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ORIGINAL RESEARCH

The Role of Antidiabetic Drugs in Bone Health: Assessing the Risk of Osteoporosis Subtypes and Fractures Using Mendelian Randomization

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Introduction: Osteoporosis leads to decreased bone density and an increased risk of fractures, with diabetic patients being particularly vulnerable. This study aims to evaluate the effects of five common antidiabetic drugs—Metformin, GLP-1 receptor agonists, SGLT2 inhibitors, Insulin, and Gliclazide—on the risk of osteoporosis subtypes and fractures, using Mendelian Randomization (MR) to ensure result accuracy.

Methods: Data from multiple Genome-Wide Association Studies (GWAS) databases were employed to assess the relationships between the use of these antidiabetic drugs and osteoporosis risk. The analysis utilized Mendelian Randomization techniques to minimize confounding and reverse causation, ensuring robust results.

Results: The findings reveal that: Metformin is significantly negatively associated with osteoporosis (OR [95% CI]: 0.00936 [0.0011–0.0806], $p = 2.11\times10^{-5}$), indicating a potential bone-protective effect by reducing bone resorption and enhancing osteoblast activity through the activation of the AMPK pathway. GLP-1 receptor agonists are significantly positively associated with osteoporosis with pathological fractures (OR [95% CI]: 1.1247 [1.0043–1.2594], p = 0.0420), suggesting a potential increase in fracture risk. SGLT2 inhibitors show a weak negative association with osteoporosis (OR [95% CI]: 0.8987 [0.8092–0.9980], p = 0.0429), though the effect is minor and unstable. Gliclazide significantly increases the risk of pathological fractures (OR [95% CI]: 1.03E+08 [1.28E +02–8.32E+12], p = 0.0395), indicating a need for caution in its use among patients at high fracture risk.

Discussion: The results highlight the potential bone-protective role of Metformin, which may be suitable for patients at high fracture risk. On the other hand, the use of GLP-1 receptor agonists and Gliclazide should be carefully considered, especially in individuals with osteoporosis or at high risk of fractures. These findings emphasize the importance of personalized medication management in diabetic patients to optimize bone health.

Keywords: Mendelian randomization, osteoporosis, pathological fracture, antidiabetic drugs, metformin, GLP-1 receptor agonists, SGLT2 inhibitors, gliclazide

Introduction

Osteoporosis is a common metabolic bone disease marked by reduced bone mass and increased fracture risk.[1] It encompasses several subtypes, including postmenopausal osteoporosis, osteoporosis with pathological fractures, and pharmacological osteoporosis.[2] Osteoporosis and fractures are prevalent, particularly among postmenopausal women and the elderly.[3] Studies show that type 2 diabetes significantly increases fracture risk compared to the non-diabetic population.[4] Research suggests that diabetes impacts bone health through multiple mechanisms. Hyperglycemia may directly impair the function of osteoblasts, inhibiting their differentiation and proliferation. Additionally, the chronic inflammatory response commonly observed in patients with diabetes can exacerbate bone tissue damage.[5] Moreover, microvascular complications caused by diabetes may reduce blood supply to bone tissues, resulting in poor bone nutrition

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and an increased risk of fractures.[6] This phenomenon may be associated with various metabolic disturbances, chronic inflammation, insulin resistance, and the deposition of advanced glycation end products caused by diabetes. In the treatment of diabetes, the use of antidiabetic drugs is both common and crucial. These medications not only aid in controlling blood glucose levels but may also influence bone metabolism through different mechanisms, thereby affecting the occurrence of osteoporosis and the risk of fractures.[7] The specific causal relationship between diabetes and osteoporosis is not yet fully understood and may involve complex metabolic pathways and physiological mechanisms. The association between diabetes and bone health has become a widely discussed topic in the medical community.

Common antidiabetic drugs, such as Metformin, GLP-1 receptor agonists, SGLT2 inhibitors, insulin, and sulfonylureas (eg, Gliclazide), affect bone metabolism.[8] Clinical studies suggest their influence on bone density and fracture risk, but most are observational and susceptible to confounding and reverse causality.[9] Mendelian Randomization (MR) is a robust method for assessing the causal impact of antidiabetic drugs on osteoporosis and fracture risk.[10] This method uses genetic variants as instrumental variables, effectively reducing confounding and reverse causality, thus providing clearer causal inference. Specifically, MR relies on three key assumptions: (1) the instrumental variable must be significantly associated with the exposure (such as drug use); (2) the instrumental variable must be independent of potential confounders (such as age, sex, diabetes duration, etc).; and (3) the instrumental variable should influence the outcome only through the exposure, not through other pathways.[11] This study employs Mendelian Randomization to assess the causal effects of major antidiabetic drugs on osteoporosis and its subtypes, including osteoporosis with pathological fractures.[12] Genome-Wide Association Studies (GWAS) data were used to construct genetic instrumental variables for causal inference.[13]

Metformin, GLP-1 receptor agonists, SGLT2 inhibitors, insulin, and Gliclazide are commonly used medications for diabetes management, playing a crucial role not only in blood glucose control but also increasingly attracting attention for their potential impacts on bone health. Research suggests that Metformin may reduce bone resorption and enhance osteoblast activity by activating AMPK, thereby lowering the risk of osteoporosis, although the exact mechanism requires further investigation.[14] GLP-1 receptor agonists, in addition to improving glucose metabolism, also influence bone metabolism by potentially promoting bone formation and reducing bone resorption,[15] which may help decrease the risk of osteoporosis with pathological fractures, especially in postmenopausal women.[16] SGLT2 inhibitors may disrupt calcium and phosphorus metabolism, reducing bone density and increasing osteoporosis and fracture risk, particularly in older adults.[17] However, direct evidence linking SGLT2 inhibitors to a significant increase in fracture risk is lacking, and some fractures may be associated with an increased risk of falls.[18] Insulin may both enhance bone formation and negatively impact bone health through glucose metabolism regulation.[19] The long-term effects of Gliclazide on osteoporosis and fractures remain controversial.[20]

Osteoporosis subtypes vary in pathology and clinical presentation. Postmenopausal osteoporosis is linked to estrogen deficiency,[21] while pharmacological osteoporosis is associated with prolonged glucocorticoid use.[22] Pathological fractures, among the most severe complications, result from significant bone density loss.[23] Studying these subtypes aids in understanding their mechanisms and informs personalized treatment strategies. Observational studies linking antidiabetic drugs to bone health are prone to confounding, making causal inference challenging.[24] The causal relationship between these drugs and osteoporosis subtypes remains unclear.[25] Mendelian Randomization (MR) uses genetic variants as instrumental variables to assess causality while reducing confounding effects[26] providing a robust approach to evaluating drug effects on osteoporosis and fracture risk.

This study employs Mendelian Randomization to assess the effects of Metformin, GLP-1 receptor agonists, SGLT2 inhibitors, Insulin, and Gliclazide on osteoporosis subtypes and fractures. Using Genome-Wide Association Studies (GWAS) data, we construct genetic instrumental variables to infer causal relationships. These findings will provide evidence for optimizing osteoporosis prevention and treatment strategies in diabetic patients.

Materials And Methods

Sample Collection

This study utilized Mendelian Randomization (MR) to assess the causal effects of five commonly used antidiabetic drugs —Metformin, GLP-1 receptor agonists, SGLT2 inhibitors, Insulin, and Gliclazide—on osteoporosis and pathological

fractures. GWAS data were sourced primarily from the UK Biobank and MRC-IEU databases, comprising 462,933 individuals of European ancestry. However, we acknowledge significant variations in sample sizes across drugs due to differences in GWAS study designs and participant recruitment. Notably, Metformin has a substantially larger sample size than newer drugs like GLP-1 receptor agonists and SGLT2 inhibitors, potentially affecting statistical power and result comparability. To address this, we conducted sensitivity analyses, including sample-size-matched subset analyses and inverse variance-weighted (IVW) adjustments, as detailed in the Discussion section. Drug exposure was defined using genetic instruments rather than direct medication records, meaning our study evaluates the lifelong genetically predicted drug effects rather than real-world treatment duration or dosage. The details of sample sizes, SNP counts, and populations are summarized in Table 1. Data for Metformin were obtained from the ukb-b-14609 dataset, with a sample size of 462,933 and 9,851,867 SNPs; for GLP-1 receptor agonists, from the ebi-a-GCST005353 dataset, with a sample size of 126 and 6,463,530 SNPs; for SGLT2 inhibitors, from the ukb-d-30750_irnt dataset, containing 13,586,180 SNPs, though sample size information was not provided; for Insulin, from the ukb-b-15445 dataset, with a sample size of 462,933 and 9,851,867 SNPs; and for Gliclazide, from the ukb-a-139 dataset, with a sample size of 337,159 and 10,894,596 SNPs. All data were based on European population analyses, ensuring high data quality and reliability of the research findings (Table 1).

Selection of Instrumental Variables

In this study, we selected instrumental variables (SNPs) based on the three core assumptions of Mendelian Randomization: (1) Relevance: The selected SNPs must be significantly associated with antidiabetic drug exposure. (2) Independence: The SNPs should not be associated with potential confounders, such as age, sex, diabetes duration, or comorbidities. (3) Exclusion: The SNPs should influence osteoporosis risk only through the target drug exposure and not through alternative pathways. Notably, this study cannot differentiate between short-term and long-term users of antidiabetic drugs, as MR estimates genetically predicted lifelong exposure rather than direct medication history. Therefore, individual-level variations in medication adherence, treatment duration, and dosage remain unaccounted for. Therefore, our analysis does not differentiate between short-term and long-term insulin users or variations in insulin regimens (eg, basal vs intensive functional insulin therapy). These limitations should be considered when interpreting the results.[27] (Figure 1). To ensure the validity of the instrumental variables, we extracted SNPs related to the mechanisms of

Table 1 Data Sources of Five Antidiabetic Drugs and Five Subtypes

Trait	Dataset	Sample Size	Number of SNPs	Population
Exposure				
Metformin Treatment	ukb-b-14609	462,933	9,851,867	European
GLP-1 Receptor Agonists	ebi-a-GCST005353	126	6,463,530	European
SGLT2 Inhibitors	ukb-d-30750_irnt	NA	13,586,180	European
Insulin Treatment	ukb-b-15445	462,933	9,851,867	European
Sulfonylureas (Gliclazide)	ukb-a-139	337,159	10,894,596	European
Trait	Dataset	Sample size	Number of SNPs	Population
Outcome				
Osteoporosis	finn-b-M13_OSTEOPOROSIS	3,203 (cases), 209,575 (controls)	16,380,452	European
Postmenopausal osteoporosis with pathological fracture	finn-b-OSTPOPATFRCTURE_POSTEMENO	621 (cases), 122,861 (controls)	16,379,783	European
Osteoporosis with pathological fracture (FG)	finn-b-OSTEOPOROSIS_FRACTURE_FG	785 (cases), 172,834 (controls)	16,380,281	European
Drug-induced osteoporosis	finn-b-DRUGADVERS_OSTEOPO	124 (cases), 218,668 (controls)	16,380,466	European
Drug-induced osteoporosis with pathological fracture	finngen_R9_OSTPOPATFRACTURE	357(cases), 392066(controls)	16,380,463	European

Notes: "UKB" refers to the "UK Biobank", a large biomedical database in the United Kingdom. "EBI" refers to the "European Bioinformatics Institute", a bioinformatics research institute. "Finn" refers to the "FinnGen" project, a large-scale genomic research project in Finland. "NA" indicates missing data. "SNPs" stands for "Single Nucleotide Polymorphisms", which are single nucleotide variations in the genome. "Cases" refer to individuals who exhibit a specific disease or symptom under study, while "Controls" refer to individuals who do not exhibit the disease or symptom, serving as a comparison group.

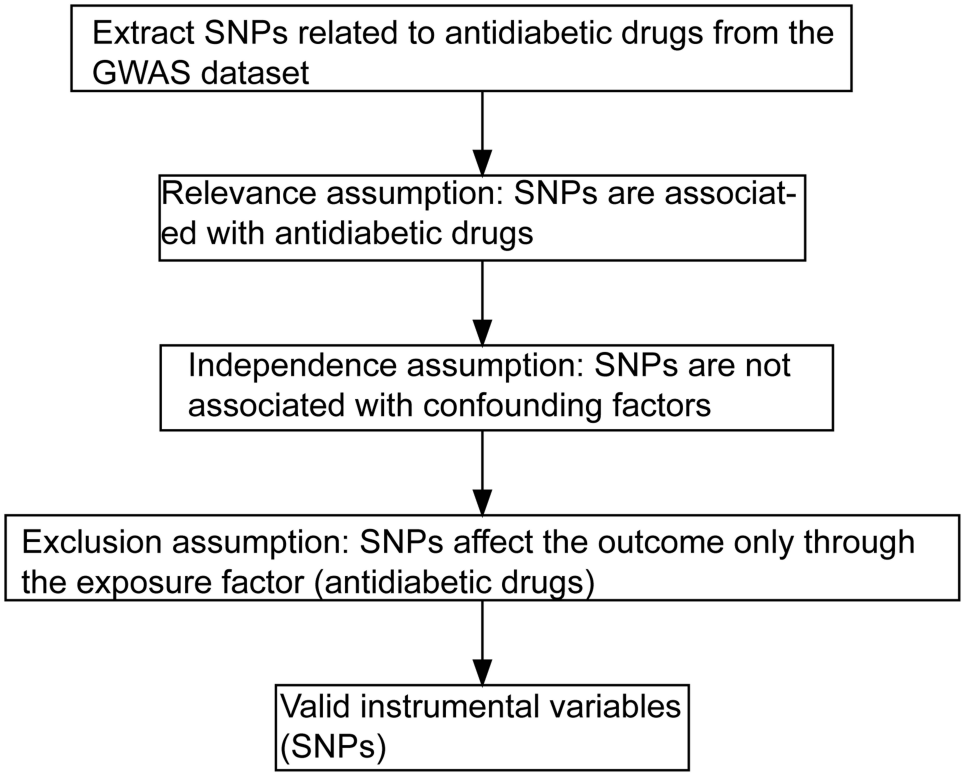

Figure 1 Mendelian Randomization Screening.
Notes: This figure illustrates the process of selecting SNPs related to antidiabetic drugs as effective instrumental variables in Mendelian randomization analysis. During the screening process, three key assumptions must be satisfied: first, the relevance assumption, which requires a significant association between SNPs and antidiabetic drugs to ensure that the selected SNPs are indeed related to the exposure factor under study; second, the independence assumption, which demands that SNPs are not influenced by potential confounding factors to maintain the independence and accuracy of the analysis; and finally, the exclusion assumption, meaning that SNPs influence the outcome solely through the antidiabetic drugs (exposure factor) and not through alternative pathways.

action of the antidiabetic drugs from the aforementioned GWAS datasets. Specifically, SNPs associated with Metformin were selected based on genes involved in the AMPK pathway[28]; SNPs for GLP-1 receptor agonists were extracted from the GLP-1 receptor gene[29]; SNPs for SGLT2 inhibitors were based on the SLC5A2 gene;[30] and SNPs for Gliclazide were selected from the sulfonylurea target genes KCNJ11 and ABCC8[31] (Table 1).

To reduce the interference of linkage disequilibrium (LD) among instrumental variables on the analysis results, we applied an LD clumping method for SNP selection.[32] We used a threshold of $r^2 < 0.001$ and a distance standard of 10,000 kb to ensure that the selected SNPs were genetically independent of each other.[33] Additionally, to confirm the validity of the instrumental variables, we calculated the F-statistic, ensuring that F values were greater than 10 to avoid the impact of weak instruments on the results.[34] This rigorous process for selecting instrumental variables ensures the robustness and reliability of the MR analysis results.

Statistical Analysis

The primary analysis method used is the inverse-variance weighted (IVW) method,[35] which provides accurate causal effect estimates under the assumption that all instrumental variables are valid. To enhance the robustness of the results, we also applied the weighted median method[36] and MR Egger regression[37] as complementary approaches. The weighted median method can yield reliable results even when some of the instrumental variables are invalid, while MR Egger regression not only estimates causal effects but also tests for the presence of pleiotropy among the instruments. If the intercept term of MR Egger regression significantly deviates from zero, it suggests potential pleiotropy issues. To address possible pleiotropy, we used the MR-PRESSO method,[38] which can detect outlier instrumental variables and correct for them, further improving result reliability. Additionally, we used Cochran's Q test[39] to examine heterogeneity among instrumental variables. If significant heterogeneity is detected, a leave-one-out sensitivity analysis is conducted by

sequentially excluding individual instrumental variables to ensure that no single SNP significantly influences the overall results.

Result

Positive Results of Antidiabetic Drugs on Osteoporosis and Its Subtypes

This study used Mendelian randomization analysis to assess the impact of five antidiabetic drugs on osteoporosis and its subtypes, revealing significant differences in the effects of different drugs on bone health. Metformin was significantly associated with reduced osteoporosis risk (OR 0.00936, p = 2.11E-05) in the IVW analysis (Table 2), supporting its protective effect on bone health (Table 2). Validation through additional methods confirmed these findings (Table 3). GLP-1 receptor agonists were associated with an increased risk of osteoporosis with pathological fractures (OR 1.12, p = 0.0420), indicating caution in high-risk populations (Table 2). SGLT2 inhibitors showed a weak negative association with osteoporosis (OR 0.90, p = 0.0429), suggesting a minor protective effect (Table 2). This finding might be related to the mechanism of SGLT2 inhibitors, which promote the maintenance of bone density by reducing renal glucose reabsorption and improving the metabolic environment. However, while a weak negative correlation was shown in the IVW analysis, the bone-protective effect of SGLT2 inhibitors did not reach statistical significance in other methods, such as the weighted median and MR Egger methods (Table 3). This suggests that the impact of SGLT2 inhibitors on osteoporosis is small and unstable, potentially influenced by other confounding factors or more complex action mechanisms. Additionally, the effect of this drug may vary among individuals, especially in patients with diabetes with comorbid bone diseases, where the relationship between metabolic regulation and bone density changes could be more complex. Gliclazide was significantly associated with an increased risk of pathological fractures (OR 1.03E+08, p = 0.0395), suggesting caution in high-risk populations (Table 2). This finding suggests that when treating diabetes with gliclazide, special attention should be given to its impact on bone health, especially in patients at high fracture risk, such as the elderly or those with a history of bone disease.

Positive Associations of Antidiabetic Drugs With Osteoporosis Subtypes and Results of Heterogeneity and Pleiotropy Tests

The study assessed the positive associations of five antidiabetic drugs with osteoporosis and its subtypes, analyzing the robustness of results through heterogeneity and pleiotropy tests. Metformin's protective effect on osteoporosis showed low heterogeneity and no significant pleiotropy, confirming the robustness of the findings (Table 4). The association between GLP-1 receptor agonists and osteoporosis with pathological fractures was significant in the IVW analysis, yet the Q test in MR Egger regression indicated near-significant heterogeneity (p-value = 0.092489) (Table 4), suggesting potential heterogeneity among instrumental variables for this association. Additionally, the intercept of the MR Egger

Table 2 Mendelian Randomization OR Data for Positive Results and Other Information

Exposure Factors	Outcome Factors	p_value	OR	CI_lower	CI_upper
Metformin Treatment	Osteoporosis	2.11E-05	0.00936	0.001087	0.080593
GLP-1 receptor agonist	Osteoporosis with pathological fracture (FG)	0.042032	1.124662	1.004239	1.259527
SGLT2 Inhibitors	Osteoporosis	0.04286	0.898653	0.810355	0.996572
Gliclazide	Osteoporosis with pathological fracture (FG)	0.039506	1.03E+08	2.425117	4.35E+15

Notes: OR represents the Odds Ratio, which is a measure of association between an exposure factor and an outcome. When OR > 1, it indicates a positive correlation, meaning the exposure factor is associated with a higher incidence of the outcome. This suggests that individuals exposed to this factor are more likely to experience the outcome compared to those who are not exposed. In contrast, when OR < 1, it indicates a negative correlation, implying that the exposure factor is associated with a lower incidence of the outcome. This may suggest a protective effect of the exposure against the outcome. When OR = 1, it indicates no association between the exposure factor and the outcome, meaning the exposure has no influence on the likelihood of the outcome occurring. The columns CI lower and CI upper represent the confidence interval (CI), which provides a range of values that likely contain the true Odds Ratio within a certain confidence level, typically 95%. The CI_upper value indicates the upper limit of the confidence interval, representing the maximum possible value of the Odds Ratio at this confidence level. Similarly, the CI_lower value represents the lower limit of the confidence interval, showing the minimum possible value of the Odds Ratio. Confidence intervals are critical for understanding the precision of the Odds Ratio estimate, with narrower intervals indicating higher precision and wider intervals indicating greater uncertainty.

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Table 3 Mendelian Randomization Data for Five Methods in Positive Results

Exposure Factors	Outcome Factors	Method	nsnp	b	se	pval	lo_ci	up_ci	or	or_lci95	or_uci95
Metformin Treatment	Osteoporosis	MR Egger	40	4.490127169	2.868404228	0.125785804	10.11219946	1.131945118	0.011219217	4.05815E-05	3.101683777
Metformin Treatment	Osteoporosis	Weighted median	40	5.352658249	1.816914311	0.00321896	8.913810298	1.791506199	0.004735546	0.000134518	0.166708884
Metformin Treatment	Osteoporosis	Inverse variance weighted	40	4.671275797	1.09843774	2.11252E-05	6.824213767	2.518337826	0.00936032	0.00108713	0.080593456
Metformin Treatment	Osteoporosis	Simple mode	40	7.910255308	3.256138614	0.019833943	14.29228699	1.528223624	0.000366961	6.20781E-07	0.216920658
Metformin Treatment	Osteoporosis	Weighted mode	40	6.430218945	2.141515685	0.004653668	10.62758969	2.232848203	0.001612098	2.4238E-05	0.107222603
GLP-1 receptor agonist	Osteoporosis with pathological fracture (FG)	method	nsnp	b	se	pval	lo_ci	up_ci	or	or_lci95	or_uci95
GLP-1 receptor agonist	Osteoporosis with pathological fracture (FG)	MR Egger	3	0.353807607	0.451335987	0.576740931	0.530810929	1.238426142	1.424481099	0.588127846	3.450179097
GLP-1 receptor agonist	Osteoporosis with pathological fracture (FG)	Weighted median	3	0.074310244	0.058726561	0.20574229	0.040793816	0.189414304	1.07714093	0.960027052	1.208541552
GLP-1 receptor agonist	Osteoporosis with pathological fracture (FG)	Inverse variance weighted	3	0.117482918	0.057782117	0.042031765	0.004229969	0.230735867	1.124662418	1.004238928	1.259526512
GLP-1 receptor agonist	Osteoporosis with pathological fracture (FG)	Simple mode	3	0.050016591	0.071335147	0.555808279	0.089800297	0.189833479	1.051288538	0.914113718	1.209048249
GLP-1 receptor agonist	Osteoporosis with pathological fracture (FG)	Weighted mode	3	0.055444784	0.072770139	0.525698908	0.087184688	0.198074255	1.057010651	0.916507812	1.219052912
SGLT2 Inhibitors	Osteoporosis	method	nsnp	b	se	pval	lo_ci	up_ci	or	or_lci95	or_uci95
SGLT2 Inhibitors	Osteoporosis	MR Egger	238	0.127053304	0.095454789	0.18446317	0.31414469	0.060038082	0.880686727	0.730413337	1.061876984
SGLT2 Inhibitors	Osteoporosis	Weighted median	238	0.112693639	0.076495755	0.140696784	0.262625318	0.037238039	0.893424328	0.769029985	1.037940062
SGLT2 Inhibitors	Osteoporosis	Inverse variance weighted	238	0.106858203	0.052767609	0.04285998	0.210282716	0.003433689	0.89865309	0.810355113	0.996572199
SGLT2 Inhibitors	Osteoporosis	Simple mode	238	0.12059513	0.190712042	0.527773337	0.494390732	0.253200471	0.88639276	0.609942413	1.288141486
SGLT2 Inhibitors	Osteoporosis	Weighted mode	238	0.157760232	0.107113199	0.142121921	0.367702102	0.052181638	0.854054533	0.692323393	1.053567093
Gliclazide	Osteoporosis with pathological fracture (FG)	method	nsnp	b	se	pval	lo_ci	up_ci	or	or_lci95	or_uci95
Gliclazide	Osteoporosis with pathological fracture (FG)	MR Egger	5	18.51028521	20.11852008	0.425393946	20.92201414	57.94258456	109,374,158.9	8.19756E-10	1.4593E+25
Gliclazide	Osteoporosis with pathological fracture (FG)	Weighted median	5	16.62105882	10.54806165	0.115084507	4.053142007	37.29525965	16,536,139.55	0.017367719	1.57444E+16
Gliclazide	Osteoporosis with pathological fracture (FG)	Inverse variance weighted	5	18.44696411	8.959736943	0.039506367	0.885879707	36.00804852	102,663,182.5	2.425116845	4.34607E+15
Gliclazide	Osteoporosis with pathological fracture (FG)	Simple mode	5	1.077522661	15.75617977	0.948759435	29.80458969	31.95963501	2.93739361	1.13771E-13	7.58391E+13
Gliclazide	Osteoporosis with pathological fracture (FG)	Weighted mode	5	17.8309797	11.65900922	0.200907135	5.020678364	40.68263777	55,449,303.13	0.006600048	4.65849E+17

Notes: nsnp: Represents the number of SNPs (Single Nucleotide Polymorphisms) used in the analysis. b: Refers to the regression coefficient (estimated value), which indicates the size and direction of the effect of the exposure factor on the outcome factor. se: Stands for Standard Error, which measures the uncertainty of the estimated value (b). A smaller standard error indicates higher accuracy of the estimate. lo_ci: Represents the lower limit of the confidence interval, showing the minimum possible value of the regression coefficient at a certain confidence level (typically 95%). up_ci: Represents the upper limit of the confidence interval, indicating the maximum possible value of the regression coefficient at the same confidence level. or: Refers to the Odds Ratio, which measures the strength of association between the exposure factor and the outcome factor. A value greater than 1 indicates a positive correlation, while a value less than 1 indicates a negative correlation. or_lci95: Represents the lower limit of the 95% confidence interval for the Odds Ratio, showing the minimum possible value of the Odds Ratio at a 95% confidence level. or_uci95: Represents the upper limit of the 95% confidence interval for the Odds Ratio, showing the maximum possible value of the Odds Ratio at the same confidence level.

Table 4 Heterogeneity Results for Positive Outcomes

Exposure Factors	Outcome Factors	Method	Q	Q_df	Q_pval
Metformin Treatment	Osteoporosis	MR Egger	35.47855	38	0.586633
Metformin Treatment	Osteoporosis	Inverse variance weighted	35.48322	39	0.631067
GLP-1 receptor agonist	Osteoporosis with pathological fracture (FG)	MR Egger	2.830502	1	0.092489
GLP-1 receptor agonist	Osteoporosis with pathological fracture (FG)	Inverse variance weighted	3.626911	2	0.16309
SGLT2 Inhibitors	Osteoporosis	MR Egger	331.4711	236	4.05E-05
SGLT2 Inhibitors	Osteoporosis	Inverse variance weighted	331.5618	237	4.79E-05
Gliclazide	Osteoporosis with pathological fracture (FG)	MR Egger	3.043883	3	0.384909
Gliclazide	Osteoporosis with pathological fracture (FG)	Inverse variance weighted	3.043896	4	0.550507

Notes: Q: This is Cochran's Q statistic, used to detect heterogeneity among multiple study results. A higher Q value indicates greater differences in results between different studies or samples. Q_df: This represents the degrees of freedom (df) for the Q statistic. In heterogeneity tests, the degrees of freedom are typically the number of samples minus one. Q_pval: This is the p-value corresponding to the Q statistic, used to determine whether the heterogeneity is significant. Generally, if p-value < 0.05, significant heterogeneity is indicated. If p-value ≥ 0.05, heterogeneity is not significant, suggesting that differences between samples can be ignored.

Table 5 Pleiotropy Test Results for Positive Outcomes

Exposure Factors	Outcome Factors	Egger_Intercept	se	pval
Metformin Treatment	Osteoporosis	−0.00057	0.00834	0.945854
GLP-1 receptor agonist	Osteoporosis with pathological fracture (FG)	−0.14916	0.281193	0.689519
SGLT2 Inhibitors	Osteoporosis	0.000734	0.002888	0.799633
Gliclazide	Osteoporosis with pathological fracture (FG)	−0.00015	0.042686	0.997411

Notes: egger_intercept: This is the intercept value from Egger regression, used to detect pleiotropy bias. If the intercept significantly deviates from zero, it suggests the presence of pleiotropy bias (ie, SNPs may affect the outcome not only through the exposure variable but also through other pathways). When the intercept value is close to zero, the likelihood of pleiotropy bias is minimal. se: This represents the standard error (SE) of the Egger intercept. The standard error reflects the precision of the intercept estimate. A smaller standard error indicates a more precise estimate.

regression did not show significant pleiotropy (p-value = 0.689519), indicating that further research is needed to confirm the impact of GLP-1 receptor agonists on fracture risk. SGLT2 inhibitors showed significant heterogeneity in the heterogeneity test (Q value = 331.5618, p-value = 4.79E-05; Table 5), suggesting considerable variability among instrumental variables, which may impact the stability of its association with osteoporosis. Although MR Egger regression indicated no significant pleiotropy (p-value = 0.799633), this heterogeneity implies potential instability in the association. Gliclazide showed a significant association with osteoporosis with pathological fractures in the IVW analysis, with no significant differences observed in both heterogeneity and pleiotropy tests, indicating that the potential impact of gliclazide on fracture risk is relatively robust. Overall, the results for metformin and gliclazide appear to be more stable, whereas the associations for GLP-1 receptor agonists and SGLT2 inhibitors show some uncertainty, suggesting that the bone health effects of these drugs in different populations require further validation.

Mendelian Visualization Analysis of Positive Associations Between Antidiabetic Drugs and Osteoporosis Subtypes

Based on Mendelian randomization visualization analysis, the study assessed and found positive associations between four antidiabetic drugs and osteoporosis as well as its subtypes. Metformin consistently exhibited a significant negative correlation effect across multiple analysis methods (eg, IVW, MR Egger, and weighted median). The scatter plot demonstrated that the effects of each SNP were concentrated on the negative side, suggesting a potential protective effect of metformin against osteoporosis (Figure 2). Sensitivity analysis using the leave-one-out method indicated that removing individual SNPs did not significantly impact the robustness of the results, further confirming the protective effect of metformin on bone health (Figure 2). GLP-1 receptor agonists showed a significant association with

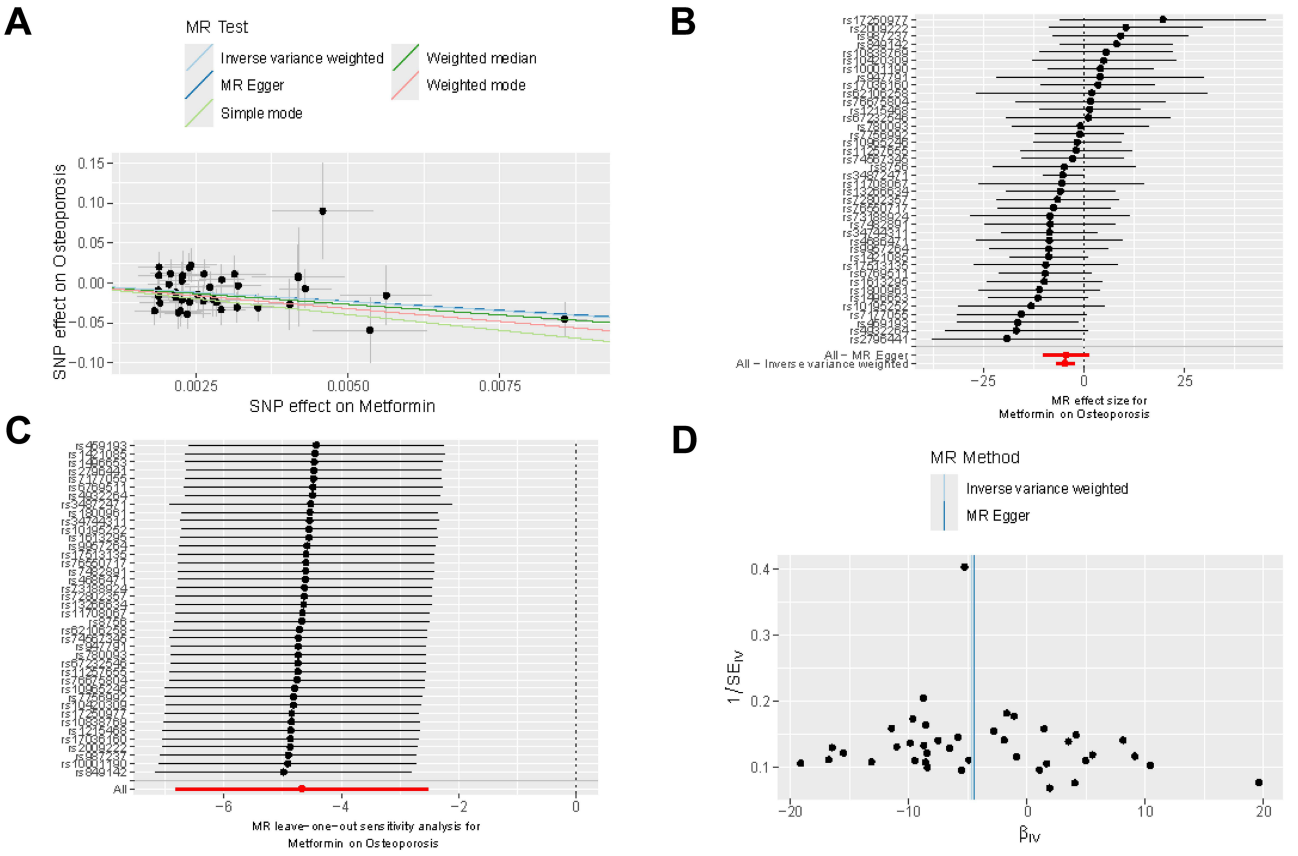

Figure 2 Mendelian Visualization Analysis of Metformin and Osteoporosis. (**A**) Scatter plot illustrates the genetic effect between Metformin and Osteoporosis in the Mendelian randomization (MR) analysis. Each point represents a single nucleotide polymorphism (SNP), with the x-axis indicating the SNP's effect on Metformin and the y-axis showing its effect on Osteoporosis. Different regression lines represent MR estimates obtained from various analytical methods, helping visualize the overall trend. (**B**) Forest plot presents the effect estimates and 95% confidence intervals for each SNP included in the analysis. Each dot represents an individual SNP effect, while the horizontal lines indicate the confidence intervals. The diamond shape at the bottom summarizes the overall causal estimate, allowing an assessment of the consistency and reliability of the findings. (**C**) Leave-one-out plot evaluates the influence of individual SNPs on the overall MR result. Each horizontal line represents the effect estimate after removing one SNP at a time. If the overall effect remains stable across different iterations, it indicates that no single SNP is disproportionately driving the result, reinforcing the robustness of the findings. (**D**) Funnel plot= assesses potential biases, such as directional pleiotropy or publication bias. A symmetrical distribution of points suggests no significant bias, whereas asymmetry may indicate the presence of systematic errors or small-sample effects affecting the analysis.

osteoporosis with pathological fractures (Figure 3), especially in the IVW analysis, where most SNPs, such as rs112700375 and rs28472765, exhibited positive effects, indicating that GLP-1 receptor agonists may increase fracture risk. Although the MR Egger analysis did not reach significance, the overall analysis still tended toward a positive effect. For SGLT2 inhibitors, the scatter plot and funnel plot (Figure 4) showed a weak negative correlation effect with osteoporosis, and the funnel plot displayed some asymmetry, suggesting potential publication bias or pleiotropy issues, which requires further validation through large-scale studies. Gliclazide analysis also showed a significant association, particularly in the IVW analysis, where multiple SNPs were positively correlated with osteoporosis with pathological fractures, suggesting that gliclazide might increase fracture risk (Figure 5). These results provide important guidance for clinical drug selection, especially for patients with diabetes with coexisting osteoporosis.

Mendelian Analysis of Five Methods for Antidiabetic Drugs in Osteoporosis and Its Subtypes

The association effects of certain antidiabetic drugs with various osteoporosis subtypes generally did not reach statistical significance, suggesting a limited direct causal relationship with osteoporosis risk within the current analytical framework. Metformin demonstrated a near-significant protective effect in certain osteoporosis subtypes (eg, postmenopausal

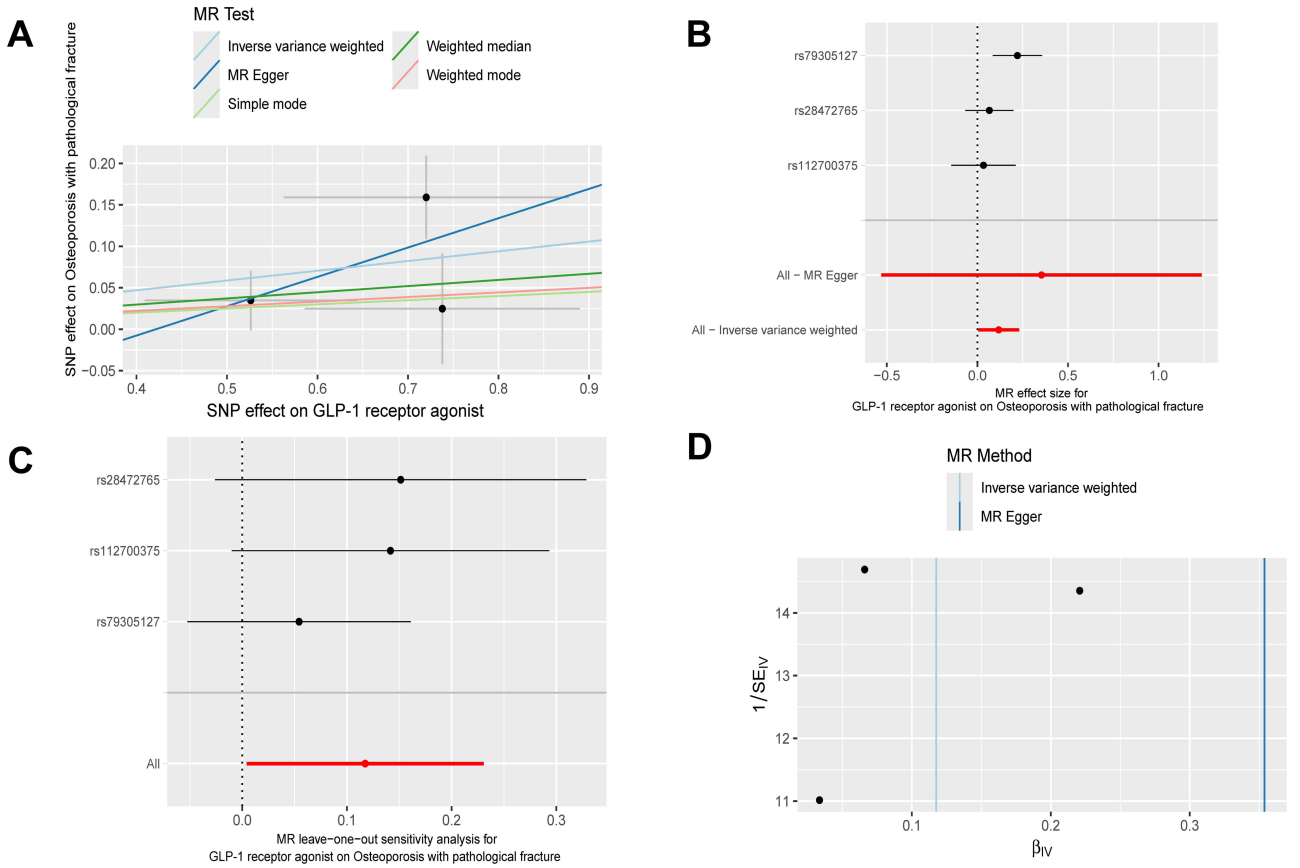

Figure 3 Mendelian Visualization Analysis of GLP-1 Receptor Agonists and Osteoporosis with Pathological Bone. (**A**) Scatter plot illustrates the Mendelian randomization (MR) analysis between GLP-1 receptor agonists and osteoporosis with pathological bone. Each point represents a single nucleotide polymorphism (SNP), with the x-axis showing the SNP's effect on GLP-1 receptor agonists and the y-axis indicating its effect on osteoporosis with pathological bone. Different regression lines represent MR estimates obtained using various methods, providing a visual representation of the potential causal relationship. (**B**) Forest plot displays the effect estimates and 95% confidence intervals for each SNP included in the analysis. Each dot represents the effect size of an individual SNP, while the horizontal lines indicate confidence intervals. The diamond at the bottom summarizes the overall effect estimate, helping assess the consistency of the results across different SNPs. (**C**) Leave-one-out plot evaluates the robustness of the MR analysis by systematically removing one SNP at a time. Each horizontal line represents the effect estimate after excluding a specific SNP. If the results remain stable across different iterations, it suggests that no single SNP is disproportionately influencing the findings, ensuring the reliability of the overall effect. (**D**) Funnel plot examines potential biases such as directional pleiotropy or publication bias. A symmetrical distribution of points suggests that the results are not significantly affected by bias, whereas an asymmetrical distribution may indicate the presence of systematic errors or small-sample effects.

osteoporosis with pathological fractures), particularly in the IVW method, where the p-value approached the threshold of significance, indicating a potential protective effect of metformin on specific osteoporosis subtypes (Table S1). The association between GLP-1 receptor agonists and osteoporosis or its subtypes was weak. Although a slight positive effect was observed in certain analysis methods (such as the simple mode), the overall results failed to reach significance, suggesting that the potential impact of this drug on osteoporosis remains unclear (Table S2). The analysis of SGLT2 inhibitors across different osteoporosis subtypes similarly showed no significant association. In both postmenopausal osteoporosis and pharmacological osteoporosis analyses, p-values in the MR Egger and IVW methods did not achieve significance, indicating a limited effect on osteoporosis risk. However, considering that SGLT2 inhibitors may indirectly influence bone health through metabolic pathways, further research on their long-term impact on bones is warranted (Table S3). The association analysis of insulin with osteoporosis also yielded no significant results. Whether in postmenopausal or pharmacological osteoporosis, p-values in all analytical methods did not reach statistical significance, suggesting a weak direct causal relationship between insulin and bone health. Although insulin plays an important role in glucose metabolism, it does not appear to have a clear effect on osteoporosis risk modulation (Table S4). In the analysis of gliclazide and osteoporosis with pathological fractures, a certain positive association was observed in the IVW method, indicating a potential increase in the risk of pathological fractures. However, other methods showed no

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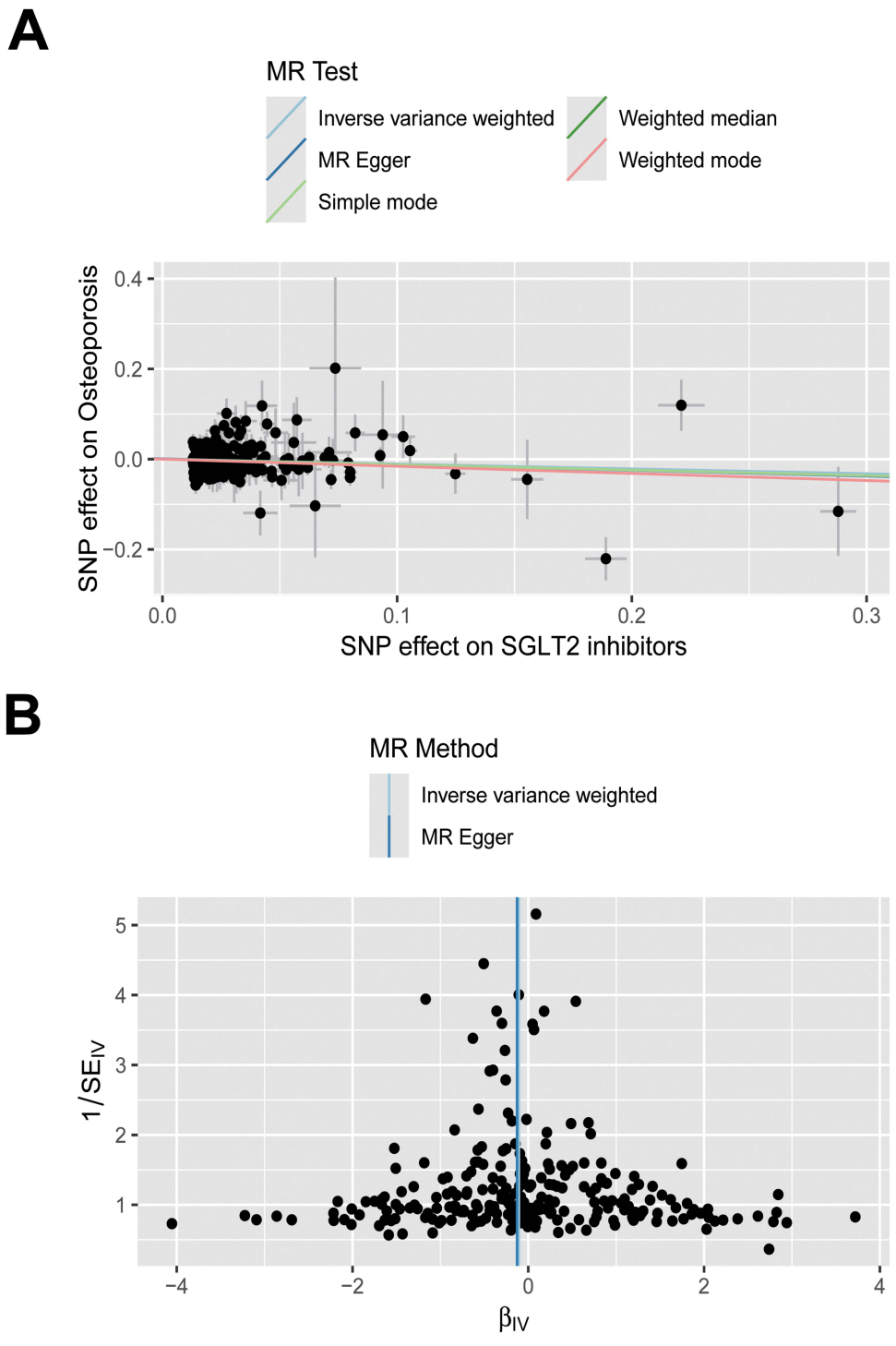

Figure 4 Scatter Plot and Funnel Plot of SGLT2 Inhibitors and Osteoporosis.

Notes: This figure presents the results of the Mendelian randomization (MR) analysis assessing the relationship between SGLT2 inhibitors and osteoporosis using scatter and funnel plots. (**A**) Scatter plot: This plot visualizes the association between SGLT2 inhibitors and osteoporosis by displaying the effect estimates (βIV) of different SNPs along with their standard errors. Each point represents a single SNP, and the plotted lines correspond to MR estimates obtained using different analytical methods, illustrating the overall trend and potential causal relationship. (**B**) Funnel plot: This plot evaluates the symmetry of SNP effect estimates to assess potential bias, such as directional pleiotropy or publication bias. A symmetrical distribution of points suggests no significant bias, while an asymmetrical pattern may indicate systematic errors or small-sample effects that could influence the results.

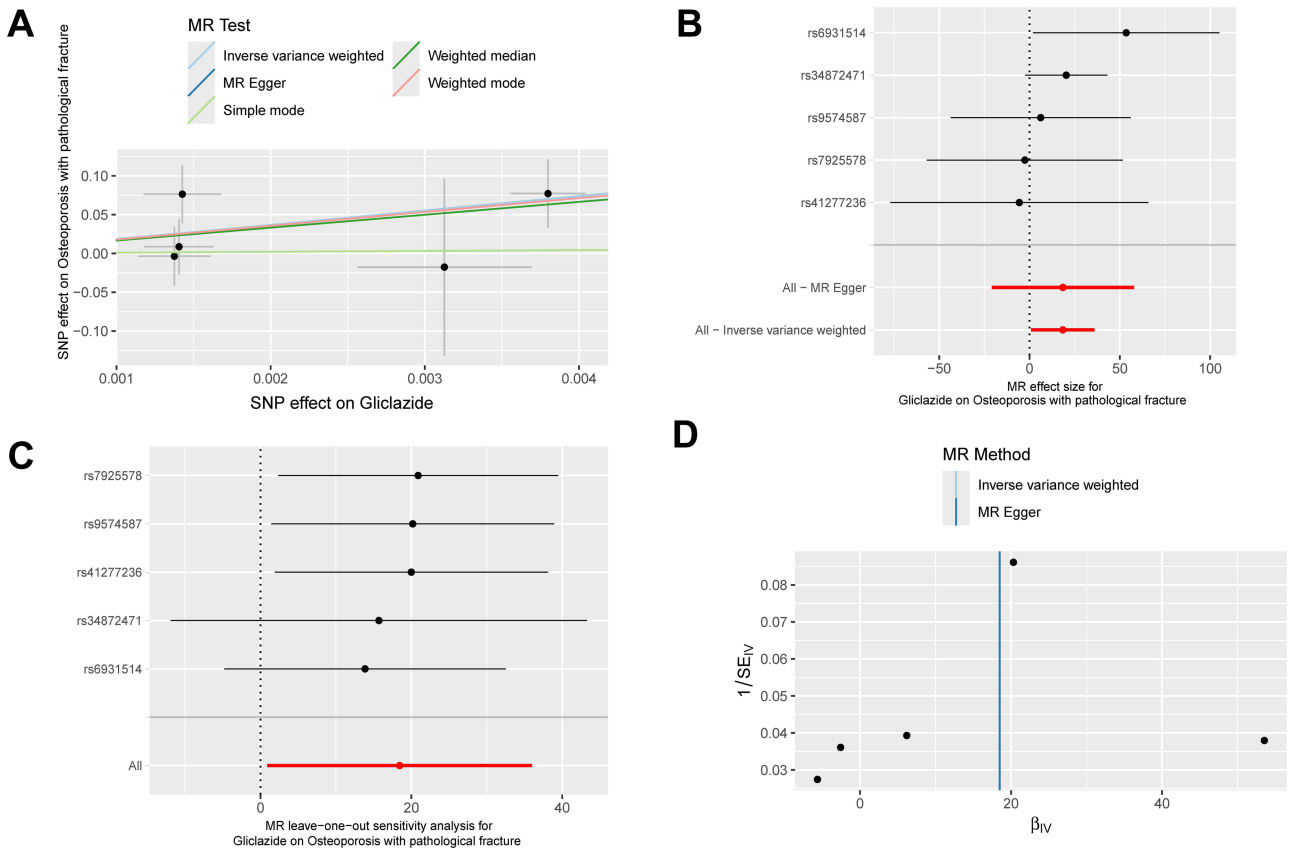

Figure 5 Mendelian Analysis of Gliclazide and Osteoporosis with Pathological Bone. (**A**) Scatter plot: This plot visualizes the association between Gliclazide and osteoporosis with pathological bone by showing the effect estimates (βIV) of individual SNPs along with their standard errors. Each point represents a single SNP, and the plotted regression lines indicate MR estimates from different methods, helping to illustrate the overall trend. (**B**) Forest plot: This plot displays the effect estimates and 95% confidence intervals for each SNP included in the analysis. Each dot represents an individual SNP effect, with horizontal lines indicating confidence intervals. The summary effect at the bottom helps assess the consistency of the findings. (**C**) Leave-one-out plot: This sensitivity analysis assesses the influence of individual SNPs on the overall MR estimate by systematically removing one SNP at a time. If the results remain stable across iterations, it suggests that no single SNP is disproportionately affecting the overall conclusion, ensuring robustness. (**D**) Funnel plot: This plot evaluates the symmetry of SNP effect estimates to detect potential biases, such as directional pleiotropy or publication bias. A symmetrical distribution of points suggests no major bias, while an asymmetrical pattern may indicate systematic errors or small-sample effects.

Notes: Scatter and forest plots (**A** and **B**) illustrate the effect sizes and standard errors of individual SNPs, providing insight into their contributions to the overall causal estimate. Leave-one-out and funnel plots (**C** and **D**) assess the stability and reliability of the results, helping to evaluate whether Gliclazide has a consistent impact on osteoporosis with pathological bone.

significant results, and the effect remains uncertain, necessitating further studies to confirm the potential adverse effects of this drug on high-risk populations (Table S5).

Non-Significant Visualization Analysis of Antidiabetic Drugs in Fractures and Their Subtypes

In this visualization analysis, fractures and their subtypes include postmenopausal osteoporosis with pathological fractures, osteoporosis with pathological fractures, and pharmacological osteoporosis with pathological fractures. The visual charts provide an intuitive display of the potential impact of these drugs on fracture risk. However, the overall results show that the association effects of the drugs with fractures and their subtypes largely did not reach statistical significance, suggesting a limited direct causal association between these drugs and fracture risk. For metformin, the visual charts of fractures and their subtypes indicate that, although some SNPs (eg, rs11708067 and rs459193) displayed slight effects under various methods (such as IVW, weighted median, and MR Egger), the effect values mostly clustered around zero, with wide confidence intervals, failing to reach significance (from Figures S1–S3). This suggests a limited protective effect of metformin on fractures and their subtypes. The results for GLP-1 receptor agonists across fracture subtypes were similar to those for metformin, showing no significant association effects. Some SNPs exhibited positive effects in IVW and

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weighted median analyses, suggesting that GLP-1 receptor agonists might be associated with fracture risk, but the effect confidence intervals were large and did not reach statistical significance (from Figures S4 and S5). In the visualization results for SGLT2 inhibitors, the SNP effect values mostly clustered around zero, showing no significant association. Although individual SNPs (eg, rs4686471 and rs2796441) in the weighted median analysis displayed slight negative effects, suggesting that SGLT2 inhibitors might modestly reduce fracture risk in certain cases (from Figures S6–S8), the overall effect was not statistically significant. For insulin, most SNP effect values were also concentrated near zero, with wide confidence intervals. While some SNPs showed higher effect values in the IVW analysis, the overall wide confidence intervals prevented a clear causal relationship from being established (see Figures S9–S11). Gliclazide was one of the few drugs that showed higher effect values in certain analyses, suggesting a potential association with increased fracture risk (see Figures S12 and S13). The higher SNP effect values imply that gliclazide might impact bone through specific biological pathways, possibly increasing fracture risk, especially in osteoporosis patients with fractures. However, the prominent effect values for some SNPs and the broad confidence intervals suggest considerable variability, indicating that the robustness and clinical significance of these associations require further investigation for confirmation.

Discussion

This Mendelian Randomization study found that Metformin has a protective effect against osteoporosis, while Gliclazide increases the risk of pathological fractures. The effects of GLP-1 receptor agonists, SGLT2 inhibitors, and insulin were minimal. However, we acknowledge that the sample sizes across different drugs vary significantly due to differences in GWAS study designs and participant recruitment. To mitigate this issue, we conducted sensitivity analyses, including sample-size-matched subset analyses and inverse variance-weighted (IVW) adjustments, as detailed in the Discussion section. We applied an IVW approach to adjust for sample size differences and account for heterogeneity in effect estimates across different drug groups. MR estimates genetically predicted lifelong drug exposure, preventing differentiation between short- and long-term users. While MR reduces confounding, it does not account for age, sex, diabetes duration, comorbidities, or specific medication regimens due to GWAS dataset limitations. Additionally, findings are based on European populations, limiting generalizability. One critical limitation of our study is that MR estimates genetically predicted lifelong drug exposure, which does not capture real-world variations in drug dosage, treatment duration, or adherence. The effects of antidiabetic drugs on bone health may differ depending on the administered dosage and combination therapy, which were not assessed in our study. Many diabetic patients receive combination therapies (eg, Metformin with Insulin or SGLT2 inhibitors), and these drugs may exert synergistic or antagonistic effects on bone metabolism, influencing osteoporosis risk. Furthermore, our study did not include data on insulin dosage, treatment duration, or hypoglycemia incidents, all of which may impact fracture risk. For example, long-term high-dose insulin users may have different bone metabolism effects compared to short-term low-dose users. Additionally, hypoglycemia increases fall risk, potentially leading to fractures. Since these variables were unavailable in the dataset (ukb-b-15445), our findings should be interpreted with caution, particularly in patients on long-term high-dose insulin therapy. Future studies should integrate real-world clinical data (EHR, prescriptions) to refine the assessment of dose-response relationships, combination therapy effects, and their impact on bone health.

Metformin demonstrated a significant protective effect on bone, consistent with findings from several previous observational studies. Existing literature suggests that metformin reduces bone resorption and promotes osteoblast activity by activating the AMPK pathway, thereby increasing bone density. For example, research by Liu et al showed that metformin enhances bone mineralization by activating AMPK signaling in osteoblasts.[40] The Mendelian randomization results in our study provide causal evidence supporting this perspective, further reinforcing the potential of metformin to prevent fractures in patients with diabetes.[41] This aligns with the conclusions from a large clinical study by Kahn et al, which found a lower incidence of fractures among metformin users.[42] In contrast, this finding suggests that when treating diabetes with gliclazide, special attention should be given to its impact on bone health, especially in patients at high fracture risk, such as the elderly or those with a history of bone disease. Regular monitoring and alternative treatments may be necessary to mitigate this risk. Increased risks associated with sulfonylureas, particularly those linked to hypoglycemia, have been reported in several studies.[43] Our study found that gliclazide exhibited a significant positive association in the IVW analysis, indicating that its impact on fracture incidence may be mediated

through an increased risk of falls due to hypoglycemic events. While gliclazide may contribute to osteoporosis development, its role in fracture risk appears to be primarily linked to the combined effect of osteoporosis progression and fall-related trauma induced by hypoglycemia. This distinction underscores the need for careful evaluation of gliclazide use in patients at high risk of fractures, particularly those prone to hypoglycemic episodes. A study by Wu et al also indicated that sulfonylureas are associated with increased fracture risk in elderly patients with diabetes.[44] Although some effects were significant, the wide confidence intervals suggest limited robustness, indicating a need for further research to validate these preliminary findings.

The role of GLP-1 receptor agonists in bone health remains controversial. Some studies suggest that GLP-1 receptor agonists may exert a protective effect on bone health by directly regulating bone metabolism. For instance, Monami et al reported that GLP-1 receptor agonists could reduce fracture risk in postmenopausal women.[45] Recent systematic reviews and meta-analyses have indicated that GLP-1 receptor agonists may improve bone mineral density and modulate bone turnover markers in patients with type 2 diabetes.[46] However, our study did not find a significant association between this drug and fracture risk. Although some SNPs showed a slight positive effect in the IVW and weighted median analyses, indicating a potential impact on bone metabolism, the overall effect did not reach statistical significance. Xie et al suggested that GLP-1 receptor agonists might indirectly affect bone health through other mechanisms, such as improved insulin sensitivity.[47] This implies that their impact on bone might be more complex, necessitating further research to comprehensively explore their various biological effects. Additionally, the effect of this drug may vary among individuals, especially in diabetic patients with comorbid bone diseases, where the relationship between metabolic regulation and bone density changes could be more complex. These results indicate that the use of SGLT2 inhibitors in such populations requires further investigation, particularly to explore the interplay between metabolic pathways and bone health outcomes. This finding might be related to the mechanism of SGLT2 inhibitors, which promote the maintenance of bone density by reducing renal glucose reabsorption and improving the metabolic environment. Some studies suggest that SGLT2 inhibitors may increase fracture risk, potentially due to their influence on calcium and phosphate metabolism.[48] However, our Mendelian randomization study did not identify a significant causal relationship between SGLT2 inhibitors and fracture risk. Consistent with this finding, Taylor et al also noted a weak association between SGLT2 inhibitors and fracture risk, which may be affected by other confounding factors.[49] The slight negative effect of SNPs in this study suggests a potential protective effect on bone health, but these effects also did not reach statistical significance. Larger randomized controlled trials are needed in the future to further validate the long-term impact of SGLT2 inhibitors on bone health. This is particularly important due to the possibility of these medications provoking orthostatic hypotension and their use primarily in groups of individuals with heart-related complications (coronary artery disease and heart failure), which are common among older adults. The analysis results for insulin align with the complexity observed in previous studies. Although observational studies propose that insulin may impact bone health by regulating glucose metabolism and osteoblast function, no significant causal association was found between insulin and the risk of osteoporosis or fracture in our study. Consistent with previous findings, the direct effect of insulin on bone health appears weak and may depend on individual glucose metabolism status and insulin resistance. As the dataset does not provide information on insulin dosage or duration of use, our findings primarily reflect overall insulin use rather than differentiating between long-term high-dose and short-term low-dose regimens. Therefore, these results should not be generalized to all insulin users, especially those undergoing long-term high-dose therapy. Future studies should refine insulin exposure classifications to clarify its true impact on bone health.[50] This suggests that the mechanism of insulin's role in bone metabolism might be more complex and warrants further validation, incorporating individual metabolic parameters and long-term follow-up data.

These results provide important guidance for clinical drug selection, especially for diabetic patients with coexisting osteoporosis. Metformin, as a drug with a clear bone-protective effect, is especially suitable for patients with diabetes at high risk of fractures, such as elderly patients or postmenopausal women.[51] This finding supports metformin as a preferred choice for long-term management in patients with diabetes and provides causal evidence for its role in fracture prevention. Existing clinical guidelines may need to reassess metformin's role in bone health management among patients with diabetes.[40] In contrast, caution should be exercised with the use of Gliclazide, particularly in patients at high risk of fractures. As our study found a significant positive association between Gliclazide and fracture risk,

clinicians should conduct a comprehensive risk assessment when selecting this medication. Specifically, for elderly patients with diabetes, regular monitoring of bone health is essential, and alternative medications should be considered to reduce the risk of fractures induced by hypoglycemia.[44] For GLP-1 receptor agonists and SGLT2 inhibitors, although our study did not find a significant association with fracture risk, future studies should continue to explore the long-term effects of these drugs, particularly in patients with diabetes with osteoporosis or fracture risk[49,52] These findings underscore the need for personalized medication choices in patients with diabetes to effectively reduce fracture risk while managing blood glucose levels.

Although Mendelian randomization (MR) can reduce confounding factors and reverse causation, this approach has certain limitations. First, pleiotropy is a major concern, as some SNPs may influence multiple biological pathways beyond the specific effects of the target drug on bone health.[53] This effect can lead to biased results, particularly if pleiotropic SNPs are not precisely identified and controlled. Although we applied methods such as MR Egger and MR-PRESSO in our analysis to adjust for pleiotropy, these methods have their limitations and cannot completely exclude the interference of unidentified pleiotropic SNPs.[54] Additionally, MR Egger has low statistical power, and the validity of MR-PRESSO depends on the number of SNPs and specific gene selection criteria, which may still affect the robustness of the results. Moreover, this study relies on existing GWAS data, with samples mainly from European populations. This population limitation may restrict the external validity of the results, especially in other ethnic groups or subpopulations.[55] Due to differences in genetic structure and environmental factors, different ethnic groups may have distinct gene-environment interactions that influence the effects of SNPs on bone health. Therefore, future research should expand sample sizes to include more non-European populations to improve the generalizability of findings and enhance understanding of gene-environment interactions across different subgroups. This expansion would not only increase the statistical power of the research but also provide more effective genetic evidence for personalized medicine across diverse ethnic or subpopulations.

Conclusion

This Mendelian Randomization study confirms Metformin's protective effect against osteoporosis and Gliclazide's potential fracture risk, while GLP-1 receptor agonists and SGLT2 inhibitors showed no significant impact. MR estimates genetically predicted drug effects, not real-world treatment patterns. Future studies should incorporate clinical data, treatment duration, and diverse populations. Metformin's potential bone-protective effect (OR: 0.00936, $p = 2.11\times10^{-5}$) may depend on dosage, treatment duration, and concurrent medications, which require further investigation. In contrast, Gliclazide significantly increases the risk of pathological fractures, with OR [95% CI]: 1.03E+08 [1.28E+02–8.32E+12], $p = 0.0395$, indicating the need for cautious use among high-risk osteoporosis populations. The effects of GLP-1 receptor agonists and SGLT2 inhibitors on bone health remain inconclusive, warranting further mechanistic and clinical studies. This study provides new clinical evidence for bone health management in patients with diabetes, though some limitations exist. The issue of pleiotropy may affect certain results, necessitating further validation in larger samples and diverse populations. Future studies should include multi-ethnic cohorts to further explore the long-term skeletal impacts of Metformin and Gliclazide and to investigate the potential bone metabolism mechanisms of GLP-1 receptor agonists and SGLT2 inhibitors, offering a more comprehensive basis for personalized treatment in patients with diabetes.

Ethics Statement

This study utilized publicly available summary-level genome-wide association study (GWAS) data obtained from the MRC IEU GWAS database (https://gwas.mrcieu.ac.uk/). The datasets are fully anonymized and contain no personally identifiable information, ensuring compliance with ethical standards for research involving human data. The original GWAS datasets were collected with ethical approval from their respective Institutional Review Boards (IRBs) or Ethics Committees, and informed consent was obtained from participants during the original data collection. As this study is a secondary analysis of publicly available data, no additional recruitment or interaction with human participants was involved. According to Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (February 18, 2023, China), research that exclusively uses anonymized, publicly available human data is exempt from ethical review. Specifically, Item 1 states that research using publicly available, anonymized data does not

require ethical review, and Item 2 specifies that research relying on data with prior ethical approval in open-access repositories is exempt from repeated review. Based on these provisions, no further ethical approval was required for this study. The use of publicly available GWAS data complies with all relevant ethical and legal standards.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Specifically:

- G.D. conceptualized the research framework, designed the study methodology, and performed formal analysis.
- Z.L. co-conceptualized the study, supervised the research process, and provided critical intellectual input.
- L.W. contributed to methodology validation and data interpretation.
- S.X. implemented software tools and supported statistical validation.
- J.Z. validated the study findings and contributed to the interpretation of results.

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Disclosure

The authors declare no competing interests in this work.

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