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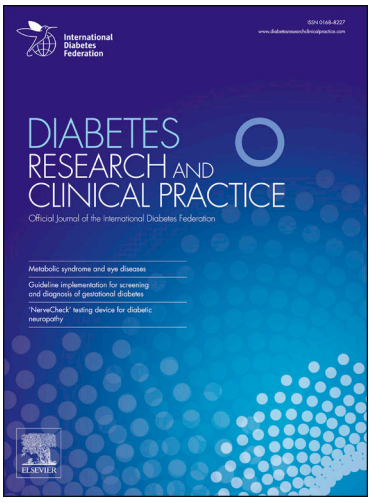

"Incidence and Prevalence of Hypoglycaemia in Type 1 and Type 2 Diabetes Individuals: A Systematic Review and Meta-analysis"

Hassan Alwafi, Alaa A Alsharif, Li Wei, Dean Langan, Abdallah Y Naser, Pajaree Mongkhon, J Simon Bell, Jenni Ilomaki, Mansour S Al Metwazi, Kenneth KC Man, Gang Fang, Ian CK Wong

PII: S0168-8227(20)30779-8
DOI: https://doi.org/10.1016/j.diabres.2020.108522
Reference: DIAB 108522

To appear in: *Diabetes Research and Clinical Practice*

Received Date: 4 February 2020
Revised Date: 30 September 2020
Accepted Date: 13 October 2020

Please cite this article as: H. Alwafi, A.A. Alsharif, L. Wei, D. Langan, A.Y. Naser, P. Mongkhon, J. Simon Bell, J. Ilomaki, M.S. Al Metwazi, K. KC Man, G. Fang, I. CK Wong, "Incidence and Prevalence of Hypoglycaemia in Type 1 and Type 2 Diabetes Individuals: A Systematic Review and Meta-analysis", *Diabetes Research and Clinical Practice* (2020), doi: https://doi.org/10.1016/j.diabres.2020.108522

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Number of words in abstract: 219 words

Number of words in main body text: 3,555 words

Number of tables in main body text: 1

Number of figures in main body text: 3

Number of references in main body text: 109

ABSTRACT

BACKGROUND

Previous meta-analysis investigating the incidence and prevalence of hypoglycaemia in both types of diabetes is limited. The purpose of this review is to conduct a systematic review and meta-analysis of the existing literature which investigates the incidence and prevalence of hypoglycaemia in individuals with diabetes.

METHODS

PubMed, Embase and Cochrane library databases were searched up to October 2018. Observational studies including individuals with diabetes of all ages and reporting incidence and/or prevalence of hypoglycaemia were included. Two reviewers independently screened articles, extracted data and assessed the quality of included studies. Meta-analysis was performed using a random effects model with 95% confidence interval (CI) to estimate the pooled incidence and prevalence of hypoglycaemia in individuals with diabetes.

RESULTS

Our search strategy generated 35,007 articles, of which 72 studies matched the inclusion criteria and were included in the meta-analysis. The prevalence of hypoglycaemia ranged from 0.074% to 73.0%, comprising a total of 2,462,810 individuals with diabetes. The incidence rate of hypoglycaemia ranged from 0.072 to 42,890 episodes per 1,000 person-years: stratified by type of diabetes, it ranged from 14.5 to 42,890 episodes per 1,000 person-years and from 0.072 to 16,360 episodes per 1,000-person years in type 1 and type 2 diabetes, respectively.

CONCLUSION

Hypoglycaemia is very common among individuals with diabetes. Further studies are needed to investigate hypoglycaemia-associated risk factors.

KEYWORDS

Incidence, Meta-analysis, Prevalence, Type 1 diabetes, Type 2 Diabetes

1. INTRODUCTION

Individuals with diabetes require continuous medical care to achieve the optimal glycaemic control in order to prevent the development of its complications (1). Optimal glycaemic control can be achieved with intensive antidiabetic treatment; however, it is also associated with an increased risk of hypoglycaemia (2).

Hypoglycaemia can be defined based on clinical symptoms, from being mildly symptomatic and/or a blood glucose level of < 70 mg/dL (4 mmol/litre) to more severe hypoglycaemia requiring third-party assistance and/or hospitalisation (3). Symptoms of hypoglycaemia may range from hunger, thirst, diaphoresis, or blurred vision, to more serious symptoms such as confusion, seizures and coma (3, 4) Hypoglycaemia impacts quality-of-life and healthcare expenditure (5-7) and is associated with an increased risk of death (8).

Previous reviews investigating the incidence and prevalence of hypoglycaemia in both types of diabetes are limited, and the majority of the published reviews focused on randomised clinical trials settings (RCT); however, RCTs often underestimate the frequency of hypoglycaemia and are not reflective of the real-world burden (9). A systematic review and meta-analysis published in 2015 investigated the incidence and prevalence of hypoglycaemia only in individuals with type 2 diabetes on glucose-lowering medications (10); however, they did not consider the differences between studies in duration of follow-up; hence, the overall results are difficult to interpret. In addition, their review includes citations only until February 2014. Since then, newer drugs with a lower risk of hypoglycaemia have been more frequently used (11). Besides this, to the best of our knowledge there are no previous reviews that have investigated the incidence and prevalence rates of hypoglycaemia in individuals with type 1 diabetes. Therefore, a systematic review and meta-analysis was performed to investigate the incidence and prevalence of hypoglycaemia in individuals with type 1 and type 2 diabetes treated with insulin and oral hypoglycaemic agents.

2. METHODS

This systematic review and meta-analysis was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (12), and reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (13). The study protocol was registered with PROSPERO (Ref: CRD42017077013).

2.1. Literature search and study selection

Observational studies were included if: 1) the incidence and/or prevalence of hypoglycaemia in type 1 and type 2 diabetes was reported; 2) all study samples had diabetes mellitus; 3) all study samples were prescribed one or more medications for diabetes; and 4) the number of individuals with diabetes who experienced hypoglycaemia and/or the incidence of hypoglycaemic episodes was reported (or data were available to determine these numbers). We excluded studies if they were: randomised controlled trials, animal studies, included individuals with gestational diabetes, conference proceedings or abstracts or not published in English. In addition, studies that did not clearly describe the calculation methods used to estimate the prevalence or incidence rate were excluded from the meta-analysis.

We used an extensive search strategy developed by a specialised librarian to search electronic bibliographic databases including: PubMed, Embase and Cochrane Library up to 1st of October 2018. Keywords, Emtree and MeSH terms were used with both British English and American English spellings. The search terms used covered diabetes, hypoglycaemia, prevalence and incidence (Tables S1 and S2). Following removal of duplicate articles, the titles/abstracts and full texts were screened independently by two reviewers (HA, AA), with any disagreement resolved by a third reviewer (AN).

2.2. Data extraction and Study quality Assessment

Data were extracted from included studies using a data collection form. Two reviewers (HA, AA) extracted data independently. The following details were extracted: 1) study details: study design, year published, author's name, sample size and country in which the study was conducted; 2) population and clinical details: mean age, gender, treatment regimen, type of diabetes and diabetes duration; 3) data source: self-report questionnaires, prospective diaries, hospital charts, clinical data registries, emergency department admission records and electronic healthcare databases; 4) definition of hypoglycaemia used in the study: international classification of diseases (ICD) codes, third-party assistance, blood glucose level or symptoms of hypoglycaemia. We extracted hypoglycaemia data for the percentage of individuals with diabetes who experienced a hypoglycaemic event and the incidence rate of hypoglycaemia (defined as the number of episodes per 1,000 person-years).

Two reviewers (HA, AA) independently assessed methodological quality and risk of bias using the Newcastle Ottawa Scale for Observational Studies (14), which was modified to meet the requirement of this review (15, 16). A total of six criteria were evaluated: representativeness of the population, sample size, statistical analysis, missing data, methodology to report the outcome of interest and methods to detect or report the outcome of interest. Each criterion was rated using a scale ranging from 0 to 3, where 3 represented the highest quality; the highest possible overall score is 18. In addition, we categorised the quality assessment score into three categories: good quality (> 12), moderate quality (> 6) and low quality (≤ 6) points.

2.3. Outcomes

The outcomes of this study were the incidence rate per 1,000 person-years and the prevalence rate of hypoglycaemia in type 1 and type 2 diabetes individuals.

2.4. Data Synthesis and Analysis

A random-effects model was used to estimate the prevalence and incidence rates. All analyses were performed using R, the package *meta* (17). The function *metaprop* was used for analysis of prevalence, which uses a logit transformation of the outcome. The function *metarate* was used for analysis of incidence rates, using a natural log transformation. Heterogeneity among included studies in the meta-analysis was assessed using the standard χ^2 tests and the I^2 statistic. If high heterogeneity was indicated ($I^2 \geq 75\%$), the range of the prevalence and the incidence was reported. The incidence rates reported by the authors of each study were normalised to rates per 1,000 person-years when it was not provided in this format in the original research article. For the meta-analysis related to prevalence, only studies that were of 12 months' duration (study period) were included for prevalence calculation. For the meta-analysis relating to incidence, studies were excluded if both number of episodes and total follow-up time were not presented or could not be derived. To explore possible sources of heterogeneity, the analyses were stratified further by type of diabetes, country or location of the study, study design, treatment regimen and data source. Sensitivity analysis was also conducted to investigate the pooled estimate of prevalence after removing outlier studies (18, 19). Data source was categorised into two groups: self-reported (where hypoglycaemia was reported by individuals through surveys) and electronic databases (where hypoglycaemia was reported by a healthcare provider through healthcare databases or clinical data registries). Asymmetry of prevalence results was assessed via funnel plots with pseudo 95% confidence interval around the fixed effect.

3. RESULTS

3.1. Study search and study characteristics

A total of 35,007 citations were identified from our search strategy. Full text screening was performed for 959 original research articles and 149 articles were included in this systematic

review. A total of 72 studies were included in the meta-analysis (Figure 1). Studies included in the meta-analysis were most frequently in Europe (n=38) (18-55), followed by North America (n=18) (56-73), Asia (n=10) (74-83), Australia (n=3) (84-86), multinational studies (n=2) (87, 88), while the data for location in one study was missing (89). Hypoglycaemia was self-reported by the individuals in 35 studies, while 37 were based on health care databases. The ethnicity of the population included in the review was poorly reported. From the studies, 59 were retrospective, while 13 were prospective in their design. The definition of hypoglycaemia was heterogeneous between studies, with some studies reporting it as the need for third party assistance or hospitalization, while others reported it as mild symptoms or loss of consciousness, and some studies depended only on ICD codes, with no clear definition based on guidelines or classification. Insulin was the most frequently reported treatment in the studies included in this review (n=28), followed by sulfonylureas (n=5) and other oral antidiabetic agents. Details of studies characteristics are presented in (Table1).

Table 1. Characteristics of all studies included in the meta-analysis

Author	Country	Study design	Sample size	Data Source	Diabetes type	Mean age	Sex M/F	Diabetes duration	Treatment regimens	Prevalence data	Incidence data	Definition of hypoglycaemia
Akirov et al (2018) *(89)*	NA	Prospective	5301	Self-reported	Both types of diabetes	73 ± 13	M 51%	12 ± 11	A combination of oral or Insulin	Yes	No	Hypoglycaemia and serious hypoglycaemia were defined as at least one blood glucose measurement ≤ 70 and < 54 mg/dl
Alexiu et al (2017) *(30)*	North America	Retrospective	232898	Database	Both types of diabetes	NA	NA	NA	A combination of oral and insulin	No	Yes	Mild, moderate, and severe hypoglycaemia severity is typically defined on the basis of service use, medical setting, and/or hospitalization
Alonso-Moran et al (2015) *(44)*	Europe	Retrospective	134413	Database	T2DM	NA	M 53.9%	NA	NA	No	Yes	ICD codes
Aung et al (2012) *(20)*	Europe	Retrospective	1066	Self-reported	T2DM	67.9 ± 4.2	M 51%	8.1 ±6.5 years	A combination of oral and insulin	Yes	No	Severe hypoglycaemia was defined as self-reported episodes of hypoglycaemia requiring external help
Barkai et al (1998)*(21)*	Europe	Prospective	130	Self-reported	T1DM	NA	M 52.3 %	NA	Insulin	No	Yes	A hypoglycaemic event was defined as an episode which was accompanied by typical common symptoms of hypoglycaemia and which was corrected by oral carbohydrate, parenteral glucose or glucagon therapy, irrespective of whether hypoglycaemia had been demonstrated by blood glucose measurement. Severe hypoglycaemia was defined as any event requiring the assistance of another person for treatment
Birkebaek et al (2017) *(22)*	Europe	Retrospective	8806	Database	T1DM	11	M 52%	5.1±3.1 years	Insulin	No	Yes	SH was defined in accordance with the guidelines of the International Society of Paediatric and Adolescent Diabetes as an event associated with severe neuroglycopenia resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose)
Blasetti et al (2011) *(24)*	Europe	Prospective	195	Database	T1DM	13.9 ± 6.6	M 51.79 %	NA	Insulin	No	Yes	< 50 mg/dl associated with altered status of consciousness including seizure or coma or confusional state

Bognetti et al (1997) *(25)*	Europe	Retrospective	187	Self-reported	NA	NA	M 56.1%	NA	Insulin	Yes	Yes	NA
Bramlage et al (2012) *(26)*	Europe	Retrospective	3810	Self-reported	T2DM	NA	M 48.9%	NA	A combination of oral only	Yes	No	Patients with mild hypoglycaemia were defined as being with or without specific symptoms but manageable without help. These were usually detected by self-measurements of blood glucose (<2.22 mmol/l; 40 mg/dl in any case; 2.22-2.78 mmol/l or 50 mg/dl in case of symptoms). Patients with moderate hypoglycaemia experienced symptoms of hypoglycaemia and required assistance from a second person (e.g. a relative or friend), but no attention of a medical professional was necessary. Patients with severe hypoglycaemia were seeking medical attention or were admitted to hospital because of hypoglycaemia
Bron et al (2012) *(27)*	Europe	Retrospective	212061	Database	T2DM	53.9 ± 10.6	M 56 %	NA	A combination of oral and insulin	No	Yes	ICD codes
Buyken et al (1998) *(28)*	Europe	Retrospective	2065	Self-reported	T1DM	32.7± 10.2	M 50.9	14.8 ±9.5 years	Insulin	Yes	No	Severe hypoglycaemia requiring the help of another person
Cherubini et al (2013) *(29)*	Europe	Retrospective	2025	Self-reported	T1DM	12.4 ± 3.8	M 53 %	5.6 ± 3.5 years	Insulin	Yes	Yes	Hypoglycaemia was defined as any episode leading to hospitalisation or requiring the administration of glucagon because the patient was unconscious or had seizures
Chu et al (2017) *(81)*	Asia	Retrospective	20845	Database	Both types of diabetes	NA	NA	NA	NA	Yes	No	ICD codes
Conceicao et al (2017) *(18)*	Europe	Retrospective	425706	Self-reported	T2DM	NA	NA	NA	A combination of oral and insulin	Yes	No	ER admissions
Davis et al (2010) *(85)*	Australia	Retrospective	616	Database	T2DM	6.7 ± 9.8	M 52.3%	7.7 years	NA	No	Yes	NA

Davis et al (1998) *(84)*	Australia	Prospective	709	Self-reported	T1DM	12.3 ± 4.4	M 52 %	4.9± 3.8 years	Insulin	No	Yes	Moderate hypoglycaemia defined as hypoglycaemia requiring the assistance of another person for treatment. Severe hypoglycaemia as an event resulting in coma or convulsion
Deusenberry et al (2012) *(56)*	North America	Retrospective	692	Database	T2DM	NA	M 51.3 %	NA	Sulfonylureas	Yes	No	Glucose <70 mg/dl
Donnelly et al (2004) *(31)*	Europe	Prospective	267	Database	Both types of diabetes	NA	NA	NA	Insulin	No	Yes	Patients were encouraged to use their own glucose meter to take their recording, together with the nature of the remedial action taken and whether the episode required assistance of a third-party
Faerch et al (2011) *(32)*	Europe	Prospective	128	Self-reported	T1DM	45± 12 years	M 56.2%	19±11 years	Insulin	Yes	No	Severe hypoglycaemia was defined as an episode at which the patient needs assistance from another person
Feher et al (2016) *(33)*	Europe	Retrospective	1569	Self-reported	T2DM	NA	M 66%	NA	A combination of oral and insulin	Yes	No	Mild hypoglycaemia was defined as any of the above symptoms where a third-party was not required, and severe hypoglycaemia was defined as the above symptoms with third-party involvement or where there was loss of consciousness
Farmer et al (2012) *(34)*	Europe	Retrospective	3562	Self-reported	NA	NA	NA	NA	NA	Yes	No	NA
Green et al (2012) *(57)*	North America	Retrospective	3000	Self-reported	T2DM	NA	NA	NA	NA	Yes	No	Hypoglycaemia was based on self-reported low blood sugar
Guisasola et al (2008) *(35)*	Europe	Retrospective	1709	Self-reported	T2DM	62.9 ± 10.6	M 54.9%	7.8 SD ± 5.1	A combination of oral only	Yes	No	NA
Henderson et al (2003) *(19)*	Europe	Retrospective	215	Self-reported	T2DM	68	NA	13 years	Insulin	Yes	Yes	Mild hypoglycaemia was defined by the ability to have self-treated the episode and severe hypoglycaemia as having required external assistance to effect recovery
Hirai et al (2007) *(58)*	North America	Retrospective	537	Self-reported	T1DM	45.3 ± 9.9	M 50.1%	31.3 ± 7.9 years	Insulin	Yes	No	Severe hypoglycaemia required ED visit or hospitalisation

Honkasalo et al (2011) *(36)*	Europe	Retrospective	1776	Self-reported	Both types of diabetes	61.6± 13.5 years	NA	12.8 ± 11.0 years	insulin	Yes	No	SH was defined as a condition for which the patient needs the assistance of another person to recover from a hypoglycaemic episode
Ikeda (2018) *(82)*	Asia	Retrospective	166806	Database	T2DM	66.2 ± 11.8	M 62.1%	NA	A combination of oral and insulin	No	Yes	ICD codes
Ishtiak-Ahmed et al (2017) *(37)*	Europe	Retrospective	17230	Database	T1DM	NA	M 57.3 %	NA	Insulin	No	Yes	ICD codes
Jabbar et al (2017) *(87)*	Multinational	Retrospective	3250	Self-reported	T2DM	56.9 ± 10.7 years	M48.5%	8.4± 6.3	A combination of oral and insulin	Yes	No	NA
Johnston et al (2012) *(59)*	North America	Retrospective	361210	Database	T2DM	NA	NA	NA	A combination of oral only	Yes	No	ICD codes
Johansen et al (2015) *(90)*	Europe	Retrospective	3320	Database	T1DM	NA	M 52.4%	NA	Insulin	No	Yes	Severe hypoglycaemia was defined as a hypoglycaemic event leading to loss of consciousness and/or seizure
Karges et al (2015) *(39)*	Europe	Retrospective	31330	Database	T1DM	NA	M 52.8 %	NA	Insulin	No	Yes	NA
Katz et al (2012) *(60)*	North America	Prospective	255	Self-reported	T1DM	NA	M 49%	NA	Insulin	No	Yes	hypoglycaemia requiring assistance from another person for oral treatment and hypoglycaemia with seizure/coma (altered consciousness) as determined by report of seizure or coma, requirement for parenteral therapy (i.e., glucagon or intravenous dextrose), or use of emergency services
Kim et al (2016) *(75)*	Asia	Retrospective	307107	Database	T2DM	NA	M 41.7%	NA	A combination of oral and insulin	No	Yes	ICD codes
Kostev et al (2014) *(40)*	Europe	Retrospective	32545	Database	T2DM	70.2±11.2 years	M 50.3%	NA	Insulin	Yes	No	ICD codes
leckie et al (2005) *(41)*	Europe	Prospective	243	Self-reported	NA	NA	NA	NA	Insulin	No	Yes	Mild hypoglycaemia was defined as any symptomatic episode that was self-treated. Severe hypoglycaemia was defined as an episode that required treatment by another person and was

												associated either with a blood glucose concentration of ⬍2.8 mmol/l or with prompt recovery after administration of oral carbohydrate, or the parenteral administration of dextrose or glucagon
Leese et al (2003) *(42)*	Europe	Retrospective	977	Database	T1DM	NA	NA	NA	Insulin	Yes	Yes	Episodes of severe hypoglycaemia were defined as blood glucose <3.5 mmol/l associated with the need for treatment with glucagon or intravenous dextrose to effect recovery or paramedic confirmation of hypoglycaemia with rapid recovery following treatment
Leonard et al (2016) *(61)*	North America	Retrospective	592872	Database	T2DM	NA	NA	NA	Sulfonylureas	No	Yes	ICD codes
Lipska et al (2013) *(63)*	North America	Retrospective	9094	Database	T2DM	59.5± 9.8	NA	10.6± 8.4 years	A combination of oral and insulin	Yes	No	ICD codes
Lipska et al (2014) *(62)*	North America	Retrospective	33952331	Database	NA	NA	NA	NA	NA	No	Yes	ICD codes
Lundkvist et al (2005) *(55)*	Europe	Retrospective	309	Self-reported	T2DM	65±11	M60 %	NA	A combination of oral and insulin	No	Yes	Symptomatic hypoglycaemia was considered biochemically verified by a blood glucose concentration less than 3.3 mmol/1. Severe hypoglycaemia was defined as a hypoglycaemic event for which the patient required assistance from another person to resolve the situation. Mild hypoglycaemia was defined as manageable by the patient (e.g. by eating a sandwich)
Ly et al (2009) *(86)*	Australia	Retrospective	656	Self-reported	T1DM	12.8 ±4.0	M 48.3%	5.4 ± 3.9 years	Insulin	No	Yes	Severe hypoglycaemia was defined as an event leading to loss of consciousness or seizure. Recurrent hypoglycaemia was defined as the occurrence of episodes of severe hypoglycaemia in the preceding year
Lyngsie et al (2016) *(48)*	Europe	Retrospective	307016	Database	NA	NA	NA	NA	NA	No	Yes	ICD codes

Maltoni et al (2013) *(43)*	Europe	Retrospective	269	Self-reported	T1DM	NA	M 50.2%	NA	Insulin	No	Yes	Hypoglycaemic episode as an event of coma, seizures and/or altered mental status requiring third-party assistance
Muhlhauser et al (1985) *(45)*	Europe	Retrospective	384	Self-reported	T1DM	30±13 years	NA	12±9 years	Insulin	Yes	No	hypoglycaemia with loss of consciousness treated with glucagon or intravenous glucose
Muller et al (2017) *(46)*	Europe	Retrospective	7900000	Database	T2DM	NA	NA	NA	A combination of oral and insulin	No	Yes	ICD codes
Murata et al (2005) *(73)*	North America	Prospective	344	Database	T2DM	65.5±9.7 years	M 96.5%	14.7 ± 9.9 years	A combination of oral and insulin	Yes	Yes	Glucose <60 mg/dl
Nunes et al (2017) *(65)*	North America	Retrospective	143635	Database	T2DM	NA	M 51.3%	NA	Sulfonylureas	Yes	No	ICD codes
Nunes et al (2016) *(64)*	North America	Retrospective	844683	Database	T2DM	NA	M 48.5 %	NA	A combination of oral only	No	Yes	NA
Odawara et al (2014) *(76)*	Asia	Retrospective	4219	Self-reported	T2DM	62.8 ± 12.1	M 58.9%	NA	A combination of oral and insulin	No	Yes	Severe hypoglycaemia included hypoglycaemic episodes satisfying any of the following 1) resulted in death, 2) life-threatening, 3) required or prolonged inpatient hospitalization, 4) persistently or significantly disabling/ incapacitating, 5) a congenital anomaly, and/or 6) medically important
Olsen et al (2014) *(47)*	Europe	Retrospective	440	Self-reported	T1DM	NA	M 51.0%	NA	Insulin	Yes	No	NA
Ooi et al (2011) *(77)*	Asia	Retrospective	170	Self-reported	T2DM	67.32 +5.45	M 41.2%	9.00 ±6.77	A combination of oral and insulin	Yes	No	NA
Pathak et al (2016) *(66)*	North America	Prospective	917440	Database	NA	57.9 ± 13.2	M 52.1%	NA	NA	No	Yes	ICD codes
Pedersen-Bjergaard et al (2003) *(23)*	Europe	Prospective	171	Self-reported	T1DM	44 ± 12	M 54%	19 ±11 years	Insulin	No	Yes	Severe hypoglycaemia was defined as hypoglycaemic episodes with a need for assistance from other persons in order to restore glucose levels

Pedersen-Bjergaard et al (2004) *(49)*	Europe	Retrospective	1076	Self-reported	T1DM	NA	M 55.5%	NA	Insulin	Yes	No	Mild hypoglycaemic events defined as episodes with symptoms of hypoglycaemia manageable by the patient. Severe hypoglycaemic events were defined as episodes where assistance from others was needed to restore blood glucose
Pilemann-Lyberg et al (2015) *(50)*	Europe	Prospective	161	Database	T2DM	76±12 years	M 54.0 %	NA	Sulfonylureas	No	Yes	We defined a severe hypoglycaemic event as an episode requiring external help for recovery
Pirags et al (2012) *(88)*	Multinational	Prospective	991	Self-reported	T2DM	57.9±10.1	M 52.2%	9.2± 5.9 years	Insulin	Yes	Yes	Severe hypoglycaemia was defined as an event that required assistance from another person who actively administered carbohydrate, glucagon or other resuscitative actions and was associated with either a blood glucose level less than 3.9 mmol⁄l (< 70mg⁄dl) or prompt recovery after restoring normoglycaemia
Rajendran et al (2015) *(78)*	Asia	Retrospective	132	Database	Both types of diabetes	59±20	M 52.2%	NA	A combination of oral and insulin	Yes	No	NA
Raju et al (2016) *(67)*	North America	Retrospective	11536	Database	T2DM	55.7 ± 10.1	M 58.8%	NA	A combination of oral only	No	Yes	NA
Sako et al (2015) *(79)*	Asia	Retrospective	25071	Database	NA	73.4 ± 13.1	M 53.3%	NA	NA	No	Yes	ICD codes
Samann et al (2013) *(51)*	Europe	Retrospective	4854	Self-reported	Both types of diabetes	NA	NA	NA	A combination of oral and insulin	Yes	No	SH was defined as hypoglycaemia with coma or the need for intravenous glucose or intramuscular glucagon injection
Sarkar et al (2010) *(68)*	North America	Retrospective	14357	Self-reported	T2DM	58 ± 10	M 51.0 %	10 ± 8 years	A combination of oral and insulin	Yes	No	Severe low blood sugar reaction, such as passing out or needing help to treat the reaction
Schloot et al (2016) *(52)*	Europe	Retrospective	29485	Database	T2DM	NA	M 51.1%	NA	Sulfonylureas	Yes	No	NA
Seligman et al (2010) *(69)*	North America	Retrospective	711	Self-reported	T2DM	NA	NA	NA	NA	Yes	No	NA

Shriraam et al (2017) *(80)*	Asia	Retrospective	366	Self-reported	T2DM	NA	M 23.5%	10.9± 5.9 years	A combination of oral and insulin	Yes	No	Severe hypoglycaemia required ED visit or hospitalisation
Stuart et al (2017) *(70)*	North America	Retrospective	9584	Self-reported	NA	NA	NA	NA	A combination of oral and insulin	Yes	No	Glucose <4 mmol/L
Tschope et al (2012) *(53)*	Europe	Retrospective	3347	Self-reported	T2DM	NA	M 53.1 %	NA	NA	Yes	No	NA
Wang et al (2015) *(71)*	North America	Retrospective	63972	Database	NA	NA	M 48.4%	NA	NA	No	Yes	ICD codes
Weinstock et al (2013) *(72)*	North America	Retrospective	4973	Database	T1DM	NA	M 45.8%	NA	Insulin	Yes	No	SH was defined as an episode in which the assistance of another individual was needed or glucagon was given
Yun et al (2013) *(83)*	Asia	Retrospective	878	Database	T2DM	55.3 ± 9.8	NA	9.8 6 ± 6.5 years	A combination of oral and insulin	No	Yes	Hypoglycaemia episodes requiring the assistance of another person to actively administer carbohydrate, other resuscitative actions, hospitalization, or medical care in an emergency department.
Yun et al (2018) *(74)*	Asia	Retrospective	1366692	Database	T2DM	57.7± 11.7	M 59.3%	NA	A combination of oral and insulin	Yes	No	ICD codes
Zhong et al (2017) *(54)*	Europe	Retrospective	23246	Database	T1DM	NA	NA	NA	Insulin	No	Yes	ICD codes

Abbreviations; ICD: International classification of diseases; NA: Not available; SH: severe hypoglycaemia; Sex M/F: Male/Female

3.2. Quality assessment

The quality of studies included in this review varied considerably, ranging from 8 as the lowest score to 18 as the highest score recorded. The majority of the studies (83.0%) included in this review were of good quality and scored more than 12 (n =60), while the remaining studies (n =12) were of moderate quality. The details of the quality assessments are presented in (Table S3).

3.3. Prevalence of Hypoglycaemia

We only included studies that measured hypoglycaemia prevalence over a 12-months period in the meta-analysis and this resulted 39 studies being included, with a total of 2,462,810 individuals with diabetes. The prevalence of hypoglycaemia varied between studies included, some studies reported a high prevalence rate of 73.0% (19), while other studies reported a low prevalence rate of less than 1.0% (18). When stratifying by type of diabetes, the prevalence of hypoglycaemia ranged from 1.3% to 38.0% for type 1, and from 0.074% to 73.0% for type 2. The 39 studies included in the meta-analysis of prevalence had a high-level of heterogeneity (I^2=100%), which was also found after the sensitivity analysis of removing two studies (18, 19). Stratification by geographical location, data source and treatment regimen showed a high level of heterogeneity (I^2=100%). The prevalence of hypoglycaemia varied between studies from different data sources. Self-reported studies had a higher prevalence range than studies using electronic health records: the prevalence of hypoglycaemia ranged from 0.074% to 73.0% for self-reported studies, and from 1.0% to 19.0% for studies using electronic health records, respectively. When stratified by treatment regimen, the range of the prevalence of hypoglycaemia was higher among studies that included only individuals using insulin 2.2% to 73.0%, compared to studies that included individuals using sulfonylureas 2.8% to 19.0%.

Further stratification by combining studies from similar geographical location, study design and data source showed that the pooled estimate of prevalence of hypoglycaemia was 35.0 % (95% CI, 32.0 – 38.0) (I^2=59%) among studies that were cross-sectional in design, self-reported in source of data, and were conducted in Europe (Figure 2). While the pooled estimate of prevalence of hypoglycaemia was 11.0 % (95% CI, 11.0 – 13.0) (I^2=38%) among studies that were cross-sectional in design, self-reported in source of data, and were conducted in North America (Figure 3).

3.4. Incidence rates of hypoglycaemia

A total of 39 studies involving 45,768,950 individuals met our inclusion criteria and were included in the meta-analysis. Given the high heterogeneity (I^2=100.0%), the incidence rate of hypoglycaemia was reported as a range of 0.072 to 42,890 episodes per 1,000 person-years. The incidence rate of hypoglycaemia stratified by diabetes type ranged from 14.5 to 42,890 episodes per 1,000 person-years experienced by individuals with type 1 diabetes and from 0.072 to 16,360 episodes per 1,000 person-years experienced by individuals with type 2 diabetes.

3.5. Publication bias

Funnel plots comparing the transformed effect sizes with the estimated standard error were generated for the prevalence and the incidence, respectively, to investigate the relationship between the outcome and size of the studies. The funnel plots were asymmetric and showed a stark contrast between the results of the fixed effect and random effects models, with most studies falling outside the dotted CI within which we would expect 95% of studies to reside assuming a fixed effect holds (Figure S1).

4. DISCUSSION

This systematic review and meta-analysis aimed to assess the incidence and prevalence of hypoglycaemia in both type 1 and type 2 diabetes, taking methodological differences into consideration. The prevalence of hypoglycaemia ranged from 0.074% to 73.0%. The incidence rate of hypoglycaemia ranged from 0.072 to 42,890 episodes per 1,000 person-years: stratified by type of diabetes, it ranged from 14.5 to 42,890 episodes per 1,000 person-years and from 0.072 to 16,360 episodes per 1,000-person years in type 1 and type 2 diabetes, respectively.

In addition, this review highlighted that the range of the prevalence of hypoglycaemia is higher among diabetes individuals using insulin-based therapy compared to individuals on sulfonylureas-based therapy.

Previous reviews investigating the incidence and prevalence of hypoglycaemia in type 1 and type 2 diabetes in observational studies are limited. Two previous systematic reviews only examined the incidence and the prevalence of severe/mild to moderate hypoglycaemia in type 2 diabetes; however, they did not investigate hypoglycaemia in type 1 diabetes and did not report an overall estimate for the prevalence or the incidence of hypoglycaemia in type 2 diabetes (10, 91).

A meta-analysis of clinical trials investigating the proportions of hypoglycaemia in individuals with type 2 diabetes reported that the pooled average of the prevalence of hypoglycaemia in individuals with diabetes and treated with sulfonylureas is 10.1 % (95% CI, 7.3 - 13.8). In our study, the prevalence of hypoglycaemia in individuals with diabetes and treated with sulfonylureas ranged from 2.8 % to 19.0 % (92). In addition, in three clinical trials that were included in their review, the proportion of hypoglycaemia in individuals with diabetes and treated with insulin ranged from 8.0 % to 56.0 %, while in our study the prevalence of hypoglycaemia in individuals with diabetes and treated with insulin ranged from 2.2 % to 73.0 % (92).

The result of this study demonstrates that the prevalence and incidence of hypoglycaemia are high,

as shown above, and that hypoglycaemia is a very common complication that many individuals with diabetes may experience. However, it is important to mention that the risk of hypoglycaemia is different between both types of diabetes (93), as individuals with type 1 have a higher risk of hypoglycaemia compared to individuals with type 2 diabetes; this was highlighted in our results. In addition, these high numbers could be related to the fact that recent guidelines recommend intensification of diabetes treatment to control blood sugar levels and to prevent macrovascular and microvascular complications which may put the individuals under higher risk of experiencing hypoglycaemic events (94). A recent study by Naser et al. has found that individuals with diabetes who were using intensive antidiabetic therapy were at a five-fold higher risk of hypoglycaemia compared to individuals using antidiabetic monotherapy (95). Besides this, another previous large database study in the UK has confirmed the increased risk of hypoglycaemia among individuals with diabetes who were using intensive antidiabetic therapy consisting of antidiabetic combination therapy (whether dual or triple antidiabetic therapy) (96).

Regarding the prevalence of hypoglycaemia, there was considerable variation in the data source. Studies that were self-reported had higher prevalence rates of hypoglycaemia compared to studies that were based on health record databases. This could likely be because self-reported studies are able to report mild hypoglycaemia. However, this is also influenced by precision of individual review, which can be poor, especially for non-severe hypoglycaemic events. It is further dependent upon the patient's ability to perceive hypoglycaemia when it happens, which is restricted by impaired hypoglycaemia awareness, and to accurately separate them from symptoms inconsequential to hypoglycaemia. It is further dependent upon the individual's ability to perceive hypoglycaemia when it happens, which is restricted by impaired hypoglycaemia awareness, and to accurately separate them from symptoms inconsequential to hypoglycaemia (97). Moreover,

only 5% of self-reported hypoglycaemic events are managed by the healthcare system or emergency medical services (98). On the other hand, health record databases are more likely to report more severe cases of hypoglycaemia that require either emergency visits or hospital admissions, in which the events are confirmed by healthcare professionals.

Furthermore, studies in which the individuals were on insulin treatment had higher prevalence rates of hypoglycaemia compared to studies that were based on sulfonylureas therapy. Insulin and sulfonylurea-based antidiabetic therapies are commonly associated with hypoglycaemic events, compared to other antidiabetic therapies (99, 100). The higher risk of hypoglycaemia with the use of insulin or sulfonylurea among individuals with diabetes is due to their mechanisms of action, which is mainly based on triggering the pancreatic secretion of insulin inside the body (for sulfonylurea-based therapy) or the administration of exogenous insulin formulations (101), while the mechanism of action of other antidiabetic therapies is based on increasing the sensitivity of insulin and limiting the absorption of glucose, leading to a lower risk of experiencing hypoglycaemic events (102). However, it is important to highlight that other risk factors, such as polypharmacy and drug-induced hypoglycaemia could also increase the risk of hypoglycaemia (103, 104).

The quality of studies included in this review varied between the studies: the health records database studies were better in quality compared to self-reported studies (details are presented in the Supplement). Health record databases mainly use the ICD system or hospital codes that were entered by either physicians or healthcare professionals, so they may be more accurate than self-reported diagnosis; however, it is important to mention that even health record databases are subject to misreporting or under-reporting bias (105).

In recent years hypoglycaemia has been a major topic of research and clinical practice, which was

highlighted after the publication of some post-hoc RCTs showing an increased risk of complications and death in individuals experiencing hypoglycaemia (8, 106, 107). Our study has demonstrated that hypoglycaemia is a common event among individuals with diabetes in real life in both type 1 and type 2 diabetes, different countries and different treatments. More research should focus on identifying risk factors and predictors of hypoglycaemia, including newer oral hypoglycaemic agents such as GLP and SGLT. Furthermore, healthcare providers must be aware of such events and monitor their patients on a continuous basis, and more importantly to educate them about their disease and its associated events.

To the best of our knowledge, this is the first systematic review and meta-analysis to review the incidence and prevalence of hypoglycaemia in individuals with type 1 and type 2 diabetes mellitus. Unlike previously published meta-analysis, we standardised the prevalence to one year to allow appropriate meta-analytical data pooling and interpretation. We included observational studies which reported the prevalence and incidence rates of hypoglycaemia in diabetes populations representing real-life situations. RCTs are considered as the gold standard for demonstrating clinical efficacy. However, the rates and nature of hypoglycaemic events reported from clinical trials may not be generalised to real-world practice. Large RCTs generally include individuals who are restricted to their suggested regimens, subjected to close monitoring and support rather than individuals in routine clinical practice. In addition, RCTs do not include individuals with a history of severe hypoglycaemia, the elderly or those with poor health status (9).

However, our study had several limitations. Firstly, the heterogeneity among the studies included in this review was high. Heterogeneity could not be explained by any of the study level covariates considered in the subgroup analysis. Therefore, the high heterogeneity is likely to be due to study characteristics which were not measured or reported in the original citations (108). Moreover, high

statistical heterogeneity is more frequent in meta-analyses of prevalence compared to meta-analyses of binary outcomes (109). However, we reported the range of the prevalence if high heterogeneity was indicated ($I^2 \geq 75\%$).

Secondly, the definition of hypoglycaemic episodes varied between studies; therefore, it was not possible to stratify our results based on the severity of hypoglycaemia. In addition, due to the difference in study designs between studies included in this review (questionnaire/medical records/database), it should be recognised that this causes difficulties when combining results across studies, resulting in under- or over-reporting of hypoglycaemic episodes; however, we tackled this issue by stratifying the pooled average based on data sources.

5. CONCLUSION

In conclusion, this review highlighted the fact that hypoglycaemia is a very common event among both type 1 and type 2 individuals with diabetes treated with diabetes medications. The frequency of hypoglycaemia among individuals with type 1 diabetes and among individuals treated with insulin were higher compared to other antidiabetic medications and to individuals with type 2 diabetes. However, the quality of information available in the literature varied largely. Over the last ten years the quality of the evidence has improved compared to previous published studies. Studies using data from health records databases had a higher quality in recording the incidence and prevalence of hypoglycaemia. Further studies are needed to investigate the hypoglycaemia-associated risk factors.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

ACKNOWLEDGEMENTS

The authors thank Dr. Francesco Zaccardi for the contribution and providing his expertise in preparing the publication of this manuscript.

AUTHORS CONTRIBUTIONS

Alwafi, Alsharif, Wei and Professor Wong had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Alwafi, Alsharif, Wei and Wong had the original idea for this study. Alwafi, Alsharif, Wei, Naser and Wong contributed to the design of the study. Alwafi and Alsharif contributed to their literature screening, data extraction and quality assessment of the studies included. Alwafi and Langan contributed in the statistical analysis. Alwafi, Alsharif, Wei, Langan, Bell, Ilomak and Wong wrote the first draft. All the authors contributed to interpretation and edited the draft report.

FUNDING:

This research was funded by the Deanship of Scientific Research at Princess Nourah bint Abdulrahman University through the Fast-track Research Funding Program, and by PharmAlliance and UCL-HKU strategic partnership funds.

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FIGURE LEGENDS

Figure 1. Flow chart of studies included in the meta-analysis

Figure 2. Prevalence of hypoglycaemia meta-analysis stratified by European studies, self-reported and cross-sectional studies

Figure 3. Prevalence of hypoglycaemia meta-analysis stratified by North American studies, self-reported and cross-sectional studies

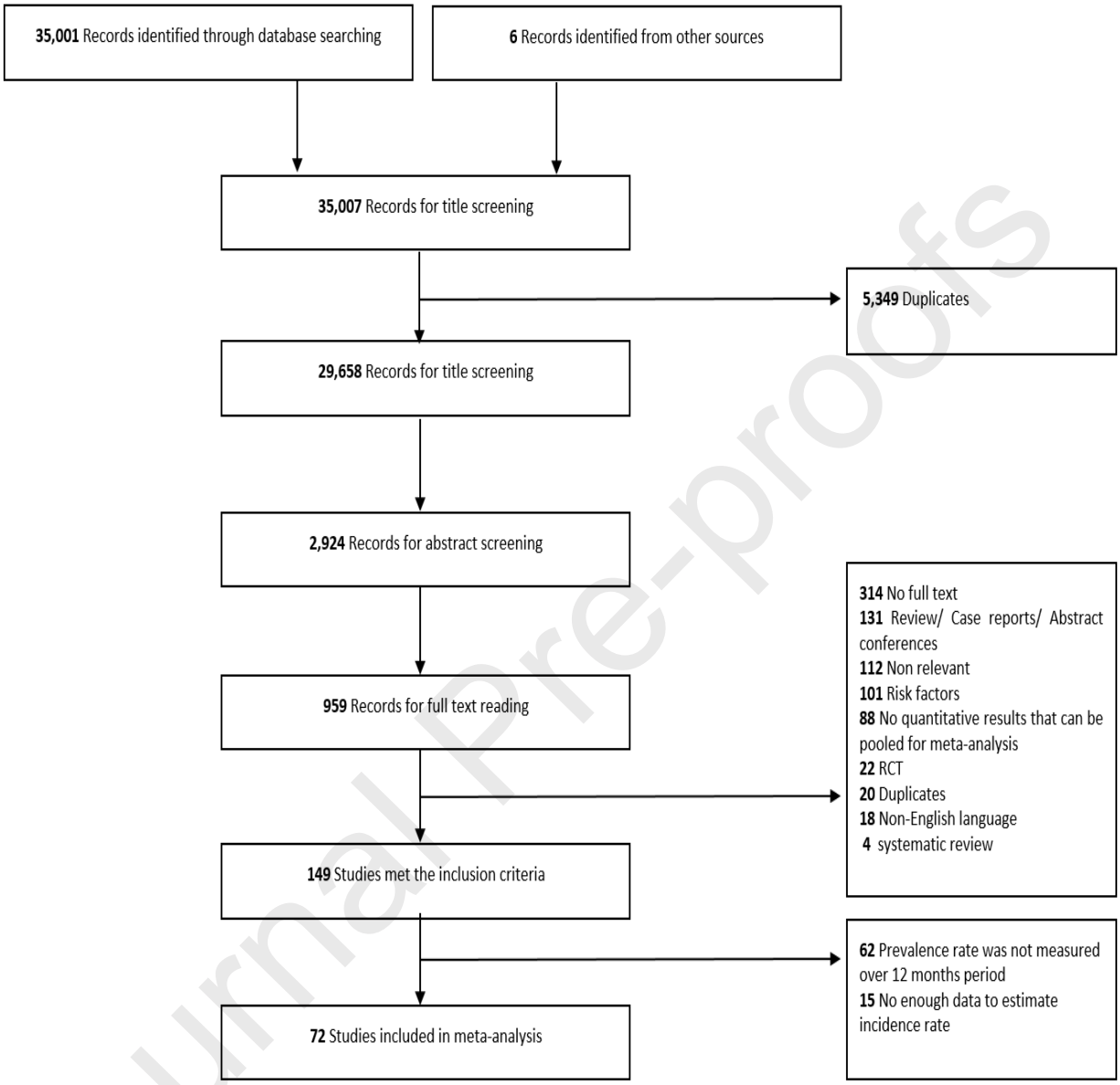
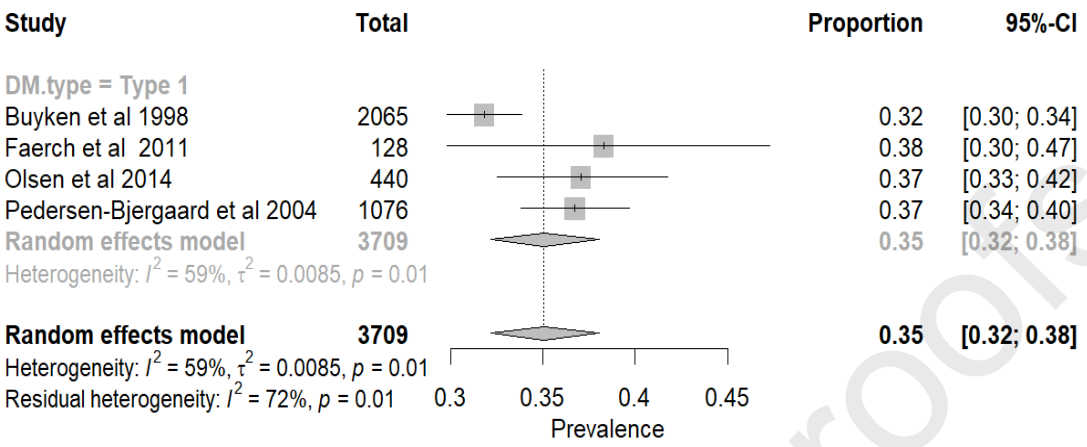


Figure 1. Flow chart of studies included in the meta-analysis



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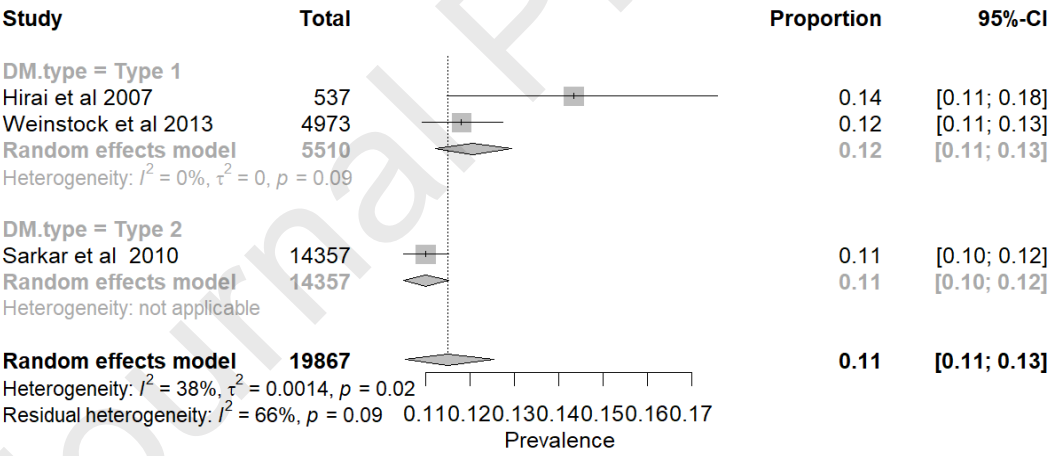

Figure 3. Prevalence of hypoglycaemia meta-analysis stratified by North American studies, self-reported and cross-sectional studies