 6 months, respectively)
Pathan et al. (2018)	[38]	Yes/no	1	Grade 2–3	40.6% and 97.3.1% reported 1+ episodes (at baseline and 1 month, respectively)
				Grade 3	52.2% and 76.9% reported 1+ events (at baseline[b] and 1 month, respectively)
		Frequency		Grade 2–3	12.2 and 22.6 episodes per person-year (at baseline and 1 month, respectively)
				Grade 3	2.2 and 12.2 events per person-year (at baseline[b] and 1 month, respectively)
Peyrot et al. (2008)	[30]	Frequency	16	Grade 2	2.3 episodes per person-year
Pichayapinyo et al. (2019)	[31]	Severity	3	Grade 2	NR
Polonsky et al. (2018)	[39]	Yes/no	24	Grade 2	86% reported 1+ episodes
				Grade 3	41% reported 1+ events
Ritter et al. (2016)	[37]	Symptom severity	6	NR	NR
Torre et al. (2019)	[32]	Yes/no	26	Grade 2–3	22.8% reported 1+ episodes
				Grade 3	<1% reported 1+ events

(Continues)

TABLE 2 (Continued)

Authors (year)	Reference	Measure characteristics: Type of record	Recall period (months)	Severity classification	Occurrence of hypoglycaemia[a]
Wieringa et al. (2018)	[33]	Yes/no	3	Grade 2–3	37.2%, 42.5% and 43.5% reported 1+ episodes (at baseline, 3 and 6 months, respectively)
				Grade 3	3.1%, 4.3% and 5.6% reported 1+ events (at baseline, 3 and 6 months, respectively)
Yang et al. (2014)	[34]	Frequency	6	Grade 2	2.17 and 1.54 episodes per person-year (at baseline and 6 months, respectively)
				Grade 3	0.15 and 0.0 events per person-year (at baseline and 6 months, respectively)

Note: Grade 1, asymptomatic hypoglycaemia; Grade 2, self-treated symptomatic hypoglycaemia; Grade 3; severe hypoglycaemia requiring assistance; Grade 4, severe hypoglycaemia requiring hospitalisation.

Abbreviation: NR, not reported.

[a]Unless otherwise stated, values reflect occurrence of hypoglycaemia during the study period. Occurrence of hypoglycaemia at baseline is presented when reported by the study.

[b]Recall period was 6 months for baseline occurrence of severe (Grade 3) hypoglycaemic events.

clear, with EQ-5D studies reporting no impact, and SF-36 studies reporting mixed results for mental health.

3.4.2 | Facets in the physical domain of QoL

Energy and sleep

Two glucose monitoring studies examined energy level using the Energy subscale of the Well-Being Questionnaire (W-BQ), with one reporting no change in energy among those experiencing one or more asymptomatic or self-treated symptomatic hypoglycaemic episodes over a 12-month period,[25] and the other reporting a decline in energy following four or more episodes of unspecified severity within 30 days.[29] A small-sample study[31] examined sleep quality using a subscale of the Patient-Reported Outcomes Measurement Information System (PROMIS), revealing a weak, non-significant correlation between more frequent symptoms of hypoglycaemia and greater sleep disturbance (see Table 3 for effect sizes).

Everyday functioning

Two studies assessed impairment in the workplace among participants from Eastern Europe[23] and Southeast Asia.[38] Over a 30-day period, approximately 3% of adults with type 2 diabetes reported having been absent from work, and 2%–5% reported having left work early, as a direct consequence of hypoglycaemia. Impairment during non-work activities (e.g. shopping) was examined in one study using the Activity Impairment subscale of the Work Productivity and Activity Impairment questionnaire,[21] revealing that an increase in the frequency of hypoglycaemia over a 12-month period was followed by greater impairments in everyday functioning than those who experienced no change or a decrease.

3.4.3 | Facets in the psychological domain of QoL

Mood

The most commonly assessed facet within the psychological domain of QoL, mood, was examined in 25% of studies. Three studies investigated general mood using the Profile of Mood States survey[36] or the Positive and Negative Mood subscales of the 12-item[25] and 22-item[29] W-BQ. These studies provided no evidence for an association between hypoglycaemia and general mood, regardless of mood valence (i.e. positivity or negativity) or hypoglycaemic severity.

Symptoms of mood disorders were examined in three studies. One study using the broad Anxiety subscale of the 22-item W-BQ found that those experiencing one, two or three hypoglycaemic episodes (but not four or more) reported *reduced* anxiety.[29] However, a study using the narrower General Anxiety Disorder scale reported that those who experienced at least one self-treated hypoglycaemic episode in 24 months developed elevated anxiety symptoms.[39] Three studies assessed depressive symptoms using either the 8-item Patient Health Questionnaire[31,39]

TABLE 3 Relative size of impact of hypoglycaemia in included studies

Authors (year)[a]	Reference	Analysis	Quantified impact on measures of quality of life
Ali et al. (2012)	[35]	Linear regression	No; 1+ severe hypoglycaemic events did not lead to changes in mental or physical health; compared to those reporting no events, those reporting severe events experienced a decline in SF-36 Mental Component scores, $B = -2.14$, and a rise in SF-36 Physical Component scores, $B = 1.05$, though none of these impacts were significant, ps > 0.05
Briggs et al. (2017)	[20]	Linear regression	Yes; 1+ severe hypoglycaemic events led to a decrease in general health; following hospitalisation for hypoglycaemia, EQ-5D Utility Index scores dropped ($M_\Delta = -0.019$, $SE_\Delta = 0.024$), $p < 0.05$
Haluzik et al. (2018)	[23]	NA (targeted question)	Yes; 1+ hypoglycaemic episodes impaired attendance at school or work; during the 1-month study period, 2.5% of participants reported taking leave from school or work ($M = 2.8$ days), 2.7% reported arriving late and 4.9% reported leaving early as a direct consequence of hypoglycaemia
Jódar et al. (2020)	[24]	Linear regression	Mixed; 1+ hypoglycaemic episodes (of unspecified severity) led to larger improvements in physical health, but not mental health, following intervention; change in SF-36 Physical Component scores was larger and more positive for those reporting hypoglycaemic episodes ($M_\Delta = 1.04$, $SE_\Delta = 2.4$) compared to those reporting no episodes ($M_\Delta = 0.5$, $SE_\Delta = 0.2$), $p < 0.01$, while change in SF-36 Mental Component scores did not differ between those reporting episodes ($M_\Delta = -0.5$, $SE_\Delta = 0.4$) and those who did not ($M_\Delta = 0.3$, $SE_\Delta = 0.2$), $p = 0.08$
Malanda et al. (2011)	[25]	ANCOVA (adjusted for gender, age, education, diabetes duration, intervention)	Mixed; 1+ asymptomatic hypoglycaemic episodes led to increased perceived control over diabetes; pairwise comparisons showed changes in IPQ-R Control subscale scores were larger and more positive for those reporting only asymptomatic episodes ($M_\Delta = 1.04$, $SD_\Delta = 2.4$), compared to those reporting self-treated symptomatic episodes ($M_\Delta = -0.3$, $SD_\Delta = 2.7$), $p = 0.007$, $d = 0.54$, or no episodes ($M_\Delta = -0.09$, $SD_\Delta = 3.3$), $p = 0.009$, $d = 0.37$. There was no difference between those reporting symptomatic or no episodes, $p > 0.05$. Experiencing 1+ hypoglycaemic episodes did not affect general health, general well-being or diabetes distress; three-way comparisons for those reporting no episodes, only asymptomatic episodes or self-treated symptomatic episodes showed no changes in EQ-5D ($M_\Delta = -0.04$, 0.01, −0.03, $SD_\Delta = 0.2$, 0.2, 0.2), $p = 0.23$, W-BQ12 ($M_\Delta = -0.27$, 0.03, 0.16, $SD_\Delta = 5.2$, 4.7, 4.0), $p = 0.82$ or IPQ-R Emotion subscale scores ($M_\Delta = 0.39$, −0.27, −0.79, $SD_\Delta = 3.6$, 3.6, 3.9), $p = 0.24$
Nauck et al. (2019)	[28]	Linear regression (adjusted for gender, region, CVR, intervention)	Yes; 1+ severe hypoglycaemic events (requiring assistance or confirmed plasma glucose <3.1 mmol/L [56 mg/dl]) led to a decrease in general health; compared to those reporting no events, those reporting severe events experienced a drop in EQ-5D Utility Index scores ($M_\Delta = -0.018$, $SE_\Delta = 0.004$), $p < 0.001$, but no change in VAS scores ($M_\Delta = -0.009$, $SE_\Delta = 0.351$), $p = 0.98$

(Continues)

TABLE 3 (Continued)

Authors (year)[a]	Reference	Analysis	Quantified impact on measures of quality of life
Nicolucci et al. (2011)	29	Linear regression (adjusted for gender, age, HbA_{1c}, weight, intervention)	Yes; 4+ hypoglycaemic episodes (of unspecified severity) led to a decrease in general well-being and energy, and smaller improvements in mental health following intervention; compared to those reporting no episodes, those reporting 3+ episodes showed a drop in W-BQ22 total, $B = -5.41$ ($SE = 1.72$), $p = 0.002$, and W-BQ22 Energy subscale scores, $B = -1.45$ ($SE = 0.49$), $p = 0.003$, and smaller improvements in SF-36 Mental Component scores, $B = -5.03$ ($SE = 1.72$), $p = 0.004$. Those reporting 1–3 (but not 4+) hypoglycaemic episodes showed a drop in W-BQ22 Anxiety subscale scores, $B = -1.76$ ($SE = 0.65$), $p = 0.007$
Pathan et al. (2018)	38	NA (targeted question)	Yes; 1+ hypoglycaemic episodes impaired attendance at school or work; during the 1-month study period, 3.2% of participants reported taking leave from school or work, 2.1% reported arriving late and 2.8% reported leaving early as a direct consequence of hypoglycaemia
Pichayapinyo et al. (2019)	31	Pearson's correlation	No; more frequent symptoms of hypoglycaemia did not lead to changes in depression, sleep disturbance, social support, diabetes distress or diabetes self-efficacy; those reporting more symptoms showed a rise in PHQ-8 total, $r = 0.18$, and PROMIS Sleep Disturbance subscale scores, $r = 0.16$, as well as a drop in SSQ total, $r = -0.12$, DDS total, $r = -0.06$, and SEDS total scores, $r = -0.04$, though none of these impacts were significant, $ps > 0.05$
Polonsky et al. (2018)	39	ANCOVA[b] (adjusted for gender, age, insulin status)	Mixed; 1+ self-treated symptomatic hypoglycaemic episodes led to increased anxiety, diabetes distress and hypoglycaemic worry, but no change in depression or general well-being; compared to those reporting no episodes, those reporting self-treated episodes showed a rise in GAD total, $\beta = 0.16$, $p < 0.01$, DDS total, $\beta = 0.12$, $p < 0.05$, and HFS-II worry subscale scores, $\beta = 0.18$, $p < 0.01$, but no change in PHQ-8 total, $\beta = 0.09$, $p > 0.05$ or WHO-5 total scores, $\beta = 0.02$, $p > 0.05$
Torre et al. (2019)	32	Linear regression[b]	No; 1+ self-treated hypoglycaemic episodes or severe hypoglycaemic events did not lead to minimally important changes in general health; following self-treated episodes or severe events, there was a non-significant rise in EQ-5D utility index, $\beta = 0.29$, $p = 0.15$, and EQ-5D Visual Analogue Scale scores, $\beta = 0.11$, $p = 0.57$
Wieringa et al. (2018)	33	GEE (adjusted for gender, age, education, diabetes duration, HbA_{1c}, BMI, and number of complications)	Mixed; 2+ self-treated symptomatic hypoglycaemic episodes led to increased hypoglycaemic worry, but no change in general well-being; compared to those reporting no episodes, those reporting 2+ self-treated episodes showed a rise in HFS-II Worry subscale scores, $B = 1.33$ ($SE = 0.06$), $p < 0.001$, but no change in WHO-5 totals, $B = -0.79$ ($SE = 0.95$), $p = 0.30$. Experiencing 2+ severe hypoglycaemic events led to no change in hypoglycaemic worry or general well-being; compared to those reporting no events, those reporting 2+ severe events showed no change in HFS-II Worry subscale, $B = 1.13$ ($SE = 0.12$), $p = 0.23$, or WHO-5 total scores, $B = -1.63$ ($SE = 1.58$), $p = 0.31$. A non-significant interaction between time and hypoglycaemic events across all analyses suggested these impacts did not change over time

(Continues)

TABLE 3 (Continued)

Authors (year)[a]	Reference	Analysis	Quantified impact on measures of quality of life
Yang et al. (2014)	[34]	Linear regression (adjusted for gender, age, BMI, diabetes duration, insulin history, HbA_{1c})	Mixed; 1+ severe hypoglycaemic events led to smaller improvements in general health following intervention; compared to those reporting no events, those reporting 1+ severe events showed smaller increases in EQ-5D Visual Analogue Scale scores, $B = 6.96$, $p < 0.001$. When self-treated symptomatic episodes and severe events were combined, this effect was no longer significant; following any hypoglycaemic episode, EQ-5D Visual Analogue Scale scores did not change, $B = 0.02$, $p = 0.96$

Abbreviations: ANCOVA, Analysis of Covariance; CVR, Cardiovascular Risk; DDS, Diabetes Distress Scale; EQ-5D, EuroQol 5-Dimension health status instrument; GAD, General Anxiety Disorder scale; GEE, Generalised Estimating Equations; HFS-II, Hypoglycaemia Fear Survey version II; IPQ-R, Illness Perception Questionnaire Revised; PHQ-8, Patient Health Questionnaire 8-item; PROMIS, Patient-Reported Outcomes Measurement Information System; SEDS, Self-Efficacy for Diabetes Scale; SF-36, Medical Outcomes Study Short Form 36-item health survey; SSQ, Social Support Questionnaire; W-BQ12 and W-BQ22; Well-Being Questionnaire 12-item and 22-item; WHO-5, World Health Organisation 5-item well-being index.

[a]Studies which did not report estimates of effect size were omitted from this table.

[b]To facilitate comparisons across studies, OR and 95% CI values were converted to β and p, respectively.

or the Depression subscale of the 22-item W-BQ.[29] Unlike anxiety, results from these studies showed no relationship between self-treated hypoglycaemia and changes in depressive symptoms, regardless of whether assessments were made over 1, 3 or 24 months.

Emotional well-being

Four studies examined general emotional well-being. Two studies using the World Health Organisation 5-item well-being index found that, regardless of whether hypoglycaemia was self-treated or severe, emotional well-being remained unchanged.[33,39] Likewise, a study employing the 12-item W-BQ found no relationship between self-treated events and changes in general emotional well-being over a 12-month period.[25] Conversely, an RCT using the long-form 22-item W-BQ reported a significant drop in emotional well-being among those who experienced four or more hypoglycaemic episodes during a 1-month period.[29]

3.4.4 | Facets in the social domain of QoL

A single study assessed an outcome outside the physical and psychological domains of QoL. This small-sample study used the Social Support Questionnaire, reporting a weak, non-significant correlation between more frequent hypoglycaemia symptoms and declines in social support over 3 months.[31]

3.5 | Impact of hypoglycaemia on diabetes-specific QoL

Studies in this review employed five PROs related to diabetes-specific QoL. However, only one study[26] utilised a global assessment, the Diabetes Quality of Life (DQOL) survey, for which participants rated areas commonly impacted by diabetes spanning the physical, psychological and social domains. Results showed changes in DQOL totals were not associated with self-treated hypoglycaemic episodes over 12 months. Remaining studies ($n = 7$) examined the impact of hypoglycaemia on PROs related to facets of psychological diabetes-specific QoL.

3.5.1 | Diabetes distress

Using the Diabetes Distress Scale (DDS), a large-sample study with a high incidence of hypoglycaemia reported greater elevations in diabetes distress among those experiencing self-treated or severe hypoglycaemia over a 3-month period.[39] However, no impact on DDS totals was reported by studies with a small sample[31] or lower incidence of hypoglycaemia.[30] Similarly, a study assessing diabetes distress using the Emotion subscale of the revised Illness Perception Questionnaire (IPQ-R) reported no change in distress following asymptomatic or self-treated symptomatic hypoglycaemia.[25]

3.5.2 | Diabetes self-efficacy

Diabetes self-efficacy refers to a person's confidence in their ability to manage important aspects of diabetes, especially glycaemic control.[40] This outcome was assessed by one study[31] using the Self-Efficacy for Diabetes Scale and another[25] using the Control subscale of the IPQ-R, both of which reported no change in diabetes self-efficacy following self-treated symptomatic hypoglycaemia experienced over 3 or 24 months, respectively. The latter

study also reported increased self-efficacy among those who experienced only asymptomatic hypoglycaemia.[25] Gains in perceived control over diabetes represented a small improvement compared to those not experiencing hypoglycaemia, and a moderate improvement compared to those experiencing self-treated symptomatic episodes. Lastly, a study examining the impact of severe hypoglycaemia found that scores on the Diabetes Self-Efficacy Scale dropped among those who experienced at least one severe event in 6 months.[37]

3.6 | Impact of hypoglycaemia on hypoglycaemia-specific QoL

Fear of hypoglycaemia was the sole hypoglycaemia-specific impact uncovered in this review. This outcome was assessed by three studies, all using the Hypoglycaemia Fear Survey version II (HFS-II). One study[27] found those who experienced any hypoglycaemia over a 1-month period displayed increased HFS-II totals. Similarly, two studies reported increased HFS-II Worry subscale scores among those experiencing at least one self-treated episode over 3 months[33] and 24 months.[39] Finally, a study assessing the impact of severe events reported a trend towards elevated HFS-II Worry subscale scores, although this effect was non-significant.[33] Together, these findings suggest self-treated hypoglycaemia was followed by increased fear and worry concerning hypoglycaemia, though impacts for severe events were less clear.

4 | DISCUSSION

Findings from 20 longitudinal studies included in this systematic review demonstrate that, among people with type 2 diabetes, hypoglycaemia can have a detrimental impact on key facets within the physical and psychological domains of QoL. Specific impacts, however, vary widely depending upon frequency and severity of hypoglycaemia, as well as choice of QoL measure and the facet(s) and domain(s) targeted.

The largest body of evidence concerns health status, which broadly captures facets across the physical and psychological domains of generic QoL. Multiple studies corroborate that perceived health is negatively affected by severe hypoglycaemia (i.e. events requiring third-party assistance). However, evidence regarding the impact of self-treated hypoglycaemia is inconclusive. Studies using the EQ-5D, a brief instrument emphasising physical QoL, consistently report that self-treated hypoglycaemia has no impact on perceived health. In contrast, studies using the more comprehensive SF-36 provide mixed results; hypoglycaemia appears to worsen perceived mental health in some studies but not others. Conclusions in this review are partially consistent with EQ-5D research in type 1 diabetes[5] and EQ-5D and SF-36 clinical studies in type 2 diabetes,[13] all of which report that perceived physical and mental health is negatively affected by both severe and self-treated hypoglycaemia.

Regarding facets in the physical domain of QoL, approximately 2%–5% of adults with type 2 diabetes report difficulty performing everyday tasks both in and out of the workplace each month as a direct consequence of hypoglycaemia—impacts similar to those reported by adults with type 1 diabetes.[23,38] Hypoglycaemia also leads to diminished energy, but only among those experiencing frequent episodes (four or more per month). Again, this impact matches type 1 diabetes research.[41] Sleep quality may be affected as well, though evidence here is inconclusive. Findings from one small-sample study[31] reveal a non-significant trend towards progressively disturbed sleep among those experiencing more frequent symptoms of hypoglycaemia. However, significant impacts on sleep reported in large-sample cross-sectional studies in type 2 diabetes,[11] as well as laboratory studies in type 1 diabetes,[42] lend support to the notion that symptomatic hypoglycaemia lowers sleep quality.

Regarding facets in the psychological domain of QoL, there is little evidence to suggest hypoglycaemia has long-term impacts on general mood. Findings from several studies in this review indicate mood positivity and negativity remain unchanged following self-treated or severe hypoglycaemia. Evidence from multiple studies also reveals no impact on emotional well-being, as changes are comparable for those experiencing severe, self-treated and no hypoglycaemia. Nonetheless, the impact of hypoglycaemia on emotional well-being may be dose dependent. Findings from one study[29] suggest that those with frequent episodes (four or more per month) experience declines in emotional well-being, matching conclusions from research in type 1 diabetes[5] and clinical studies in type 2 diabetes.[13]

Measures of mood disorders reveal nuanced impacts. According to one study, *reductions* in anxiety are experienced by those reporting one, two or three hypoglycaemic episodes of unspecified severity (but not four or more) during a 1-month period.[29] However, this counter-intuitive finding may be due to habituation to hypoglycaemia, or a masking effect caused by the psychotherapeutic component of the intervention which produced improvements in nearly all mood-related outcomes in the study. Indeed, results from a non-intervention study in this review[39] suggest self-treated hypoglycaemia exacerbates symptoms of generalised anxiety. In contrast, results from several longitudinal studies demonstrate that self-treated

hypoglycaemia has no impact on depressive symptoms. Type 1 diabetes research reveals a similar pattern, with evidence suggesting hypoglycaemia is associated with increased symptoms of generalised anxiety[43] but not depression.[44] Conclusions in this review are somewhat consistent with earlier systematic reviews in type 2 diabetes which report increased symptoms of anxiety and depression in some, but not all, cross-sectional studies.[11,12]

Evidence concerning impacts outside the physical and psychological domains of QoL is sparse. One study in this review examined a social outcome, reporting a weak, non-significant correlation between more frequent hypoglycaemic symptoms and decreased social support.[31] This analysis was underpowered, however, and given cross-sectional evidence in type 1 diabetes research linking hypoglycaemia to reduced participation in social activities,[45] large-sample longitudinal confirmatory studies are needed.

A considerable body of evidence demonstrates that, among adults with type 2 diabetes, hypoglycaemia affects diabetes-specific QoL. However, as with generic QoL, targeted measures are more informative. A study utilising a global assessment spanning the physical, psychological and social domains[26] reveals no impact on overall diabetes-specific QoL for those experiencing self-treated hypoglycaemia. Meanwhile, evidence from a large-sample study with a high incidence of hypoglycaemia indicates self-treated and severe hypoglycaemia are followed by elevations in diabetes distress,[39] matching research in type 1 diabetes.[5]

Impacts on diabetes self-efficacy are complex. Multiple studies suggest confidence in self management of diabetes is diminished by severe hypoglycaemia but unaffected by self-treated episodes. Intriguingly, one study in this review reports that asymptomatic hypoglycaemia leads to modest *gains* in diabetes self-efficacy relative to those without hypoglycaemia.[25] Taken together, these results suggest that experiencing only symptom-free hypoglycaemia may enhance diabetes self-efficacy while experiencing severe episodes may undermine a person's confidence in their ability to manage diabetes. Nevertheless, given limited research in this area, additional research is needed to confirm these impacts in adults with type 1 and type 2 diabetes.

Finally, regarding hypoglycaemia-specific QoL, several studies conclude that self-treated hypoglycaemia increases fear of hypoglycaemia—an outcome linked to other facets of generic QoL, including anxiety and poor sleep quality.[46] Similar impacts on fear of hypoglycaemia are reported in research in type 1[5] and type 2 diabetes.[13] Conversely, one study in this review reports no change in fear of hypoglycaemia following severe events.[33] One explanation for this lack of effect may be that a focus on avoiding hyperglycaemia, coupled with minimisation of the consequences of hypoglycaemia, may result in both reduced fear and more frequent severe events.[47] A second explanation is that, unlike self-treated episodes which are managed alone, assistance rendered during a severe event may increase a person's confidence in their support network, reducing uncertainties about future hypoglycaemia. Indeed, this explanation is supported by studies linking perceived lack of social support to greater fear of hypoglycaemia.[48]

4.1 | Limitations and strengths

Findings in this systematic review were limited by the characteristics of included studies (e.g. heterogenous measures, inadequate statistical information) and by the inclusion criteria of the review itself. Searching different databases (e.g. JSTOR, PsycExtra) and relaxing the search strategy to include qualitative study designs, measures other than PROs, and additional terms for specific QoL-related outcomes may alter the scope of hypoglycaemic impacts detected. This review also has several strengths. First and foremost, although studies did not experimentally induce hypoglycaemia, focusing on longitudinal studies provides evidence that draws one step closer to forming causal inferences about the impact of hypoglycaemia on changes in QoL. Second, this review had no restrictions on language and included studies conducted internationally across Europe, North America and Asia, the majority of which recruited large and diverse samples. Finally, in comparison to earlier systematic reviews of clinical trials, this review presents findings for a wider range of outcomes, detailing impacts for 17 different QoL-related measures in the physical, psychological and social domains.

4.2 | Recommendations for future research

Gaps in understanding identified in this review suggest five directions for future investigations. First, more research differentiating the effects of symptomatic and asymptomatic hypoglycaemia is needed. Second, continuous glucose monitoring is important for improving accuracy and consistency in measuring hypoglycaemia, and for capturing moment-to-moment fluctuations in blood glucose and QoL outcomes, particularly energy and mood.[49] Third, impaired functioning at work is a commonly reported consequence of hypoglycaemia, but statistical evidence supporting this effect is needed. Fourth, effect sizes suggest hypoglycaemia has a negative impact on sleep quality and social support, but evidence from longitudinal studies

with large samples is lacking. Fifth, PROs targeting facets across all domains of QoL, particularly the social domain, and hypoglycaemia-specific QoL measures are currently underutilised.

5 | CONCLUSIONS

Evidence from longitudinal studies demonstrates hypoglycaemia is relatively common among adults with type 2 diabetes, and its impacts on QoL parallel those experienced by adults with type 1 diabetes. Severe hypoglycaemia in type 2 diabetes is associated with reduced confidence in diabetes self-management and lower ratings of perceived health. Self-treated symptomatic hypoglycaemia is followed by reductions in physical QoL, including impaired functioning at work and in daily life. Self-treated hypoglycaemia is also associated with declines in psychological QoL, including elevated symptoms of generalised anxiety, diabetes distress and fear of hypoglycaemia. Frequent hypoglycaemia is followed by diminished energy and emotional well-being. Nevertheless, available evidence is insufficient to establish whether hypoglycaemia impacts sleep quality, depressive symptoms, general mood, social support or overall diabetes-specific QoL. Further longitudinal research is needed targeting more varied facets of QoL, particularly in the social domain. Research delineating impacts on individual facets of QoL based on hypoglycaemic severity will also be important for improving existing measures,[50] developing new hypoglycaemia-specific measures which better capture the breadth of QoL and designing targeted interventions aimed at improving QoL on an outcome-by-outcome basis.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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