REVIEW

The association of hypoglycemia with stroke risk: A systematic review and meta-analysis

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ABSTRACT

Background and aim: The prevalence of stroke continues to increase worldwide, and optimal glucose control remains an important component of acute stroke management. However, the occurrence of hypoglycemia in patients with stroke, particularly hypoglycemia-induced stroke mimics, and its association with mortality remain controversial. This study was conducted to evaluate the occurrence of hypoglycemia in stroke patients, and to assess its association with mortality.

Methods: This systematic review and meta-analysis followed PRISMA guidelines and was registered in PROSPERO (CRD420261306540). PubMed, Scopus, ScienceDirect, Taylor and Francis, ProQuest, EBSCO, and Springer were searched for English-language observational studies involving adults.

Results: A total of 11 studies with 2,024,725 participants were involved. Hypoglycemia was significantly correlated with an increased risk of stroke, with a relative risk (RR) of 1.73 (95% confidence interval [CI]: 1.35–2.22; 95% prediction interval [PI]: 0.81–3.69; p < 0.01). Inter-subgroup analysis showed that severe hypoglycemia (SH) increased the risk by twofold compared to non-severe hypoglycemia (NSH) RR 1.96 (95%CI: 1.38-2.78; p <0.01). In contrast, mild hypoglycemia did not significantly increase the risk of stroke compared to normoglycemia (RR 1.27; 95% CI: 0.79-2.05; p = 0.32). In terms of mortality, hypoglycemia increased the risk of mortality (RR 2.42; 95% CI: 1.59-3.68; p <0.01). Across the analyzed comparisons, severe hypoglycemia was generally associated with higher stroke and mortality risks (RR 2.56; 95%CI: 1.36-4.81; p <0.01).

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Conclusion: Hypoglycemia is significantly associated with increased risks of stroke and mortality, with the greatest impact observed in SH episodes, underscoring the clinical importance of preventing SH. (www.actabiomedica.it)

Key words: hypoglycemia, mortality, risk, stroke

Introduction

The global prevalence of stroke in 2021 was estimated at 93.8 million cases, with an incidence of 11.9 million new cases. Between 1990 and 2021, the incidence of stroke increased by approximately 70%, while stroke-related mortality increased by 44% (1). In stroke conditions, patients may present with either hypoglycemia or hyperglycemia. According to the American Diabetes Association (ADA), hypoglycemia is defined as a blood glucose level below 70 mg/dL and is classified into three levels: level 1 hypoglycemia (glucose <70 mg/dL and ≥54 mg/dL), level 2 hypoglycemia (glucose <54 mg/dL), and level 3 hypoglycemia, which refers to severe events characterized by altered mental and/or physical status requiring assistance from another person, regardless of glucose value (2).

In the current guidelines, glucose control is one of the steps needed to maintain in acute stroke (3). However, the glucose could also initially begin a stroke condition (4). In preclinical studies, hypoglycemia leads to brain damage in the cortex and hippocampus due to cerebral hypoperfusion (4,5), whereas hyperglycemia exacerbates brain injury during stroke occurrence (6). Despite the limited evidence supporting an association between hypoglycemia and stroke, most available data come from case reports and preclinical studies.

Although hypoglycemia is well recognized to cause acute brain injury, evidence regarding its potential contribution to stroke remains limited. In particular, the relationship between stroke risk and hypoglycemia severity and mortality outcomes following hypoglycemia-related stroke has not been clearly established. Moreover, hypoglycemia can present with focal neurological deficits that mimic acute stroke and may resolve after correction of blood glucose, further complicating clinical recognition and interpretation (7).

Previous studies have shown inconsistent results regarding the relationship between hypoglycemia and stroke. Some studies reported a significant association between the two conditions (8), while others found no evidence of such a relationship (9). The primary aim of this meta-analysis was to examine the association between hypoglycemia and stroke risk. To the best of our knowledge, this is the first meta-analysis to evaluate the stroke risk among individuals with hypoglycemia versus comparator. The secondary aim was to assess stroke risk according to ADA-defined hypoglycemia severity levels and to evaluate mortality outcomes among individuals experiencing hypoglycemia-related stroke.

Methods

This review protocol has passed external peer review. It has been officially registered with the International Prospective Registration of Systematic Reviews (PROSPERO), maintained by the National Institute for Health and Care Excellence (NICE), under registration number CRD420261306540, further emphasising our compliance with international standards for systematic review protocols. No amendments were made to the protocol after registration.

Search strategy

The systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (10).

A comprehensive literature search of relevant studies was conducted across six electronic databases: PubMed, Scopus, ScienceDirect, Taylor and Francis, EBSCO, and Springer. The search strategy utilized the MESH terms with truncation where appropriate, and the following keywords and their combinations: "diabetes mellitus", "hypoglycemia", "low blood glucose", "severe hypoglycemia", "level 3 hypoglycemia", "type 2 diabetes", "type 1 diabetes", "T1DM", "T2DM", "stroke", "ischemic stroke", "hemorrhagic stroke", "cerebrovascular accident", "CVA", "transient ischemic attack", and "TIA". The last seach of all databases was conducted on 17th February 2026.

Supplementary Table S1 presents the detailed search approach for every database. The search was limited to peer-reviewed articles published in English. Furthermore, a thorough review was conducted for other pertinent papers in the reference lists of the included research. The search was conducted independently by four investigators (VB, YYPT, LTM, and FMH).

Eligibility criteria

The PECOS principles were adhered to in the inclusion criteria as follows: P (Participants): Adults (≥18 years) in any clinical or community setting with or without diabetes mellitus (T1DM or T2DM); (2) E (Exposures): Hypoglycemia classified according to American Diabetes Association (ADA); (3) C (control): No episodes of hypoglycemia (referent) or lower frequency categories; (4) O (Outcomes): There were two outcomes, primary and secondary. The primary outcome was to assess the risk of stroke in patients with hypoglycemia. The secondary outcome was to assess the mortality of patients with hypoglycemia; (5) S (Study Design): Observational study. The exclusion criteria were: (1) the full text was unavailable; (2) non-English language literature; (3) incomplete data or inability to convert and apply raw data; and (4) conference abstracts, systematic reviews, case reports, and narrative syntheses.

Study selection and screening process

The articles identified through the six databases were imported to Rayyan QCRI after deduplication for screening the study titles and abstracts in relation to the inclusion and exclusion criteria. Two investigators (VB and YYPT) independently screened the full texts. Any disagreements between the two reviewers were resolved through discussion.

Data extraction

The extracted data from the studies of interest included the first author, DOI, publication year, country in which the study was conducted, study design, age of participants, gender distribution, comorbidities, number of stroke incidents, and number of deaths.

Risk of bias assessment

Risk of bias was assessed using the ROBINS-E tool by two reviewers (VB and YYTP), which evaluates seven domains, including bias due to confounding, participant selection, exposure classification, deviations from intended exposures, missing data, outcome measurement, and selective reporting of results. Disagreements were resolved through discussion without the need for a third reviewer.

Statistical analysis

Data synthesis was performed using Review Manager 5.4 (Cochrane Collaboration, UK) and R software (metafor package) to integrate evidence from eligible studies. Risk ratios (RRs) with corresponding 95% confidence intervals (CIs) were used to estimate the association between hypoglycemia and stroke risk (primary outcome) and mortality and hospitalization rates (secondary outcomes). Statistical heterogeneity was assessed using the I^2 statistic, with values≥ 50% indicating significant heterogeneity. The prediction interval was calculated using a random-effects meta-analysis to assess the expected range of effects, specifically heterogeneity across studies. The exploratory meta-regression analyses were conducted to evaluate the influence of study-level mean age on the association between hypoglycemia and stroke risk. Subsection evaluation using meta-regression is exploratory and not intended to provide causative conclusions. Accordingly, a random-effects model was used to estimate the stroke risk ratio to account for between-study heterogeneity. Formal sensitivity analyses (e.g.,

leave-one-out analysis) were not performed because the number of included studies in several pooled outcomes was too limited to support meaningful robustness testing.

Results

Study selection and identification

The literature search across six databases identified 3,174 records. After removal of duplicates (n = 48), 3,126 records were screened. Of these, 3,115 studies were excluded for failing to meet the eligibility criteria. Finally, 11 studies were included in the systematic review and meta-analysis (Figure 1).

Risk of bias analysis

The risk of bias assessment across the seven ROBINS-E domains is summarized in two plots (Figure 2). Overall, most included studies were judged to have a moderate risk of bias across several domains, particularly bias due to confounding (D1) and bias in participant selection (D3). This likely reflects inherent limitations of registry-based observational studies, including incomplete reporting of disease severity, comorbidities, methodological details, and relevant clinical characteristics.

Several studies, were assessed as having an increased risk of bias in D3 because hypoglycemia episodes were identified through retrospective self-report, which could introduce recall bias (11). Likewise, mild hypoglycemia

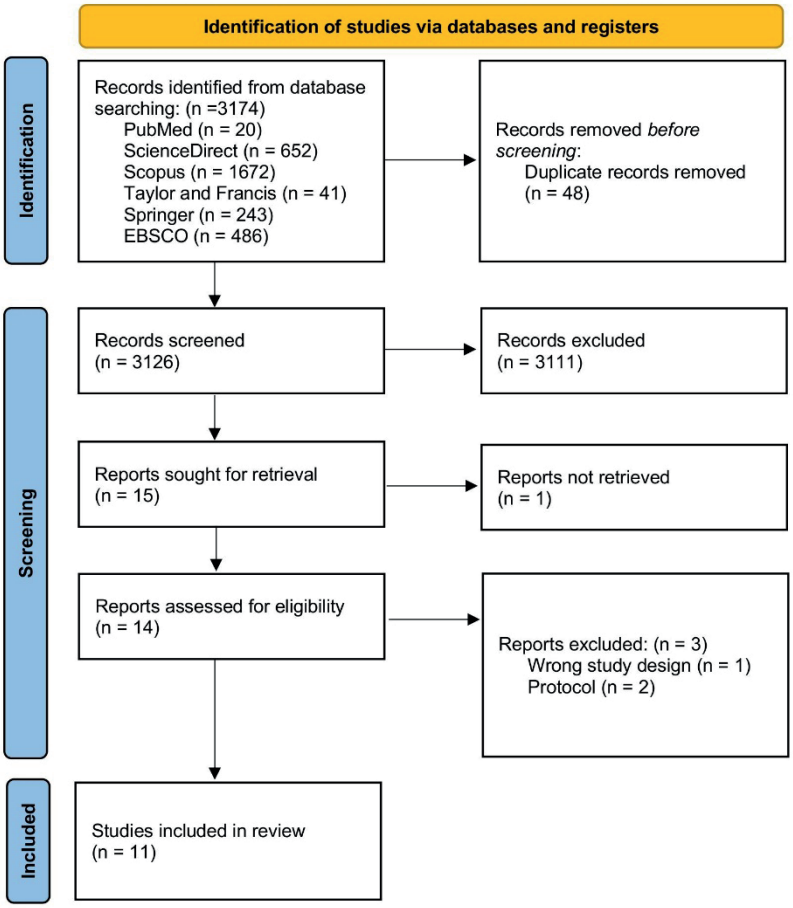

Figure 1. PRISMA flow diagram of the study-selection process.

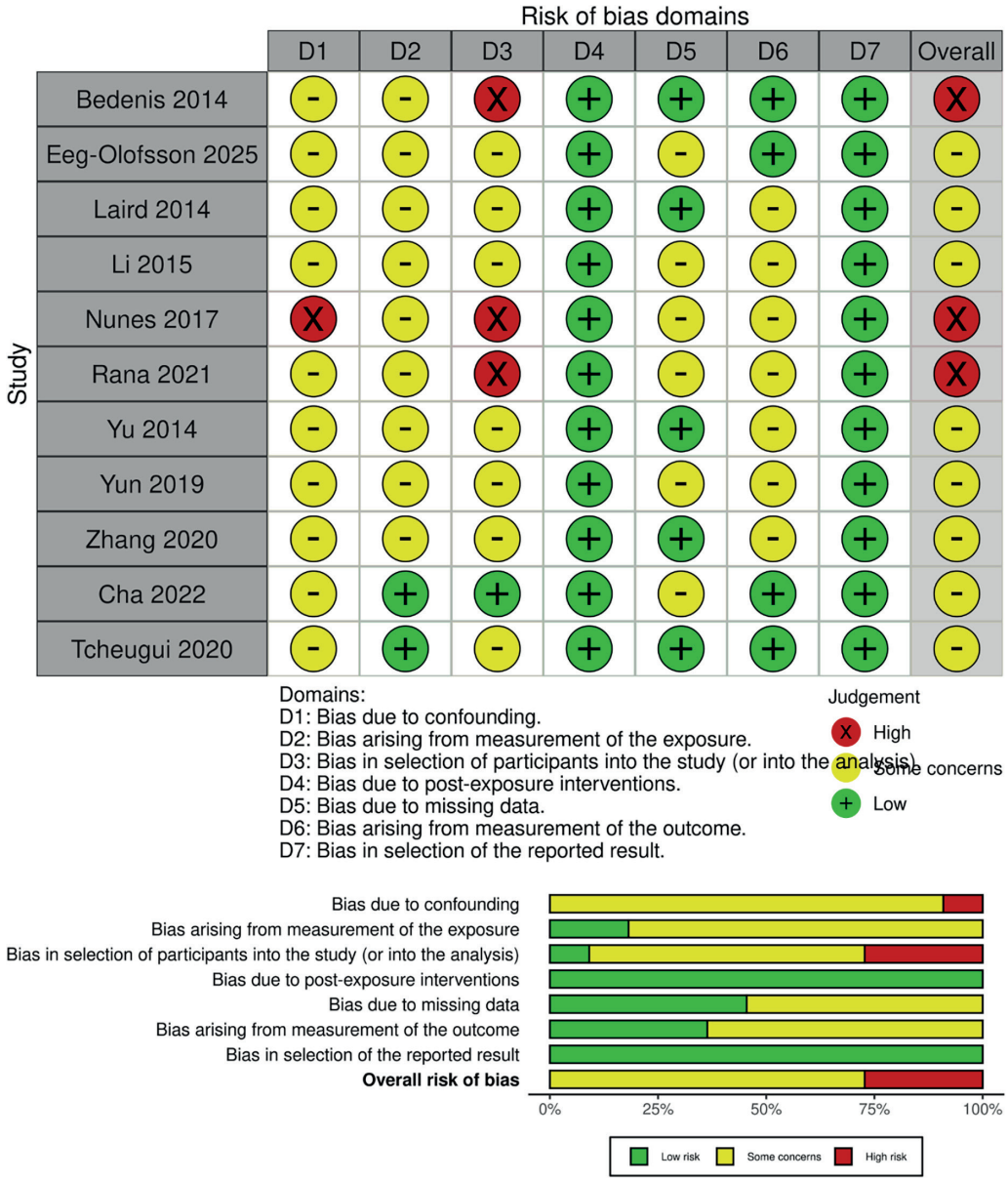

Figure 2. Risk of Bias Analysis using ROBINS-E. A) Traffic Light Plot; B) Summary Plot.

events may have been underestimated, as only cases requiring emergency care or hospitalization were recorded (12). The highest overall risk of bias was observed due to limited adjustment for confounding factors and reliance on electronic medical records to identify hypoglycemia episodes, which may have increased the likelihood of exposure misclassification (13).

The summary plot strengthens these findings by showing that the largest proportion of studies falls into the moderate-risk-of-bias category across most domains. In contrast, only a small proportion shows a serious risk of bias in certain domains. No studies were found to have a very high risk of bias due to fundamental methodological issues that could affect the results. Therefore, despite variations in bias risk across studies, the synthesis results should be interpreted with caution, given the potential for residual confounding and limitations in exposure measurement.

Summary of included studies

The data tabulation for this study comprises eleven observational studies with a total population of 2,024,725 participants. The diversity of the population in the study spans several countries in Asia, Europe, and the United States, with varying populations and a predominance of observational studies. The mean age of participants ranged from early fifties to late seventies. The proportion of male participants varied across studies, with men generally representing approximately half of the study populations.

Across the 11 included studies (Table 1), participants commonly presented with multiple comorbidities, including dyslipidemia, hypertension (HT), type 1 and type 2 diabetes mellitus, acute myocardial infarction (AMI), chronic obstructive pulmonary disease (COPD), end-stage renal disease (ERDS), chronic kidney disease (CKD), and heart failure (HF). Additional reported conditions included chronic liver disease, liver cirrhosis, mental illness, ischemic heart disease, and coronary atherosclerosis.

The relationship between hypoglycemia and stroke

In total, 11 studies analysed the relationship between the severity of hypoglycemia and the risk of stroke. The analysis was stratified into two comparisons, including: 1) normoglycemia versus any grade of hypoglycemia (non-severe and severe grade of hypoglycemia) (Figure 3); 2) non-severe versus SH, normoglycemia versus grade 1 mild hypoglycemia (Figure 4). The first classification component involved comparing stroke outcomes in the normoglycemia versus any grade of hypoglycemia group. We found that any grade of hypoglycemia was associated with a 1.73 times higher risk of stroke (RR 1.73; 95% CI: 1.35-2.22; 95% PI: 0.81-3.69; $p < 0.01$). Prediction intervals were specifically reported for the primary pooled analysis to reflect inter-study variability. They were not emphasized for the smaller subgroup analyses due to the limited number of studies.

The relationship between hypoglycemia and stroke

Six studies evaluated the relationship between non-severe hypoglycemia and SH, showing an almost 2-fold increase in stroke risk compared to the non-severe hypoglycemia group RR 1.96 (95% CI: 1.38-2.78; $p< 0.01$) (Figure. 4). The other three studies analyzed the effect of normoglycemia on grade 1 hypoglycemia (mild hypoglycemia), and found no significant association with an increased risk of stroke compared with normoglycemia (RR 1.27; 95% CI: 0.79-2.05; $p = 0.32$). Overall, the results indicate that episodes of SH primarily drive the increased risk of stroke, whereas mild hypoglycemia does not appear to confer a significant increase in risk compared to normoglycemia. The evaluation of these subgroups provided estimates that hypoglycemia conditions were associated with an increased risk of stroke RR 1.72 (95% CI: 1.18-2.49; $p < 0.01$). Inter-subgroup differences were consistent, with no significant differences between groups ($p = 0.16$).

The interesting thing to note is that when combining data on any hypoglycemia condition with normoglycemia, we did not find any significant differences in the inter-subgroup analysis. Indirect evaluation of the three subgroups showed a consistent high risk of stroke in the hypoglycemia group (non-severe and severe grade of hypoglycemia) RR 1.69 (95% CI: 1.40-2.05; $p < 0.01$), with inter-subgroup differences being aligned and consistent, with no significant differences ($p = 0.36$). However, given the conceptual differences across the analyzed comparative subgroups, including variations in exposure definitions and comparative frameworks, direct comparisons of estimates are limited.

Stratification of hypoglycemia-related mortality risk

Five studies evaluated the risk of mortality in cases of hypoglycemia. The evaluations were classified into two groups: 1) non-severe hypoglycemia versus SH, normoglycemia versus grade 1 hypoglycemia; 2) normoglycemia versus any grade of hypoglycemia (non-severe and severe grade of hypoglycemia) (Figure 5). Two studies evaluated the effect of non-severe hypoglycemia compared to severe hypoglycemia

Table 1. Sociodemographic characteristics of the included studies.

No.	First Author, year	Country	Study Design	Age (years)	Gender (male participant quantity)	Comorbidities
1	Bedenis, 2014	Scotland	Prospective Cohort	C: 67.9±4.2 E: 68.0±4.5	C: 515/979 E: 32/87	Dyslipidemia, diabetes
2	Cha, 2022	South Korea	Retrospective Cohort	C: 73.2 ± 11.3 E: 72.6 ± 13.7	C: 147/318 E: 41/79	T2DM C: 318/318 E: 79/79 HT C: 239/318 E: 62/79 Previous HF C: 58/318 E: 20/79 CKD C: 166/318 E: 54/79
3	Eeg-Olofsson, 2025	Swedish	Retrospective Cohort	C: 52.79 ±18.52 E: 54.29 ±18.66	C: 7,896/13,516 E: 759/1313	All patients have T1DM
4	Laird, 2014	Northern Ireland	Retrospective Cohort	C, 73 ± 13 E: :79 ± 17	C: 48/ 101 E: 3/ 11	Hypertension, dyslipidemia, diabetes
5	Li, 2015	China	Case Control	C: 55.5 E: 61.5	C: 158/304 E: 50/80	Diabetes C: 221,267 /231,517 E: 1,872/2,179 Hypertension C: 199,758/231,517 E: 2,028/2,179 Hyperlipidemia C: 54,681/231,517 E: 392/2,179
6	Nunes, 2017	USA	Retrospective Cohort	C: 52.79 ±18.52 E: 54.29 ±18.66	C: 67,531/131,449 E: 6,225/12,186	Hypertension: C: 858,893/1,548,437 E: 13,426/18,535 Dyslipidemia C: 586,718/1,548,437 E: 6,577/18,535 ESRD C: 862/1,548,437 E: 100/18,535 Liver cirrhosis C: 3,984/1,548,437 E: 88/18,535 COPD C: 51,244/1,548,437 E: 882/18,535 Malignancy C: 16,738/1,548,437 E: 383/18,535

Table 1 (*Continued*)

No.	First Author, year	Country	Study Design	Age (years)	Gender (male participant quantity)	Comorbidities
7	Rana, 2021	USA	Retrospective Cohort	C: 63.57 E: 67.84	C: 121.344/ 231,517 E: 1.154/2,179	Hypertension C: 5,356/7,055 I: 1,068/1,411 Dyslipidemia C: 4,051/7,055 I: 813/1,411
8	Tcheugui, 2021	USA	Prospective Cohort	C: 75.8 E: 77.1	C: 908/2114 E: 29/79	Diabetes C: 16/101 E: 2/11
9	Yu, 2014	Taiwan	Retrospective Cohort	C: 64.8 + 14.1 E: 64.2 + 13.4	C: 1,053/2,141 E: 278/576	Ischemic Heart disease C: 30,008/131,449 E: 3,562/12,186 AMI C: 2,953/131,449 E: 460/12,186 Coronary Atherosclerosis C: 26,621/131,449 E: 3,196/12,186
10	Yun, 2019	South Korea	Retrospective Cohort	Classified	C: 847,922/1,548,437 E: 9,156/18,535	Hypertension C: 1781/2114 E: 67/79 All patients had T2DM
11	Zhang, 2020	China	Retrospective Cohort	C: 58.93 + 10.75 E: 59.15 + 12.98	C: 3682/7055 E: 751/1411	Diabetes C: 1,802/2,141 I: 491/576 Hypertension C: 1,379/2,141 I: 427/576 Hyperlipidemia C: 1,036/2,141 I: 254/576 Chronic Liver Disease C: 554/2,141 I: 137/576 Mental Illness C: 764/2,141 I: 245/576

Note: Diabetes*: the study did not specify whether diabetes mellitus was type 1 (T1DM) or type 2 (T2DM). C: control group; E: exposure group; HT: hypertension; T2DM: type 2 diabetes mellitus; T1DM: type 1 diabetes mellitus; AMI: acute myocardial infarction; COPD: chronic obstructive pulmonary disease; ESRD: end-stage renal disease; CKD: chronic kidney disease; HF: heart failure.

on mortality risk. Severe hypoglycemia indicated an increased risk of up to 2.5 times compared to non-severe hypoglycemia RR 2.56 (95% CI: 1.36-4.81; $p < 0.01$). Meanwhile, the evaluation of grade 1 hypoglycemia compared to normoglycemia showed a 2-fold increase in risk compared to normoglycemia RR 2.27 (95% CI: 1.27-4.05; $p < 0.01$). The condition of hypoglycemia was significantly associated with all-cause mortality RR 2.42 (95% CI: 1.59-3.68; $p < 0.001$). Subgroup analysis revealed an increased risk with increasing severity of hypoglycemia, with consistent results across subgroups ($p = 0.78$) (Figure 4).

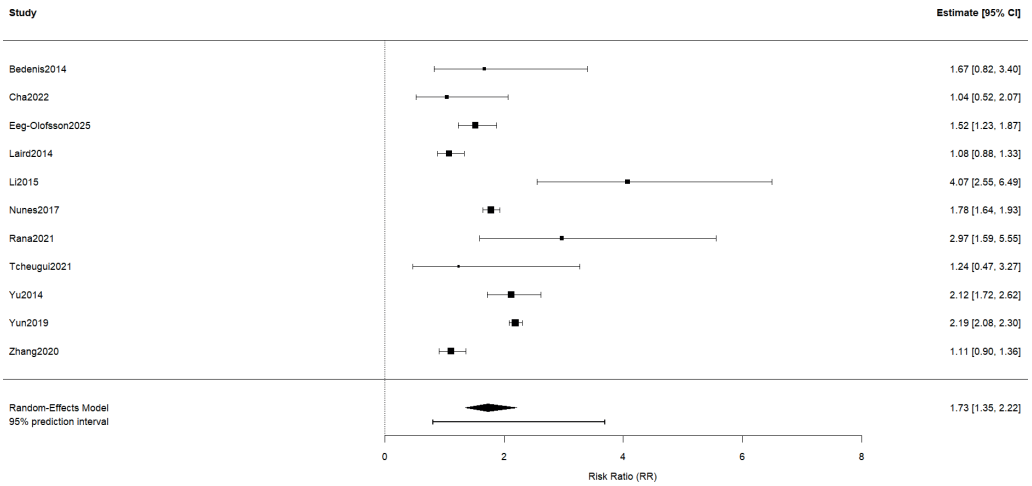

Figure 3. Forest plot of the relationship between hypoglycemia and stroke risk

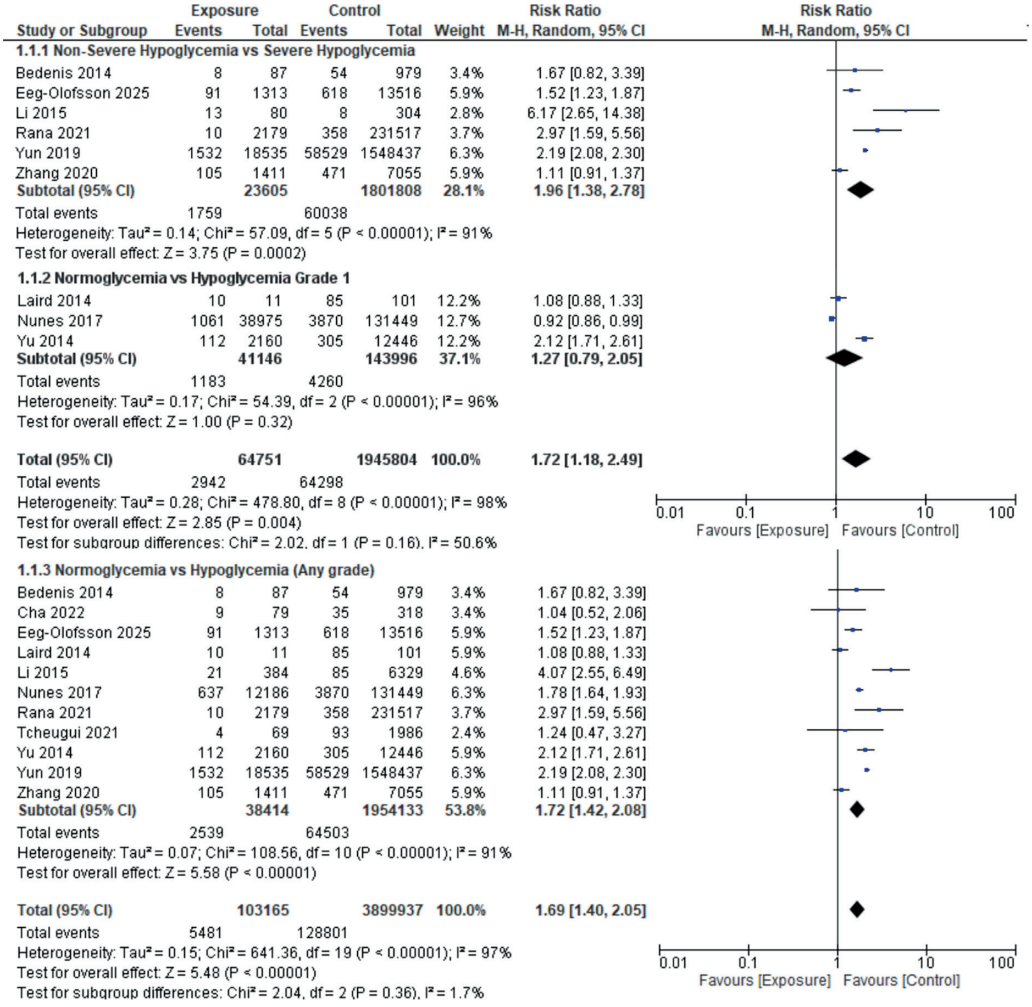

Figure 4. Forest plot of the relationship between hypoglycemia and stroke risk.

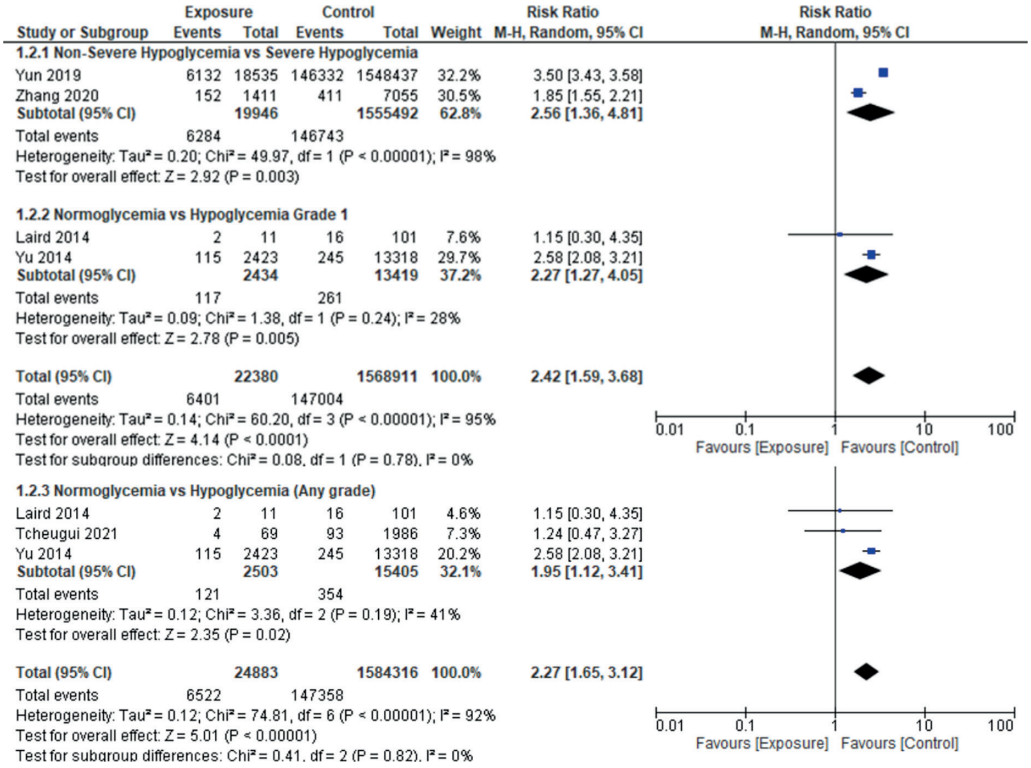

Figure 5. Forest plot of the relationship between the degree of hypoglycemia and the risk of mortality.

Second classification evaluating mortality risk in the normoglycemia group compared to any grade of hypoglycemia (NSH and SH). Three studies reported that any grade of hypoglycemia consistently increased mortality risk RR 1.95 (95% CI: 1.65-3.12; p <0.01). we found no significant differences in inter-subgroup outcomes (p = 0.82). The consistent pattern of increased mortality risk with increasing severity of hypoglycemia supports a gradient of risk, although comorbid conditions and patient vulnerability potentially confound some of this relationship.

Association between age and risk of stroke

An exploratory meta-regression was conducted to assess whether mean age at study entry modified the association between hypoglycemia and stroke risk. There was no evidence of significant effect modification by age (relative risk [RR] per 10-year increase ≈ 0.96; 95% CI: 0.59–1.56; p = 0.88) (Figure 6A), indicating that age did not significantly influence the relationship between hypoglycemia and stroke risk. Similarly, when stratified by hypoglycemia severity (Figure 6B), mean age did not significantly modify the association between hypoglycemia severity and stroke risk (RR per 10-year increase ≈ 1.44; 95% CI: 0.47–4.39; p = 0.52).

Discussion

Our study showed that hypoglycemia is associated with an increased risk of stroke and mortality, with the association effect being more pronounced in SH episodes, which may reflect both pathophysiological effects and underlying patient vulnerability. SH appeared to multiply the risk of stroke, while mild hypoglycemia (Grade 1) showed no significant association with normoglycemia. These findings confirmed that not every episode/degree of hypoglycemia has an equivalent implication for stroke risk. SH is more frequently observed and causes more serious clinical consequences than mild hypoglycemia or normoglycemia. No significant association was observed between age at the occurrence of hypoglycemia and stroke risk, even after stratification by hypoglycemia severity.

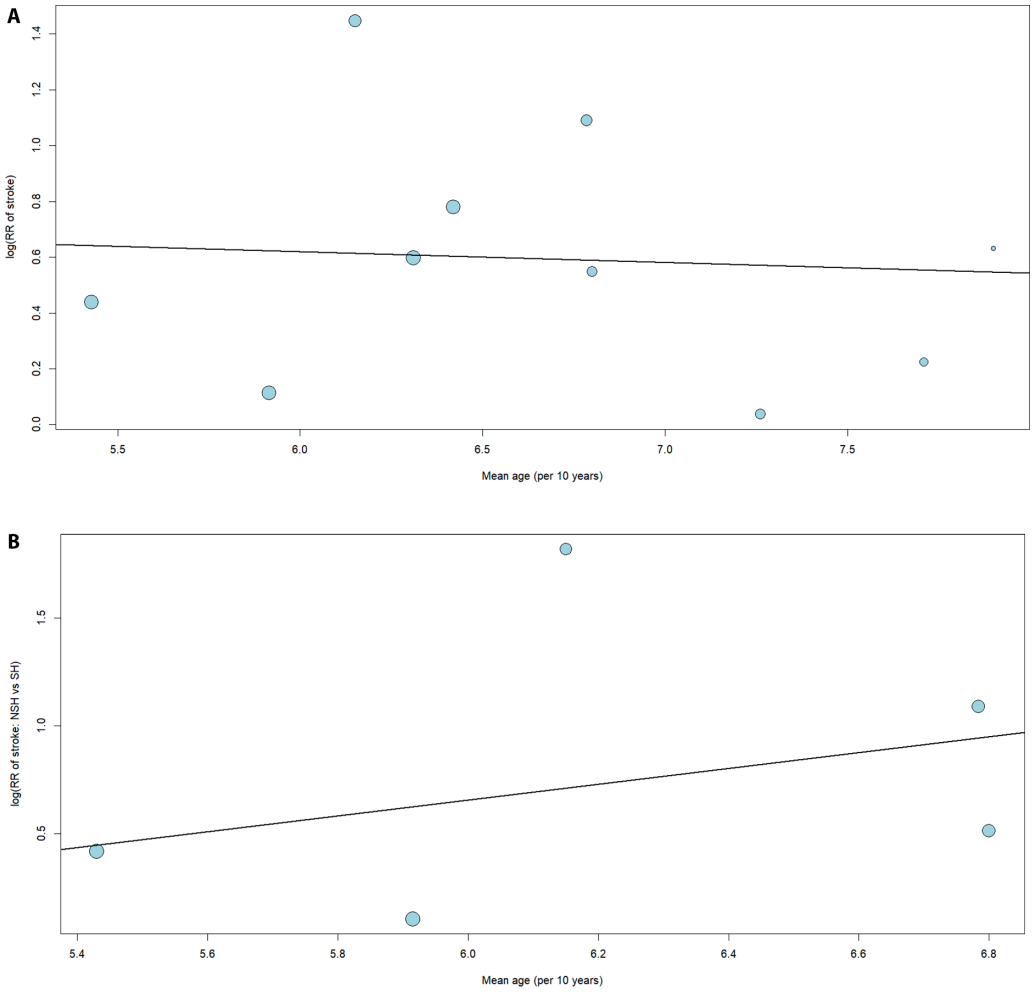

Figure 6. Association between study-level mean age and the risk of stroke related to hypoglycemia. A) Relationship between mean age (per 10-year increase) and the log risk ratio of stroke associated with hypoglycemia. B) Relationship between mean age and the log risk ratio of stroke associated with hypoglycemia severity.

In pathological terms, episodes of SH trigger a strong acute stress response and cause failure of compensatory processes, including activation of the sympathetic nervous system, a surge in catecholamines, a temporary increase in blood viscosity and pressure, peripheral vasoconstriction, and increased platelet aggregation and coagulation activation (14). This set of responses has the potential to induce a pro-thrombotic and pro-ischaemic environment, thereby potentially inducing stroke, particularly in individuals with a history of vascular vulnerability (15). In contrast, mild hypoglycemia tends to stimulate a more stable physiological compensatory response, particularly in patients with repeated exposure. The neuroendocrine adaptation may lower the threshold for sympathetic stimulation and dampen extreme hemodynamic fluctuations (15), which may explain the absence of a significant increase in stroke risk in the mild hypoglycemia group in this meta-analysis.

Disparities in acute and chronic responses to hypoglycemia remain crucial for proper interpretation of findings. SH generally occurs with an acute onset due

to counter-regulatory failure, particularly in populations with severe comorbidities, chronic diabetes, and even hypoglycemic coma (16). Therefore, this condition has the potential of provoking systemic instability, including arrhythmia, central nervous system perfusion disequilibrium, and organ failure, thus reflecting findings of increased mortality risk in parallel with the degree of hypoglycemia and may function not limited as a contributing factor but also as a marker of underlying vulnerability and disease severity (17). Recurrent mild hypoglycemia can trigger physiological adaptations and alterations in thresholds, thereby potentially progressing to hypoglycemia-associated autonomic failure, further increasing the risk of hypoglycemia recurrence and even escalating to SH. Therefore, mild hypoglycemia is clinically relevant as a continuous spectrum (18).

The clinical issue identified in this study concerns the role of hypoglycemia as a predictor of patient vulnerability (a marker of frailty/disease severity). Since SH is frequent in elderly patients with declining multi-organ system function and structure, this may reflect a poor prognosis. Furthermore, the dominant acute onset in SH may contribute to significant vascular complications and mortality compared to mild hypoglycemia (19,20).

The parallel relationship between hypoglycemia (especially SH) and an increased risk of stroke and mortality in this study represents a spectrum of related systemic risks. Stroke, as one manifestation of cerebrovascular disorders, appears to be an acute vascular manifestation resulting from hypoglycemic stress. In contrast, mortality appears to be the terminal consequence of systemic instability and limited bodily adaptation processes (20). This means that SH might be a critical point for the transition from acute metabolic disorders to fatal clinical outcomes.

From a clinical perspective, these findings confirm that the prevention of SH should be a priority in the management of diabetes, sepsis, hormonal disorders, and other conditions, especially in patients at high risk of stroke and mortality. On the other hand, mild hypoglycemia shows no increased risk of stroke, but its pathophysiology raises clinical concerns, particularly the potential for progression to more severe episodes and failure of the body's compensatory processes (21).

In comparison with previous meta-analyses, most did not specifically evaluate stroke risk, but instead assessed overall macrovascular and microvascular outcomes, reporting an increased risk of both complications associated with hypoglycemia (22,23). Furthermore, many meta-analyses primarily focused on the effects of glucose-lowering agents on vascular outcomes rather than directly examining hypoglycemia as an independent risk factor for stroke (24).

In the present analysis, no significant association was observed between age and stroke risk. However, previous meta-analyses have demonstrated that the prevalence of stroke increases with advancing age, although these studies did not specifically evaluate glucose levels or hypoglycemia status (25). One potential explanation may relate to age-associated alterations in immune function. Older individuals exhibit immunosenescence and dysregulated inflammatory responses, which may contribute to increased susceptibility to post-stroke infections and maladaptive inflammatory cascades. These processes can lead to secondary neuronal injury through excessive or unresolved inflammation (26). Such mechanisms suggest a plausible biological pathway by which advancing age could increase stroke risk or worsen outcomes. Further research is warranted to clarify these associations and to explore the interplay between age, hypoglycemia, immune dysfunction, and stroke risk.

This study has several limitations. First, a formal assessment of publication bias using funnel plot analysis or Egger's regression test was not possible due to the limited number of included studies. Second, most included studies did not report stroke subtypes or distinguish between ischemic and hemorrhagic events, which restricted more detailed interpretation of the association between hypoglycemia and specific cerebrovascular outcomes. The formal sensitivity analysis could not be performed due to the limited number of included studies, thereby limiting the ability to comprehensively assess the robustness of the pooled estimates. Therefore, in order to supplement the interpretation of inter-study variability, 95% prediction intervals are also reported; however, these should not be regarded as a substitute for a formal sensitivity analysis. Additionally, the duration and frequency of hypoglycemia episodes were not consistently reported, limiting evaluation of potential dose–response

relationships. The included studies are observational in nature; therefore, these pooled estimates should be interpreted as indicative of an association rather than as evidence of a causal relationship. Severe hypoglycaemia may not only be a potential biological trigger of vascular instability, but also a marker of frailty, the burden of comorbidity, and disease severity. Future studies should provide clearer classification of stroke subtypes, incorporate hypoglycemia duration and severity measures, and further investigate the underlying pathophysiological mechanisms linking hypoglycemia to stroke risk.

Conclusion

Hypoglycemia is significantly associated with an increased risk of stroke and all-cause mortality. Individuals with hypoglycemia have a substantially higher risk of stroke compared with normoglycemic individuals, particularly those experiencing SH. Similarly, hypoglycemia is associated with a markedly increased risk of mortality, demonstrating a clear severity-dependent gradient. No significant association was identified between age at the occurrence of hypoglycemia and stroke risk, and further studies are needed to clarify this relationship.

Ethical approval: Not Applicable

Conflict of interests: The author(s) report no conflicts of interest in this work.

Declaration on the Use of AI: None.

Authors' contributions: VB: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing – review & editing. LTM, FMH: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. TTPT: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing. NK: Conceptualization, Investigation, Writing – review & editing.

Data availability statement: The data extracted from the included studies and materials used in this review are available from the corresponding author upon reasonable request. Prisma checklist (https://doi.org/10.6084/m9.figshare.31876630)

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Annex

Supplementary file

Table S1. Search strategy.

PubMed	("Diabetes Mellitus"[Mesh] OR diabetes OR "type 2 diabetes" OR T2DM OR T1DM) AND (hypoglycemia[Mesh] OR hypoglycemia OR "severe hypoglycemia" OR "level 3 hypoglycemia") AND (stroke[Mesh] OR stroke OR "ischemic stroke" OR "hemorrhagic stroke" OR "cerebrovascular accident" OR cerebrovascular OR CVA OR TIA)
ScienceDirect	(hypoglycemia OR low blood glucose) AND (stroke OR haemorrhagic stroke OR cerebrovascular accident)
Scopus	TITLE-ABS-KEY(diabetes OR "type 2 diabetes" OR T2DM OR T1DM) AND TITLEABS-KEY(hypoglycemia OR "severe hypoglycemia" OR "level 3 hypoglycemia") AND TITLE-ABS-KEY(stroke OR "ischemic stroke" OR "hemorrhagic stroke" OR cerebrovascular OR "cerebrovascular accident" OR TIA)
Proquest	subject(hypoglycemia OR blood glucose OR hypoglycaemic OR hypoglyc*) AND title(hypoglycemia OR blood glucose OR hypoglycaemic OR hypoglyc*) AND title(stroke OR ischemic stroke OR hemorrhagic stroke OR cerebrovascular OR CVA OR TIA OR Cardiovascular)
EBSCO	TI (hypoglycemia OR blood glucose OR hypoglycaemic OR hypoglyc*) AND TI (stroke OR ischemic stroke OR hemorrhagic stroke OR cerebrovascular OR CVA OR TIA OR Cardiovascular)