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REVIEW

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Global economic burden of diabetic related hypoglycemia: a systematic review of cost of illness studies

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Abstract

Background Currently, diabetic hypoglycemic events are increasing, and this review aimed to synthesize global evidence on the economic burden of hypoglycemia.

Method We conducted a systematic search in both databases (PubMed and Scopus) and a forward citation search. We included worldwide studies regardless of publication year. Two independent authors are involved in screening, selection, extraction, and quality appraisal. We used a consensus-based checklist for quality appraisal. We reported the costs in 2024 international dollars. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, and registered the review with the International Prospective Register of Systematic Reviews (CRD420251069256).

Result We reached out to 1235 articles and included 29 in the final report from high- and middle-income countries. Most studies estimated costs using prevalence-based and health system perspectives. The average direct and indirect costs per event per patient ranged from $1.90 to $24,932.73 and $3.46 to $3,339.34, respectively. The average annual direct cost per patient ranged from $1,938.41 to $25,092.76. This direct expense emerged from medications, consultation services, hospitalization, emergency care, and other services. Indirect costs primarily identified productivity losses due to sick leave, late arrivals, and early departures from work, with annual monetary estimates per patient ranging from $2,504.22 to $16,129.64. Patient direct costs were generally higher than the indirect costs. Annual hypoglycemia attributable costs ranged from $1,431.72 to $14,414.20 per patient per year. The annual national economic burden of hypoglycemia was substantial, ranging from $39.04 to $3.03 billion. Diabetes severity, type of diabetes, treatment regimen, and health facility level are sources of cost variation.

Conclusion This systematic review concludes that diabetes-related hypoglycemia imposes a substantial economic burden, with both direct and indirect costs being significant. Preventive efforts focusing on hypoglycemia and its contributing factors are crucial to mitigate the financial impact on patients, healthcare providers, and the health system.

Keywords Diabetes, Cost of illness, Economic burden, Health care costs, Global

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Introduction

Diabetes mellitus(DM), a chronic metabolic disorder characterized by persistent elevation of blood glucose, is and global public health problem [1]. As of 2021, the International Diabetes Federation estimated 537 million adults with diabetes worldwide, projected to reach 643 million by 2030 and 783 million by 2045 [2]. Both chronic(cardiovascular disease, nephropathy, and retinopathy) [3] and acute(ketoacidosis and hypoglycemia or hyperglycemia) [4] complications pose significant risks to patients and strain the health system.

Hypoglycemia can happen when blood glucose concentration is abnormally reduced (below 70 mg/dl), a common diabetes associated acute complication in both types of DM [5]. Contributing factors include long-term insulin use, history of hypoglycemia, reduced GFR (< 60 ml/min/1.73 m^2), and high medication doses [6]. Besides, recurrent hypoglycemia is associated with poor glycemic control, decreased quality of life, and increased healthcare resource utilization [7, 8]. Additionally, mortality in severe hypoglycemia cases is up to six times higher than in those without [9].

Alongside the clinical burden of hypoglycemia, economic implications remain underexplored. The management of hypoglycemic events incurs direct medical (emergency care services, hospital admissions charges, laboratory tests, and medication costs) and indirect costs, productivity loss (lost workdays, presenteeism, and burden of family members) [10]. These costs expose an additional burden on healthcare systems [11], which substantially affects resource-limited countries where access to safe use of insulin, glucose monitoring, and limited patient education.

Well-synthesized and sufficient systematic reviews were done on the economic burden of diabetes [12–15]. However, a few systematic reviews that addressed only the national estimate of the economic burden associated with hypoglycemia from developed countries [16, 17]. This underscores the lack of globally synthesized evidence on the economic impact of hypoglycemia. Identifying global cost drivers and factors in diabetes-related hypoglycemia is essential for guiding resource allocation and developing targeted prevention and management strategies. Therefore, this systematic review aimed to generate consolidated global evidence on direct and indirect costs attributed to diabetes related hypoglycemia and highlight regional disparities and research gaps. In addition, the findings of this systematic review will provide evidence for policymakers, clinicians, and health economists to understand and mitigate the economic consequences.

Cost overview

In an economic evaluation or economic burden study, we have different types of costs, including direct and indirect. The total cost of diabetes includes both direct and indirect expenses. Direct costs cover medical expenses such as registration, lab tests, and medications, as well as nonmedical costs like transportation, food, and accommodation during hospital visits. Indirect costs accounted for lost work time and income due to illness-related absenteeism or missed business opportunities. In addition, intangible costs refer to the pain, suffering, and reduced quality of life experienced by patients, leading to social isolation and diminished personal satisfaction [13].

Methods

Protocol registration

This systematic review was conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [18] (Prisma checklist.docx). Protocol registration was done before data extraction with registration number CRD420251069256.

Data sources, search terms, and strategies

Eligible studies were identified via PubMed, Scopus, and forward citation searches. We conducted a systematic search using appropriate search terms. Firstly, we searched diabetes related studies using the following terms: ("Diabetes Mellitus"[tiab] OR DM[tiab] OR "Type 1 diabetes mellitus"[tiab] OR T1DM[tiab] OR "type II DM"[tiab] OR T2DM[tiab] OR "type II diabetes"[tiab] OR "type II diabetes mellitus"[tiab]) AND (hypoglycemia OR "severe hypoglycemia") AND (economic* OR cost* OR "cost of illness" OR resource OR "cost analysis" OR "labor market" OR "cost evaluation" OR "disease cost" OR "health care cost" OR "direct cost" OR "indirect cost" OR "economic burden"). The same search terms were used in both databases. However, we used different syntax for Scopus database: TITLE-ABS ("Diabetes Mellitus" OR DM OR "Type 1 diabetes mellitus" OR T1DM OR "type II DM" OR T2DM OR "type II diabetes" OR "type II diabetes mellitus") AND (hypoglycemia OR "severe hypoglycemia") AND (economic* OR cost* OR "cost of illness" OR resource OR "cost analysis" OR "labor market" OR "cost evaluation" OR "disease cost" OR "health care cost" OR "direct cost" OR "indirect cost" OR "economic burden"). Restricted to language and the primary article. Additionally, a forward citation search was conducted in Google Scholar. Details are available in (strategic search results.docx).

Article selection and screening process

Three steps of the process have been undertaken. Firstly, two independent authors (BK and AA) identified a title. Secondly, the same authors conducted the abstract once the title is relevant. The third procedure was that two authors performed full-length articles. Finally, any discrepancies were resolved through discussion with a third reviewer (BA). This approach ensured a comprehensive and unbiased selection of studies.

Inclusion and exclusion criteria

We included all original studies assessing the cost of diabetes-related hypoglycemia, covering direct, indirect, or combined costs. Globally published full-text articles without restriction of publication year, population, and diabetes type were included. Conference proceedings, case studies, letters to the editor, economic evaluation, gray literatures and abstracts were also excluded. Because all these documents lack methodological rigor, and might compromise our evidence. Additionally, full-text articles were excluded if they did not report cost-related data or focused on diabetes costs unrelated to hypoglycemia.

Data extraction

After full screening by two independent authors, we determined the types of data to be extracted for the systematic review. Data extraction was performed independently and included variables such as author name, publication year, population characteristics, diabetes type, hypoglycemia severity, study perspective, sample size, costing method (micro or macro), cost type (direct or indirect), study design, treatments, country, patient demographics (age, sex), and other relevant factors. To ensure consistency, all extracted data were cross-checked. Any discrepancies were resolved through discussion with a third author.

For studies lacking a clearly stated costing year, we used the data collection year as the costing year. If data collection spanned multiple years, the most recent year was assumed as the costing year. When the data collection period was not specified, the publication year was used as a proxy. For studies reporting costs in foreign currencies, values were first converted to the local currency using the exchange rate from the base year.

Data synthesis

To adjust for inflation to the target year, we then applied local Consumer Price Index (CPI) data to adjust for inflation to the target year, before converting the inflated cost to a common currency and year using purchasing power parity (PPP) [19]. To ensure ease of comparison, all costs were inflated to a common and recent year, 2024 international dollar(I$), using an online open-access web-based cost converter tool developed by the Campbell and Cochrane Economics Methods Group (CCEMG-EPPI-Center) [20]. This online tool uses PPP exchange rates and country-specific inflation to convert costs into I$, enabling a similar comparison of costs across countries. In the case of a complete cost estimate was not provided, the sum of direct and indirect costs was used to determine the total cost.

In this systematic review, only a qualitative summary was generated due to the heterogeneity, lack of cost estimates and the varied regression models employed by the authors. Following data extraction, we presented the economic burden of hypoglycemia, encompassing direct (including hospitalization, medication, emergency, and outpatient costs) and indirect costs such as productivity loss. The data were presented using appropriate tools to categorize and summarize the identified economic burden of diabetes-related hypoglycemia. Included studies presented based on World Bank income groups [21] and presented by publication year.

Quality assessment

To maintain the quality of this review, we used appropriate quality assessment tool specific to cost of illness study, consensus based checklist for the critical appraisal of cost-of-illness(COI) study [22]. This critical appraisal tool assesses various domains, including study objectives, population definition, study perspective and methods, costing approach, resource measurement, and discounting. However, discounting was not considered in this systematic review, as the costs of hypoglycemia were reported over short time horizons, making discounting inappropriate for these cost-of-illness studies. Two reviewers, BK and AA independently carried out the quality assessment included articles. During quality assessment, both authors were blind about the authors of research, the type of journals published. The third reviewer (BA), was responsible to handover any disputes between the reviewers and made discussion to arrive common consensus.

Results

As shown in Fig. 1, our search strategy furnished a total of 1235 (database:1091 and citation search:144) articles. Of these, 130 publications were removed due to duplication. The majority of studies (1044) were unrelated to our topic, and 61 papers were included for abstract screening. Following abstract screening, 18 papers were excluded, and 43 articles were retained for full-text review. Finally, we identified and included 29 (PubMed: 27, Scopus:0 and citation search: 2) studies that fulfill all the inclusion criteria.

General description of included studies

The current systematic review includes 29 studies conducted between 2006 and 2025, with sample sizes ranging from 90 to 3,293,794. The majority of studies employed a cross-sectional design, while only one study used a nested case-control design. According to the World

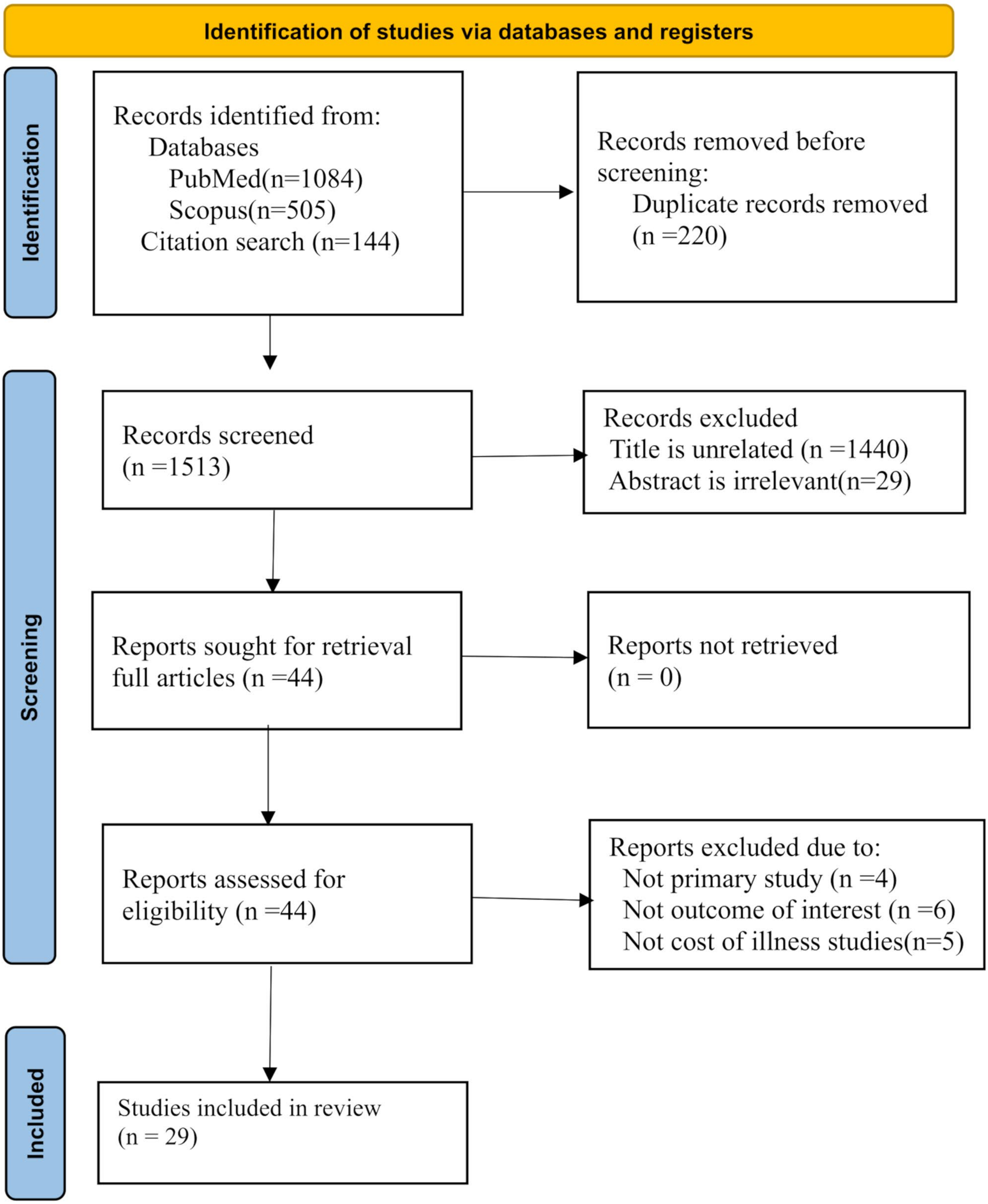

Fig. 1 PRISMA flow diagram illustrating the study selection process, including identification, screening, inclusion, and exclusion of studies

Bank income groups [21], diabetic related hypoglycemia costs were mainly estimated in high-income countries (more than 82% of the studies). USA($n=6$), European countries($n=11$), Canada($n=1$), Asian countries($n=6$). The rest studies were conducted in upper and lower-middle-income countries. More than 93% of the studies estimated diabetic related hypoglycemia costs for one country, and the rest studies included multiple countries. Nearly all of the studies included the adult population, whereas only 27.5% included pediatric participants, and additional details are available in Table 1.

Regarding disease type and population, 38% of the studies ($n=11$) focused on the cost of type 2 diabetes-related hypoglycemia, while 48% ($n=14$) addressed both types of diabetes. Only two studies examined T1DM-related hypoglycemia alone. Severity of hypoglycemia was reported in 19 studies (65%); among these, 7 (36.8%) included only patients with severe hypoglycemia, while 11 (57.9%) reported costs for both severe and non-severe events, and the remaining information is found in Table 1.

Previous review [23] has emphasized that the choice of study perspective is critical in COI studies. According to this review, COI studies can adopt various perspectives, including the societal perspective, which encompasses direct medical, direct non-medical, and indirect costs, or the health system and payer perspectives. The societal perspective is often considered the most comprehensive, as it captures all costs associated with the disease. In this systematic review, the majority of studies ($n=18$, 62.1%) employed a health system perspective, followed by the societal perspective ($n=10$, 34.5%). The remaining two studies did not report (Table 1).

Description of cost Estimation methods and cost types

Classifying the cost in COI studies is important for appropriately estimating the economic burden of a disease, guiding health care resources utilization and allocation, and identifying among various types of costs that can ensure a comprehensive assessment of the economic impact of the disease [51]. Previous studies classified costs into different classes, including direct (direct medical and non-medical) and indirect costs (productivity loss due to absenteeism or presenteeism, or both) [23]. This systematic review includes studies that included all types of costs. Direct medical cost is estimated in all (100%) studies included in the review, and only 3 studies include direct non-medical costs such as transportation and caregiver assistance. Direct medical costs include hospitalization, medication, emergency services, consultation, laboratory costs, diagnostic, ambulance, and outpatient services. Eleven (37.93%) studies estimated indirect costs as a productivity loss in terms of patient or caregiver absenteeism or presentism, such as sick leave, work time loss, late at work or out early, or inability to work (Table 2).

Some studies estimated the proportion of each cost type incurred by patients during hypoglycemic events. In 15 studies (51.7%), direct costs, specifically direct medical costs, accounted for 100% of the reported expenditures. Eight studies (27.6%) reported both direct and indirect costs, with direct costs ranging from 39.3 to 94%, and indirect costs from 6 to 72% of the total costs (Table 2). This range of cost within the study is due to disease type, T1 and T2DM [10] severity of hypoglycemia [24], mild associated with minimum share and moderate with maximum, the number of medications used, and the countries [30], the type of medication and services they used, and depending on the work loss report [44] and others.

COI studies can use either a prevalence-based or an incidence-based approach. The former, more commonly used, estimates costs over a short time horizon, typically one year, while the latter includes both current and future lifetime costs [52]. In this systematic review, 28 studies were conducted with a prevalence-based approach (Table 2). In addition, the costing approach is another important issue in COI studies, and should be reported or described in the method [23]. All but one study employed a micro-costing approach, and all studies used the human capital method to estimate indirect costs, whereby lost working hours were valued according to hourly wages (Table 2).

Costs of diabetes-related hypoglycemia

More than 65% of the studies [10, 24, 25, 28–30, 32, 34, 37, 39, 40, 43–50] presented cost as direct episodic cost per patient, ranging from $1.9 to $24 932.73. Direct cost includes medication(glucagon injection, oral antidiabetics) and ambulance services, physician home visit, hospitalization, diagnostic test, critical care, geriatrics care, ED visit, bed occupancy, nurse attendance, and short-term observations [10, 24, 25, 28–30, 32, 34, 37, 39, 40, 44–47, 50]. Only three studies [25, 37, 47] reported direct non-medical costs, including transportation, caregiver services, and food expenses. For example, Ahammed et al. quantified direct non-medical costs such as transportation ($87.63) and attendant costs ($168.20) [47]. This highlights that although many studies have failed to estimate direct non-medical costs, has a considerable economic impact.

Hospitalization costs emerged as the largest cost driver for hypoglycemia, accounting for up to 50% of the total cost [25]. Seven studies [10, 24, 25, 30, 44, 47, 48] reported both direct and indirect episodic costs, ranging from $1.90 to $4942.41 and $3.46 to $3,339.34, respectively. This indirect cost was estimated using the human capital approach, in productivity losses, including patient and caregiver workdays lost, duration of work

Table 1 Overall characteristics of included study on COI of diabetes-related hypoglycemia($n=29$)

First author	Publication year	Country	Income level	DM type	Study design	Target population	Sample size	Hypoglycemia severity	Study perspective
Jönsson [24]	2006	Sweden	High	Type 2	Cross sectional	All age group	26,942	Both sever and non-sever	Health system
J.Reviriego [25]	2008	Spain	High	Type 1	Retrospective	16–61 years of age	100	NR	Societal
Bron [26]	2012	USA	High	Type 2	Retrospective	> 18 years	212 061	NR	Health system
Geelhoed-Duijvestijn [27]	2013	7 European countries	High	Both type 1 & type 2	Cross sectional	> 15 years	3827	Non severe	NC
Kim [28]	2016	Korea	High	Type 2	Retrospective	NR	90	NR	Health system
Veronese [29]	2016	Italy	High	NR	Retrospective cross sectional	All age	3516	All are severe	Health system
M. Jakubczy [30]	2016	9 European countries	High	Both type 1 & type 2	Cross sectional	Include all age groups	67,695-3,293,794	All are severe	Societal
Rhee [31]	2016	Korea	High	Type 2	Prospective cohort	Include all age group	4350	NR	Societal
Raju [32]	2016	USA	High	Type 2	Retrospective cohort	≥ 18 years	11,536	NR	Health system
Giorda [10]	2017	Italy	High	Both type 1 & type 2	Retrospective cohort	≥ 18 years	2229(206 T1 & 2023 T2)	NR	Societal
Alemayehu [33]	2017	USA	High	Type 2	Retrospective cohort	≥ 18 years	5687	NR	health system
Parekh [34]	2017	Spain	High	Both type 1 & type 2	Cross sectional	NR	630	Both severe & non-severe	Health system
Liu [35]	2018	USA	High	Type 2	NR	Adult	148,055	Severe	Health system
Liu [36]	2018	USA	High	Type 1	Cross sectional	≥ 18 years	8734	Both severe & non-severe	Health system
Pawaskar [11]	2018	USA	High	Type 2	Cross sectional	≥ 18 years	3,630(1729 non-severe & 172 severe	Both severe and non-severe	Societal
de Groot [37]	2018	Netherlands	High	Both type 1 & type 2	Retrospective cross-sectional & prospective observational	All age groups	633(142 T1DM & 491 T2DM	Include severe and non-severe	Societal
O'Reilly [38]	2018	Canada	High	Both type 1 & type 2	Both prospective & retrospective	≥ 18 years of age	498(T1:183, T2:315)	NR	Societal
Parekh [39]	2018	Italy	High	Both type 1& type 2	Cross sectional	Adults	NR	Both severe and non-severe	Health system
Ikeda [40]	2019	Japan	High	Type 2	Retrospective	Adult	1,228	All are severe	Health
Wong [41]	2019	Hong Kong	High	Both type 1 & type 2	Retrospective cohort	All adults	22,694(1:1 ratio)	All are severe	Heath system
Strizek [42]	2019	Tiwan	High	Type 2	Nested case-control	≥ 18 years of age	144 213	Both severe and non-severe	Health system
Aljunid [43]	2019	Malysia	Upper middle	Type 2	Cross sectional	20–79 years of age	302	Both severe and non-severe	Health system
Ferreira [44]	2020	Portugal	High	Both type 1 & type 2	Cross sectional	28–98 years of age	176(86.4% type 2)	NR	Societal
Naser [45]	2020	Jordan	Lower middle	Both type 1 & type 2	Cross sectional	All age groups included	126(86.5% of them are T2DM)	Include severe and non-severe	Health system
Yue [46]	2020	China	Upper middle	Type 2 & type 1	Retrospective cohort	Adult	14 044	Both severe & non-severe	Health system

Table 1 (continued)

First author	Publication year	Country	Income level	DM type	Study design	Target population	Sample size	Hypoglycemia severity	Study perspective
Ahammed [47]	2022	Bangladeshi	Lower middle	Type 2	Cross sectional	≥ 18 years	164	All are severe	Societal
Tzogiou [48]	2023	Switzerland	High	Both type 1 & type 2	Cross sectional	≥ 18 years	NR	Both severe & non-severe	Societal
Rojas-Henao [49]	2024	Colombia	Upper middle	Both type 1 & type 2	Retrospective cross-sectional	≥ 18 years of age	101	All are severe	Health system
Naser [50]	2025	Saudi Arabia	High	Both type 1 & type 2	Cross sectional	All age groups	396(92.9% T2DM)	NR	Health system

T1 and T2 DM: type 1 and type 2 diabetes mellitus, NC: not clear, USA: United States of America

absence, monthly wages, and rates of absenteeism [10, 24, 25, 44, 47, 48]. The proportion of indirect costs varied across countries, ranging from 6.01% of the total cost in North Macedonia to 26.49% in Hungary [30]. Although many studies failed to estimate the indirect cost, a study showed that a significant contribution to the economic burden. For example, a Dutch study reported that productivity loss accounted for 72% of total costs in T1DM and 98% in T2DM [37] primarily due to sick leave, late arrivals, and early departures from work.

Of the 13 studies (44.8%) reporting annual costs, only three included indirect costs, with annual direct costs ranging from $2,101 to $25,093 and indirect costs from $864 to $16,130. Monthly costs were rarely reported ($17.40–$4,213.90, Table 3), likely because hypoglycemia is an acute, unpredictable event rather than a consistent monthly expense. Although all studies addressed the economic impact of hypoglycemia on healthcare use, only 12 reported annual national costs [10, 24, 25, 34–37, 39, 40, 42, 43, 48]. Annual national costs of hypoglycemia varied widely, from $7.85 million in Sweden [24] to $3.03 billion in the United States [35], with Malaysia [43] reporting to 0.5% of the Ministry of Health's budget and the Netherlands, showing productivity losses of $220.9 million (40.5% of total costs) [37]. This indicates the substantial economic burden at both the patient and national levels.

Cost of hypoglycemia by diabetes type and severity

The distribution of direct and indirect costs varied by diabetes type and the severity of hypoglycemic events. Twenty-four studies reported costs stratified by disease type or severity. Of these, 11 studies (45.8%) focused on type 1 diabetes, while 21 studies (87.5%) estimated costs associated with T2DM. Additionally, 8 studies (33.3%) reported costs for both types. For type T1DM, the cost per hypoglycemic event ranged from $6.20 to $2,799.81, whereas for T2DM, it ranged from $6.20 to $3,120.48 (Table 4). One study showed that in non-severe hypoglycemic events, in both T1DM and T2DM, the cost is exactly similar, which is $6.20 [37]. However, hypoglycemia-related costs were higher in T2DM than in T1DM, with indirect costs accounting for 45% in T1DM and 60% in T2DM [10].

Twelve studies (50%) quantified costs concerning severity in either type of diabetes. Specifically, 10 studies addressed severe hypoglycemia in type 1 diabetes, and 17 in type 2 diabetes. Of these, 8 studies estimated the cost of severe hypoglycemia in both T1DM and T2DM. Annual hypoglycemia costs increased with severity, ranging from $2,589–$3,814 in T1DM and $1,018–$4,495 for severe events in T2DM (Table 4). These finding highlights that the economic burden of severe hypoglycemia is substantially higher in T2DM. Similarly, Productivity losses also increased with hypoglycemia severity, with greater losses per severe episode observed in T2DM [48].

Excess costs attributable to hypoglycemia

Eight studies [25, 26, 28, 31, 33, 41, 42, 46] estimated the excess costs attributed to hypoglycemia either per year or per event, regardless of the types of disease and severity. The estimated additional cost ranged from $511.91 to $928.46 per hypoglycemic event [25], and from $1,431.72 to $14,414.20 annually per patient [46]. Alemayehu et al. reported that annual diabetes-related medical costs were three times higher in patients with hypoglycemia than in those without ($8,869.75 vs. $3,081.99) [33]. Patients with hypoglycemia were older, had more hospital visits and longer stays, and consistently incurred higher medical costs than those without hypoglycemia ($1,838–$3,154 vs. $1,722–$1,839) [31, 46]. Similarly, U.S. studies reported higher annual medical costs for patients with hypoglycemia ($5,426–$7,103), and per-episode costs were lower with certain medications, such as linagliptin ($2,284 vs. $3,280), suggesting treatment choice can influence the economic burden [26, 32]. These findings consistently show that hypoglycemia substantially increases both medical costs and healthcare resource use. The magnitude of these costs underscores the considerable financial impact on both patients and the broader healthcare system over time.

Table 2 Details of the type of costs, cost components, and shares(*n* = 29)

Studies	Cost types	Components of direct medical costs	DNMC components	Components of indirect costs	Costing method	Study method	% of cost reported	
							DC	IC
Jönsson, 2006 [24]	Direct medical and indirect	Emergency room visit, home visit by a physician	NA	Productivity loss	Bottom up (DC) & human capital (IC)	Incidence	41.26–88.1	11.9–58.7
Revir-iego,2008 [25]	Direct and indirect	hospitalization, diagnostic tests, services (consultation, medication administration, training)	Transportation and caregiver assistance	Productivity loss (inability to work)	Bottom up	Prevalence	65.4	35.6
Bron, 2012 [26]	Direct medical	Any inpatient, outpatient, or other medical service claims	NA	NA	Bottom up	Prevalence	100	NA
Geelhoed-Duijvestijn, 2013 [27]	Direct medical & indirect	Consultation with a professional, blood glucose test	NA	Productivity loss (work time loss)	Bottom up	Prevalence	NR	NR
Kim, 2016 [28]	Direct medical	Hospital services (laboratory and imag-ing tests and treatments, insertion, intubation, MRI)	NA	NA	Bottom up	Prevalence	NR	NA
Veronese, 2016 [29]	Direct medical	Hospitalization, ambulance, ED visit, ambulance call	NA	NA	Bottom up	Prevalence	100	NA
Jakubczyk, 2016 [30]	Direct medical & indirect	Emergency and inpatient services (medication, lab tests)	NA	Productivity loss	Bottom up	Prevalence	73.5–94	6-26.5
Rhee, 2016 [31]	Direct medical	Hospital visit and stay, medications, and outpatient services	NA	NA	Bottom up	Prevalence	100	NA
Raju, 2016 [32]	Direct medical	Drug-related/pharmacy costs	NA	NA	Bottom up	Prevalence	100	NA
Gior-da,2017 [10]	Direct medical and indirect	Hospitalization, ambulance services, physician home visit, treatments, ED visit	NA	Productivity loss (work days lost by patients or caregivers)	Bottom up	Prevalence	39.32–57.15	42.84–60.67
Alemaye-hu,2017 [33]	Direct medical	Inpatient, ED, office visit, and prescriptions	NA	NA	Bottom up	Prevalence	NR	NA
Parekh, 2017 [34]	Direct medical	Hospitalization, ED visit, blood test, medications cost, ambulance services	NA	NA	Bottom up	Prevalence	100	NA
Liu,2018 [35]	Direct medical	Costs for outpatient services, ED visits (treatment or observation), hospitaliza-tions, and medication costs	NA	NA	Bottom up	Prevalence	100	NA
Liu, 2018 [36]	Direct medical	outpatient services, ED visits (treat-ment & observation), hospitalization, medication	NA	NA	Bottom up	Prevalence	100	NA
Pawaskar, 2018 [11]	Direct medical & indirect	Hospitalization, ED visit, medication, lab test	NA	Productivity loss (absenteeism & presentism	Bottom up (DC) & human capit	Prevalence	NR	NR
de Groot, 2018 [37]	Direct & indirect	Patient services (medications, diagnostics and laboratory tests, and counseling)	Assistance from another person	Productivity loss (sick leave, arriv-ing at work late, or out of work early)	Bottom up(DC) & human capital(IC)	Prevalence	NR	72–98
O, Reilly,2018 [38]	Direct medical and indirect costs	Clinic appointments, admission stay, medications	NA	Productivity loss(absenteeism, leave from work early, late arrival at work)	Bottom up (DC) and human capital (IC)	Prevalence	NR	NR
Parekh, 2018 [39]	Direct medical	Hospitalization, blood glucose moni-toring, medication, ambulance	NA	NA	Bottom up	Prevalence	100	NA
Ikeda, 2019 [40]	Direct & indirect cost	Hospitalization, blood tests, drug costs, doctor's fees	NA	NR	Bottom up	Prevalence	74.2	25.8

Table 2 (continued)

Studies	Cost types	Components of direct medical costs	DNMC components	Components of indirect costs	Costing method	Study method	% of cost reported	
							DC	IC
Wong, 2019 [41]	Direct medical	Hospital, ED, consultation,	NA	NA	Bottom up	Prevalence	100	NA
Strizek, 2019 [42]	Direct medical	Hospital admissions, hospital days, ED visits, and medications	NA	NA	Bottom up	Prevalence	100	NA
Aljunid, 2019 [43]	Direct medical cost	Treatment cost (drug cost or services)	NA	NA	Top down	Prevalence	100	NA
Ferreira, 2020 [44]	Direct medical & indirect	Hospitalization, medication, lab test, consultation, examination, different diagnostic tests, bed occupancy, or length of hospital stay	NA	Productivity loss (patient and caregiver absenteeism)	Bottom up (DC) & human capital (IC)	Prevalence	54.39–91.69	8.3–45.6
Naser, 2020 [45]	Direct medical costs	Hospitalization and emergency services, costs of medical procedures, and medications	NA	NA	Bottom up	Prevalence	100	NA
Yue, 2020 [46]	Direct medical	Outpatient visits and inpatient visits (costs of medication use, laboratory tests, nursing care)	NA	NA	Bottom up	Prevalence	100	NA
Ahammed, 2022 [47]	Direct and indirect	Hospital, consultant, and investigation	Transport and the attendant cost	Productivity loss	Bottom up (DC) & human capital (IC)	Prevalence	47.43	52.57
Tzogiou, 2023 [48]	Direct medical & indirect	Hospitalization, outpatient services, medication, diagnostic and laboratory tests	NA	Production loss (absence from work)	Bottom up (DC) & human capital (IC)	Prevalence	79	21
Rojas-Henao, 2024 [49]	Direct medical	Consultations, medications, laboratory tests, procedures, diagnostic aids, and hospital stay	NA	NA	Bottom up	Prevalence	100	NA
Naser, 2025 [50]	Direct medical	Inpatient and emergency room services (personal services, lab tests, medications)	NA	NA	Bottom up	Prevalence	100	NA

DNMC: direct non-medical cost, ED: emergency department, IC: indirect cost, MRI: magnetic resonance imaging, NR: not reported, NA: not applicable

Cost of hypoglycemia and associated factors

In addition to the type of diabetes and severity of hypoglycemia, 7 studies [28, 29, 41, 44, 45, 49, 50] identified various determinants influencing hypoglycemia-related healthcare costs. These determinants include treatment setting (outpatient versus inpatient), duration of hospital stay, family history of diabetes, diabetes type, and older patient age [45]. Cost-driving factors included admission to the intensive care unit and a diabetes duration of more than nine years, the latter being associated with a 2.9-fold increase in hospitalization costs [50]. Healthcare resource use and costs per severe hypoglycemic event were higher among elderly patients, those with multiple comorbidities, and individuals on oral glucose-lowering therapies [29].

Patients receiving sulfonylurea-based therapies incurred higher average costs per hypoglycemic episode ($591.12) compared to those on other treatment regimens ($345.52) [49], further highlighting the financial implications associated with a specific therapeutic regimen. Direct medical costs varied by gender, age, glycemic control, and comorbidities, with higher costs observed in males ($16,289 vs. $14,987 for females) and in patients over 75 years ($17,393 vs. $11,042 for those under 55) [29]. Similarly, patients with poor glycemic control (HbA1c > 7%) or complications incurred higher costs ($16,674 vs. $15,513 $20,174 vs. $13,366, respectively) [41]. This reflects a near $7000 excess cost due to complications and $1161.30 due to uncontrolled blood glucose.

Per-person medical costs per event ranged from $22.91 to $2,461.92, depending on admission to a secondary or tertiary hospital [28]. Insulin-based therapy had the highest average cost per hypoglycemic episode ($3,397), 46% higher than secretagogues ($2,324). Costs increased to $3,283 for patients with recurrent hypoglycemia and $3,160 for those recovering with complications [44]. This variation likely reflects differences in resource use, case complexity, and patient severity across settings.

Quality of included studies

The majority of included studies explained and presented results following the methods utilized by the COI study [22]. Their data presentation was generally consistent with the study objective, and the conclusions were made

Table 3 Episodic, monthly, and annual cost of diabetic related hypoglycemia($n = 29$)

Country, year	Episodic cost/ patient		Monthly cost/patient		Annual cost/patient		Cost year
	Direct cost	Indirect cost	Direct cost	Indirect cost	Direct cost	Indirect cost	
Sweden, 2006 [24]	$3770.83	$2204.56	NR	NR	NR	NR	2005
Spain, 2008 [25]	$441.69	$234.70	NR	NR	NR	NR	2005
USA, 2012 [26]	NR	NA	$2091.54	NA	$25092.76	NA	2008
7European countries, 2013 [27]	NR	NR (in monetary unit)	$17.40	NR	NR	NR	2012
Korea, 2016 [28]	$164.12-$819.62	NA	NR	NA	$4415.12	$2504.22	2013
Itali, 2016 [29]	$1968.9-24932.73	NA	NR	NA	NR	NA	2009
9European countries, 2016 [30]	$570.63	$570.63	NR	NR	NR	NR	2010
Kora, 2016 [31]	NR	NA	NR	NA	$3153.58	NA	2015
USA, 2016 [32]	$2283.64-$3279.98	NA	$366.75-$1088.03	NA	NR	NA	2018
Italy 2017 [10]	$38.95-4062.88	$27.83-3339.34	NR	NR	NR	NR	2011
USA,2017 [33]	NR	NA	NR	NA	$4148.84	NA	2015
Spain, 2017 [34]	$1.90-4572.42	NA	NR	NA	$2476.56/-3813.72	NA	2017
USA, 2018 [35]	NR	NA	$2833.32-4213.90	NA	$17394.19	NR	2015
USA, 2018 [36]	NR	NA	$387.83–758.90	NA	$11467.28	NA	2015
USA, 2018 [11]	NR	NR	NR	NR	$9157.85-20428.84	$9608.58-16129.64	2013
Netherland, 2018 [37]	$6.20-1336.84	NR	$207.57–252.50	NR	NR	NR	2016
Canada, 2018 [38]	NR	NR	NR	NR	$2100.76	$864.27	2016
Italy, 2018 [39]	$7.66-1139.59	NA	NR	NA	$1938.41-3659.97	NA	2011
Japan, 2019 [40]	$56.89-4942.41	NA	NR	NA	NR	NA	2014
Hongkong, 2019 [41]	NR	NA	NR	NA	$15547.66-15578.15	NA	2013
Tiwan,2019 [42]	NR	NA	NR	NA	$4494.86	NA	2014
Malysia, 2019 [43]	$2978.79	NA	NR	NA	NR	NA	2014
Portugal, 2020 [44]	$3745.93	$2084.59	NR	NR	NR	NR	2018
Jordan, 2020 [45]	$ 2799.81-3120.48	NR	NR	NA	NR	NA	2017
China, 2020 [46]	$190.05-3376.53	NA	NA	NA	$2766.84	NA	2015
Bangladish, 2022 [47]	$874.65	$134.81	NR	NR	NR	NR	2012
Switzerland, 2023 [48]	$146.82-986.42	$3.46	NR	NR	NR	NR	2017
Colombia, 2024 [49]	$414.75	NA	NR	NA	NR	NA	2019
Saudi Arebia, 2025 [50]	$1327.44	NA	NR	NA	NR	NA	2022

NA: not applicable, NR: not reported

in agreement with the findings presented. Most included studies (>85%) clearly stated research questions and objectives focused on hypoglycemia-related healthcare costs, and 80% described study populations well, including patients with type 1 and type 2 diabetes across diverse settings. About 75% reported study methods and costing approaches, commonly using bottom-up for direct costs and the human capital method for indirect costs. Despite these strengths, methodological limitations were common: over 58% adopted a health system perspective without justification, only 34% considered broader societal costs, and many studies had short time horizons, omitting sensitivity analyses and discounting. Around 30% inadequately detailed resource use, risking underestimation of total costs. Ethical approval (>90%) and conflict of interest declarations (80%) were generally reported. Overall, the evidence highlights substantial direct costs of hypoglycemia, underscoring the need for strengthened diabetes management to reduce severe episodes and their economic impact (Quality assessment tool.docx).

Discussion

Currently, diabetic related hypoglycemia is increasing and places a huge economic burden on the patient, society, and health system due to the cost of treatment and productivity loss [10]. This is the first systematic review that generate evidences from existing primary studies across the world. Therefore, this review contributes to the understanding of the costs of diabetes related hypoglycemia. The findings revealed that profound economic burdens at both individual and health system levels, and direct medical costs were the most frequently reported component.

Table 4 Average cost of diabetic related hypoglycemia by diabetes type and hypoglycemia severity(n = 24)

Country, year	Type 1 DM		Type 2 DM		The extra cost of hypoglycemia	National annual cost of hypoglycemia
	Severe hypoglycemia	Non-severe hypoglycemia	Severe hypoglycemia	Non-severe hypoglycemia		
Sweden, 2006 [24]	NA	NA	$5187.16/E	$666.60/E	NR	$7854288.54
Spain, 2008 [25]	$676.39/E	NA	NA	NA	$511.91/E	$42.51 million
USA, 2012 [26]	NA	NA	NR	$1017.67/Y	$11794.91/Y	NR
Korea, 2016 [28]	NA	NA	$819.62/E	$164.12/E	$2107.74/Y	NR
9 European countries, 2016 [30]	$1153.16/E	NR	$1124.29/E	NR	NR	NR
Korea, 2016 [31]	NR	NR	NR	NR	$1431.72/Y	NR
Italy, 2017 [10]	$1584.76/E	$40.04–78.10/E	$2227.01/E	$40.04–78.10/E	NR	$179624670.99
USA, 2017 [33]	NA	NA	NR	$4148.84/Y	$7407.35/Y	NR
Spain, 2017 [34]	$3813.72/Y	$2589.13/Y	$3591.62/Y	$2476.56/Y	NR	$1007.04million
USA, 2018 [35]	NA	NA	$4213.90/M	$2833.32/M	NR	$3.03 billion
USA, 2018 [36]	$758.90/M	$387.83/M	NA	NA	NR	$733.13 million
USA, 2018 [11]	NA	NA	$36558.48/Y	$18899.00/Y	NR	NR
Netherland, 2018 [37]	$659.90/E	$6.20/E	$1336.84/E	$6.20/E	NR	$ 545.74 million
Italy, 2018 [39]	$216.48/E	$7.66/E	$1139.59/E	$7.66/E	NR	$2411.38 million
Japan, 2019 [40]	NA	NA	NA	$4942.41/E	NR	$82051259.92
Hongkong, 2019 [41]	$15547.66/Y	NR	$15578.15/Y	NR	$14414.20/Y	NR
Tiwan, 2019 [42]	NA	NA	$4494.86/Y	NR	$1760.72/Y	$50.27 million
Malysia, 2019 [43]	NA	NA	$3392.62/Y	$2440.03/Y	NR	39.04 million
Portugal, 2020 [44]	NR	$2757.68/E	NR	$3072.84/E	NR	NR
Jordan, 2020 [45]	$2799.81/E	NR	$3120.48/E	NR	NR	NR
China, 2020 [46]	NR	NR	$ 7215.37 /Y	$ 1958.46 /Y	$928.46/E	NR
Bangladesh, 2022 [47]	NR	NR	$1009.46/E	NR	NR	NR
Switzerland, 2023 [48]	692.14/E	$146.82/E	$986.42/E	$146.82/E	NR	44.91 million
Sadi Arebia, 2025 [50]	NR	NR	$1327.44/E	NR	NR	NR

E: Episode/event, M: month, W: week, Y: year, NA: not applicable, NR: not recorded

This systematic review, we included 29 studies that fulfilled the predefined inclusion criteria of the current review. The findings of the review shows that the annual economic burden of diabetes related hypoglycemia is huge for both the patient and national health system the country. Thirteen studies reported that annual direct medical costs ranged from $1938.41 to $25092.76 [11, 26, 28, 31, 33–36, 38, 39, 41, 42, 46]. The highest annual cost per patient was found in the USA [26], whereas the lowest cost is estimated in Italy [39]. Although both of them are belongs to high-income countries, the difference in annual direct costs is huge, nearly 13 times in the USA. The higher annual per-patient cost in the USA is associated with higher prices, less regulation, and more complex health insurance systems [53, 54]. Whereas in Italy, the government plays a significant role in funding, regulating, and delivering healthcare, and most services are publicly accessible and universally accessible [55]. This finding is consistent with USA data, where the cost of diabetes was reported at $12,746.4 per patient [56], suggesting that even though hypoglycemia occurs intermittently, its economic burden is substantial and approaches that of overall diabetes-related costs. A similar pattern has been observed in patients with hyperglycemia, where the associated costs also approach the overall economic burden of diabetes, $17755.69 [57], underscores the importance of patient vigilance to prevent the occurrence of hypo and hyperglycemia.

The national annual diabetic related hypoglycemic cost is significant, and ranged from relatively low cost, $7.85 million in Sweden, to as high as $3.03 billion in the USA [24, 35]. This huge difference could be explained by the health system difference, the use of costly technology, the use of high-cost medication, and higher health care costs. On the contrary in the United Kingdom's direct costs associated with diabetes is $21.17 billion, over 40% for diagnosis and treatment [58]. The difference might be associated with the treatment of different types of diabetes and the need for chronic treatment compared to episodic hypoglycemic events.

In many studies annual direct medical cost per patient is estimated and is much higher compared to indirect costs [11, 28, 38]. Similarly, studies [10, 24, 25, 44, 47, 48] that include direct costs, per episode per patient, direct medical costs are greater than indirect costs. However, Jacubczyk et al. reported that an equal proportion of both direct and indirect costs [30]. This indicates that indirect costs have a substantial impact on the economic burden associated with diabetes related hypoglycemia. For example, deGroot et al. found that indirect costs of hypoglycemia represented 72% of total costs in T1DM and 98% in T2DM [37].

Eleven studies [10, 25, 29, 32, 34, 39, 40, 42, 44, 45, 47] reported breakdown of types of direct medical costs(outpatient, diagnostic test costs, medication, physician home visit, ED, consultation, ambulance services) and indirect costs. Although indirect costs were estimated and reported in many studies (Table 3), only three studies estimated components of indirect costs as sick leave, leaving work early, and arriving late [37, 38] and work day loss of patient, family, and caregiver [10]. In addition, only one study reported monetary cost in terms of attendant cost, transport, and food [47]. These underscore that a substantial number of studies lacked non-medical costs. Incorporating this cost alongside direct medical and indirect costs would probably result in a significantly higher estimate of the total cost associated with diabetes related hypoglycemia. This is consistent with previous research indicating that direct medical costs are the most frequently reported cost type [59].

Both modifiable and non-modifiable factors contribute to the estimated cost of diabetes-related hypoglycemia. The type of diabetes is a key determinant of cost, with the annual national burden of hypoglycemia being 1.7 times higher in T2DM ($126.23 million) than in T1DM ($72.95 million) [60]. This huge difference might be linked with the number of T2DM cases is greater than T1DM. Similarly, the annual per-patient cost was $3,813.72 for non-severe T1DM and $3,591.62 for T2DM-related hypoglycemia [34]. The higher cost reflects recurrent hospitalizations and prolonged stays from repeated hypoglycemia, with insulin use in T1DM further heightening risk. Beyond diabetes type, the severity of hypoglycemia remains a major cost driver. Our finding is consistent with the previous COI study in which costs increased with increasing disease severity in mental disorders [61], reflecting that on-time treatment and prevention of disease progression are crucial to mitigate excess costs.

Medication type and hospitalization further compound costs: patients with severe hypoglycemia on basal insulin incurred $8,885.21 over 2.8 days, compared to $7,475.64 over 2.6 days for those on basal–bolus insulin [35]. These findings highlight that appropriate medication choice shortens hospital stay and optimizes costs, while preventing hypoglycemia-triggering events reduces admissions. Notably, hospitalization costs are 4.4 times higher in smokers, underscoring the added economic burden of smoking. Intensive care unit admissions [50], multiple comorbidities [29], sulfonylurea treatment [49], blood glucose level, and complications [41] increases the cost of hypoglycemia, with intensive care unit stays alone raising costs 2.6-fold. In addition to patient and clinical factors, the cost of a hypoglycemic event also depends on the healthcare setting [28], with tertiary hospitals incurring higher expenses due to advanced care, branded medications, specialized services, and technology. Our findings align with previous results, showing that the cost of illness varies according to the healthcare setting [62]. This underscores the importance of early, effective treatment to prevent complications, while highlighting that costs are influenced not only by disease severity or patient factors but also by healthcare setting and care complexity.

The excess cost of diabetes-related hypoglycemia substantially increases the economic burden. For example, in the USA, annual costs are $5,426 higher per patient compared to those without hypoglycemia [26], driven by treatment, hospitalization, diagnostics, and related expenses. Our findings are consistent with previous research, showing a significant increase among patients with uncontrolled hypertension [63], reflecting that appropriate treatment is crucial to reduce costs.

Policy implications: This systematic review highlights significant gaps in the global evidence of the economic burden of diabetes-related hypoglycemia, with important policy consequences. Less than half of the studies estimated the national-level economic burden. Although hypoglycemic events incur substantial costs, only eight studies have reported on them, showing limited focus on this issue. This lack of national and comparative cost data restricts policymakers from accurately quantifying the true economic impact of hypoglycemia and developing targeted interventions to address this burden. Health systems should focus on generating country-specific cost estimates to guide diabetes care strategies and budget planning.

Moreover, only a small number of studies identified key cost-associated factors that can determine hypoglycemia-related costs. These findings underscore the need for context-specific interventions that focus on high-risk populations, such as those receiving insulin therapy or experiencing recurrent hypoglycemia. Most studies excluded direct non-medical costs and the monetary value of productivity losses, leading to a likely underestimation of the total economic burden. This highlights that including these elements greatly increases the total cost of hypoglycemia. Most importantly, all studies were conducted in high- or upper-middle-income countries, indicating an evidence gap in low-income settings where the economic consequences of hypoglycemia may be more severe. Future research should adopt broader societal perspectives and include underrepresented regions to provide a more accurate and equitable global picture. These actions are vital for guiding cost-effective diabetes policies and minimizing the preventable health and financial burdens of hypoglycemia worldwide.

Limitations
Although our review has strengths, including the synthesis of global evidence and the use of I$ to enhance data comparability, it also has several limitations. These limitations arise from the inclusion criteria, scope of the included studies, and the unavailability of research from certain settings, all of which should be considered by future researchers. Firstly, this review relied solely on published studies, excluding gray literature, which may have led to missed evidence and potential publication bias. In addition, we relied exclusively on COI studies and did not include economic evaluation studies to maintain consistency. While this approach ensured methodological uniformity across the review, it may limit comprehensiveness, as economic evaluations could have provided additional insights into cost drivers and value for money. Secondly, the limitations arise from the included studies: we only synthesize qualitatively, and we skipped a meta-analysis due to the inconsistent data presentation of our samples. We did not present a detailed breakdown of costs (e.g., medication, laboratory, hospitalization, and outpatient services) because the included studies reported these components inconsistently. Due to the lack of comprehensive data reporting since most studies did not include direct non-medical and indirect costs, this review was unable to capture the full economic burden of hypoglycemia. In addition, most studies focused only on per-event, per-patient expenditures rather than estimating the broader individual and national impact of hypoglycemia. This narrow reporting limits understanding of the cumulative economic burden and hinders policymakers from recognizing its full public health and financial implications. Thirdly and finally, a limitation arises from the unequal geographical distribution of studies, with most originating from high-income countries and only a few from middle-income settings, while low-income countries remain unrepresented. This imbalance limits the generalizability of our findings and may overlook important context-specific cost drivers in resource-constrained settings.

Conclusion
This systematic review provides synthesized evidence of economic burden of diabetes related hypoglycemia. We included 29 studies, and most of them were conducted in high income countries. Significant number of studies skipped indirect and direct non-medical costs. Diabetes-related hypoglycemia imposes substantial extra costs on patients, with most studies reporting per-event or annual costs, where direct medical costs consistently exceed indirect costs. Many modifiable or non-modifiable factors can contribute to the escalation of the estimated cost. Future researchers better to include all types of costs to show full impact of hypoglycemia. In addition, health care professionals focus health strategies on prevention of hypoglycemia and appropriate inclusion of medication for patient treatment, which can reduce hospital stay and, intern mitigate financial burden.

Abbreviations and acronyms

CCEMG	Campbell and Cochrane Economics Methods Group
COI	Cost of Illness
CPI	Consumer Price Index
DL	Deciliter
DM	Diabetes Mellitus
DNMC	Direct Non-Medical Cost
ED	Emergency Department
E	Event/Episode
IDF	International Diabetic Federation
I$	International Dollar
IMF	International Monetary Fund
MRI	Magnetic Resonance Imaging
M	Month
NA	Not Applicable
NC	Not Clear
NR	Not Reported
PPP	Purchasing Power Party
PRISMA	Preferred Reporting Items Systematic Review and Meta-Analysis
T2DM	Type 2 Diabetes Mellitus
T1DM	Type 1 Diabetes Mellitus
TIAB	Title and Abstract
USA	United States of America
UC	Unclear
Y	Year

Supplementary Information
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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions
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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval
Ethical approval was not required, as this study is a systematic review of online literature and no need for direct patient interaction or manipulation.

Consent for publication
The Authors arrived at a common consensus to submit this manuscript to the journal for publication in the current version.

Competing interests
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