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Sulfonylureas and Fracture Risk in Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 7 May 2026 and was last updated on 7 May 2026.

INTRODUCTION

Review question / Objective To evaluate the association between sulfonylureas and fracture risk in patients with type 2 diabetes mellitus(T2DM).

Rationale This study comprehensively integrates the existing observational study evidence to achieve the following core objectives: (1) to quantitatively assess the strength of the association between sulfonylurea use and the overall risk of fractures in patients with T2DM, (2) to specifically focus on osteoporotic fractures as a severe outcome and analyse its specific risk, (3) to conduct subgroup analyses to thoroughly investigate the pattern of risk differences across different fracture sites and (4) to conduct an exploratory analysis of the associations between different sulfonylurea subtypes and fracture risk.

Condition being studied In the long-term management of T2DM, beyond traditional complications such as cardiovascular, renal and retinal diseases, skeletal system health has garnered increasing attention in recent years. Substantial evidence indicates that patients with T2DM are at high risk of osteoporosis and fractures; the risk of any fracture is increased by 26% in these patients. This increased risk stems from the complex interplay of multiple factors, including, but not limited to, the accumulation of advanced glycation end products induced by chronic hyperglycaemia impairing bone collagen quality, secondary hyperparathyroidism resulting from diabetic nephropathy and potential adverse skeletal effects of some glucose-lowering medications.

METHODS

Search strategy Adhering to the PRISMA 2020 statement, four electronic databases were systematically searched: PubMed, Web of Science, the Cochrane Library and Embase. The search period spanned from the inception of each database to 10 October 2025. The search strategy utilised keywords such as ‘Diabetes Mellitus, Type

2', 'Sulfonylurea Compounds' and 'Fractures, Bone'. The detailed search strategy is provided in the Supplementary file. Furthermore, to broaden the scope of literature included, we screened the reference lists of the included studies to identify potentially eligible publications.

Participant or population Study population consisted of patients with T2DM.

Intervention Studies reported the association between sulfonylurea drug use and the occurrence of fractures in patients.

Comparator Studies reported the association between sulfonylurea drug use and the occurrence of fractures in patients.

Study designs to be included Adhering to the PRISMA 2020 statement, four electronic databases were systematically searched: PubMed, Web of Science, the Cochrane Library and Embase. The search period spanned from the inception of each database to 10 October 2025. The search strategy utilised keywords such as 'Diabetes Mellitus, Type 2', 'Sulfonylurea Compounds' and 'Fractures, Bone'. The detailed search strategy is provided in the Supplementary file. Furthermore, to broaden the scope of literature included, we screened the reference lists of the included studies to identify potentially eligible publications.

Eligibility criteria The inclusion criteria were as follows: (1) studies published in peer-reviewed journals in Chinese or English, (2) study population consisted of patients with T2DM, (3) studies reported the association between sulfonylurea drug use and the occurrence of fractures in patients and (4) study design was an observational study.
The exclusion criteria included (1) non-human studies; (2) publication types such as conference abstracts, case reports and systematic reviews; (3) duplicate publications (the report with the most comprehensive or most recent data was included); and (4) studies for which the full text could not be obtained.

Information sources Adhering to the PRISMA 2020 statement, four electronic databases were systematically searched: PubMed, Web of Science, the Cochrane Library and Embase. The search period spanned from the inception of each database to 10 October 2025. The search strategy utilised keywords such as 'Diabetes Mellitus, Type 2', 'Sulfonylurea Compounds' and 'Fractures, Bone'. The detailed search strategy is provided in the Supplementary file. Furthermore, to broaden the scope of literature included, we screened the reference lists of the included studies to identify potentially eligible publications.

Main outcome(s) Through the systematic database search, 492 records were initially identified. After removing 111 duplicates, the titles and abstracts of the remaining 381 records were screened, leading to the exclusion of 294 records that did not meet the inclusion criteria. The full texts of the remaining 87 records were assessed for eligibility against the inclusion and exclusion criteria. Following this assessment, 75 records were excluded, primarily for the following reasons: study population not consisting of patients with T2DM (n = 7), no data provided on the association between fracture and sulfonylurea use (n = 29) and study design being a review, case report or animal experiment (n = 39). Ultimately, 12 studies were included in the systematic review and meta-analysis.
This review finally included 12 observational studies. These studies were published between 2005 and 2022, including 3 case–control studies and 9 cohort studies. The studies covered multiple countries/regions, including Europe (Denmark, Italy, Scotland), North America (USA) and Asia (Korea, Taiwan, China, Qatar), demonstrating a degree of geographical diversity. The combined sample size of the included studies covered 5,854,139 patients with T2DM. The mean age of patients ranged from 43 to 73.5 years. The proportion of male patients varied considerably across studies, ranging from 0% (an all-female population) to 100% (an all-male population). The fracture outcomes of interest were diverse, primarily including hip fracture, vertebral fracture, non-vertebral fracture and forearm fracture. All included studies reported multivariable-adjusted effect estimates. Most studies found that sulfonylurea use was associated with either an increased or neutral risk of fracture, with reported point estimates of RRs ranging from 0.61 to 2.39. Furthermore, all included studies were of medium to high quality.

Quality assessment / Risk of bias analysis The quality of observational studies was assessed using the Newcastle–Ottawa Scale. This scale evaluates studies across three domains: selection of study groups, comparability of groups and ascertainment of outcome of interest, with a total possible score of 9. Based on the final scores, studies were categorised as high quality (≥7 points), medium quality (4–6 points) or low quality (<4 points). The quality assessment was performed independently by two researchers. Any

discrepancies in ratings were resolved by consulting a third researcher to reach a consensus.

Strategy of data synthesis Two researchers independently performed the literature screening according to the inclusion and exclusion criteria. Initially, titles and abstracts were screened, followed by a full-text review of studies potentially meeting the inclusion criteria. In the event of disagreement between the two researchers, a third researcher was consulted, and consensus was reached through discussion. After completing the literature screening, two researchers independently extracted data using a standardised data extraction form. Extracted information included bibliographic details, demographic characteristics of the study population, study period and outcome events.

Subgroup analysis Statistical analyses were performed using Stata software version 16.0. The relative risk (RR) and its 95% confidence interval (CI) were used to estimate the effect size. For the meta-analysis, RRs and odds ratios (ORs) were extracted as the primary measures of association. Given that the incidence of fractures in patients with T2DM is relatively low, ORs and HRs were considered reasonable approximations of RRs under the rare-disease assumption, allowing their direct combination in the pooled analysis. Heterogeneity was assessed using the I^2 statistic and the Q-test; I^2 0.10 indicated acceptable heterogeneity, and a fixed-effects model was used for meta-analysis. Conversely, $I^2 \geq 50\%$ or a Q-test P-value ≤0.10 indicated significant heterogeneity, and a random-effects model was used.

Sensitivity analysis If substantial heterogeneity was present, subgroup analyses stratified by fracture site and sulfonylurea agent or sensitivity analyses using the leave-one-out method were conducted to explore its sources. Publication bias was assessed using Egger's and Begger's tests. Unless otherwise specified, the significance level (alpha) was set at 0.05.

Country(ies) involved China - The Eighth People's Hospital of Wuxi.

Other relevant information The studies covered multiple countries/regions, including Europe (Denmark, Italy, Scotland), North America (USA) and Asia (Korea, Taiwan, China, Qatar), demonstrating a degree of geographical diversity.

Keywords Sulfonylureas; type 2 diabetes mellitus; fracture risk; meta-analysis.

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