BMC Musculoskeletal Disorders

RESEARCH

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Genetically modified stem cells for osteoporosis: a systematic review and meta-analysis of preclinical studies

Miao Huang[1*], Xie-sheng Wu[2], Ningkun Xiao[3], Xinlin Huang[3] and Peng-fei Lin[1*]

Abstract

Objective Our meta-analysis aims to assess the efficacy of genetically modified stem cell therapy in preclinical osteoporosis models.

Methods We executed a thorough literature search across PubMed, Embase, Web of Science, and the Cochrane Library databases from inception to September 15, 2023. We used a random-effect model for pooled analysis of the effect of genetically modified stem cell therapy on animals with osteoporosis. The primary outcomes included bone mineral density (BMD) and bone volume fraction.

(BV/TV). All meta-analyses were performed employing the Cochrane Collaboration's Review Manager (version 5.3) in conjunction with Stata 15.0 statistical software.

Results A total of 2567 articles were reviewed, of which 16 articles met inclusion criteria. Of these, 13 studies evaluated the BMD and 11 studies evaluated BV/TV. Compared to the control group, genetically modified stem cell therapy was associated with significantly improved BMD (standardized mean difference [SMD] = 1.85, 95% Confidence Interval [CI]: 1.06–2.63, $P < 0.001$, $I^2 = 69\%$) and BV/TV (standardized mean difference [SMD] = 2.11, 95% Confidence Interval [CI]: 1.10–3.12, $P < 0.001$, $I^2 = 78\%$).

Conclusion Genetically modified stem cell therapy is a safe and effective method that can significantly improve the BMD and BV/TV in animal models of osteoporosis. These results provide an important basis for future translational clinical studies of genetically modified stem cells.

Keywords Genetically modified, Osteoporosis, Stem Cell, Meta-analysis

Introduction

Osteoporosis is a pervasive skeletal disorder marked by progressive bone mass reduction and deterioration of bone microarchitecture, leading to heightened bone fragility and an elevated fracture risk [1]. Osteoporotic fractures represent a critical sequela of osteoporosis. Individuals with osteoporosis, particularly the elderly and post-menopausal women, face an elevated susceptibility to such fractures [2, 3]. Worldwide, osteoporosis is estimated to affect approximately 200 million individuals. In numerous Asian nations, roughly one in five individuals aged 50 and older are diagnosed

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with osteoporosis [4]. Central to the pathophysiology of osteoporosis is the dysregulation between bone formation and resorption. An imbalance ensues when the rate of bone resorption surpasses that of bone formation, disrupting bone homeostasis [5].

In current clinical practice, the progression of the disease is primarily managed through pharmacological treatments that promote bone formation and inhibit bone resorption [6]. However, the clinical utility of these medications is constrained by their potential for serious adverse effects and their inability to reverse pre-existing bone loss [7]. Therefore, the development of novel treatment strategies for osteoporosis is of great clinical significance.

Mesenchymal stem cells (MSCs) possess the inherent ability to proliferate and differentiate into osteoblasts, adipocytes, and chondrocytes, playing a pivotal role in maintaining bone homeostasis [8, 9]. Clinical trials of stem cell transplantation alone for the treatment of osteoporosis are still in the exploratory phase [10]. With the widespread use of stem cell transplantation and the gradual maturation of genetic modification techniques, new possibilities for the treatment of osteoporosis have been opened up. Stem cell-mediated gene therapy has been investigated as an attractive option for the treatment of osteoporosis [11]. A recent meta-analysis showed that stem cell treatment alone increased bone strength, bone mass, and bone trabeculae in de-ovalized osteoporotic rats [12]. Compared to simple stem cell transplantation, positive gene-modified stem cell transplantation can enhance or suppress the expression of a gene fragment in stem cells, making the transplanted stem cells more susceptible to osteogenic differentiation, promoting bone repair and bone regeneration, and thus achieving the goal of treating osteoporosis [13]. While clinical studies investigating the application of transgenic stem cell transplantation for osteoporosis are yet to be reported, a multitude of animal experiments, encompassing rats, mice, rabbits, sheep, and pigs, have underscored the efficacy of this technique in osteoporosis treatment [14–17].

We conducted a meta-analysis of animal studies to evaluate the impact of genetically modified stem cell transplantation on Bone Mineral Density (BMD) and Bone Volume/Total Volume (BV/TV)—both of which are robust indicators of bone mass that reflect the extent of osteoporosis [18, 19]. In addition, we sought to explore whether factors such as different sources of stem cells, different modified genes, and different transplantation pathways have different effects on BMD and BV/TV.

Methods

This meta-analysis aimed to assess the efficacy of genetically modified stem cell treatments on BMD and BV/TV in osteoporotic animal models. We registered our study with PROSPERO (CRD42022351945) and followed PRISMA (see Appendix A) [20] and Cochrane Handbook guidelines [21].

Data source and search strategies

We conducted a systematic search in Pubmed, Embase, Web of Science, and the Cochrane Library until September 15, 2023. Keywords included terms related to osteoporosis (e.g., "Osteoporoses", "Osteoporosis, Post-Traumatic") and stem cell interventions (e.g., "Stem Cell", "Transplantation"). Additionally, we manually checked references of key articles and reviews. All findings were organized in EndNote, version X9.

Eligibility criteria

The following inclusion criteria were set: (1) the study involved animal models of osteoporosis (all species and sexes); (2) all animal models of osteoporosis were treated with stem cells; (3) stem cells in the experimental group must be genetically modified; (4) studies that include efficacy outcomes, such as BMD and BV/TV; (5) studies have a control group.

Studies were excluded from the meta-analysis for the following reasons: (1) all inclusion criteria were not fulfilled; (2) stem cells without genetic modifications; (3) meeting abstracts, case reports, books and case series; (4) review or meta-analysis; (5) the study was duplicated;(6) studies published in a non-English language; (7) experimental groupings are not set up properly, data clearly wrong, incomplete or unclear data, no relevant data and unavailable literature.

Study selection and data extraction

Two investigators (MH and WZ) independently evaluated article quality and extracted data by screening abstracts and full texts. Any disagreements were reviewed and resolved by a third investigator (NX). After identifying articles that met the inclusion and exclusion criteria, all relevant data were recorded in Microsoft Excel including the first author; year; subject animal, disease model, ages; group numbers; modified carriers; modeling duration; gene modification category; type and source of stem cells; transplantation routes; intervention time. Then measured the correlation with our primary outcome. The SYRCLE risk of bias tool was used to evaluate the quality of animal studies() [22]. The assessment results are presented as

"yes", "no" and "not available" for low risk of bias, high risk of bias, and uncertain risk of bias respectively.

Types of outcome measures

In both preclinical and clinical research, BMD and BV/TV are widely regarded as pivotal endpoints in evaluating the therapeutic efficacy of osteoporosis treatments. Accordingly, for this meta-analysis, we selected BMD and BV/TV as the primary outcome measures across all included studies.

Statistical analysis

All the data review and meta-analysis were performed using the Review Manager 5.3 (Version 5.3; Cochrane, Oxford, UK) and Stata (Version 15.0; Stata, College Station, TX) software. The difference between the control group and the intervention group was estimated. Continuous variable data were selected for the standardized mean difference (SMD) analysis. Each effect volume was expressed as a 95% confidence interval (CI). Among-study heterogeneity was observed using the I^2 test. $I^2 \leq 50\%$ indicated homogeneity between the studies, which was calculated using the fixed-effects model. $I^2 > 50\%$ indicated heterogeneity between studies, and a random-effects model was used instead [23]. $I^2 < 35\%$ is low heterogeneity, $35\% \leq I^2 < 75\%$ moderate heterogeneity, and $I^2 \geq 75\%$ high heterogeneity. Subgroup analyses were performed to evaluate heterogeneity. Publication bias Egger's test based on regression, $p \geq 0.05$ for no publication bias and sensitivity analysis was also performed. $P < 0.05$ was used to determine the statistical significance of comparisons between groups. Funnel plots were drawn to investigate publication bias visually when no fewer than 10 studies reported the same outcome measure.

Results

Study selection

A flowchart detailing the literature search and study selection process is depicted in Fig. 1. A total of 2569 studies were retrieved, from which 373 duplications were initially removed. A total of 2164 articles were excluded after screening the titles and abstracts, mainly because 339 of them were reviews or meta-analyses, 35 articles were in non-English, 1041 articles treatments were not based on stem cells or animal models were non-osteoporotic fractures, the other 749 articles belonged to conference abstracts, newspapers, experimental methods, etc. Of the 32 potentially relevant studies, 16 were further excluded after the review of the full texts because 12 studies of stem cell therapy without genetic modification and other inclusion criteria for the 4 articles do not match. Finally, 16 articles were included in this meta-analysis after study selection.

Study characteristics

The essential characteristics of the 16 selected studies are summarized in Table 1. These studies were published between 2006 and 2021. The animal models used in seven studies were C57Bl/6 mice [24–30]. Animal models used in six studies were SD rats and mice [31–36]. One study in Wister rats [37], one study in ddY mice [38], and one study in C3H/HeN mice [39]. Twelve studies used bone marrow mesenchymal stem cells [24, 25, 27–29, 31–35, 37, 39], three used adipose-derived stem cells [30, 36, 38], and one used dental pulp-derived stem cells [26]. In the included studies, the primary outcome was shown to be the value of change in BMD and BV/TV. The duration of follow-up across the included studies ranged from 2 to 12 weeks. For studies reporting outcomes at multiple time points, data from the final time point were utilized. In cases with multiple gene modification interventions, data of individual modifier genes associated with stem cell osteogenic differentiation were prioritized. For studies assessing multiple anatomical sites, measurements from long bones were prioritized, followed by irregular bones, with whole-bone measurements being considered last.

Risk of bias (SYRCLE tool)

Figure 2 and Appendix B (Table 2 and Fig. 1) present the risk of bias for each included article. None of the 16 studies met all ten criteria for a low risk of bias. No study blinded its researchers or outcome evaluators. All had inadequate allocation concealment. Due to the inherent nature of mesenchymal stem cell administration, blinding during cell acquisition is challenging, though this doesn't impact the experimental results. No other biases were detected.

Efficacy of genetically modified stem cell therapy on osteoporosis

BMD and BV/TV

The results of BMD and BV/TV changes in this meta-analysis are shown in Fig. 3. Thirteen studies have reported the effect of genetically modified stem cells on BMD in osteoporotic animals compared to stem cells alone [25–28, 30, 31, 33–39]. Significant heterogeneity was detected in this study ($I^2 = 69\%$ and $P < 0.01$); thus, a random effects model was used. The results showed that the BMD of the genetically modified stem cell group was significantly higher than that of the stem cell-only group (SMD = 1.85, 95% CI: 1.06–2.63), see Fig. 3A. Eleven studies have reported the effect of genetically modified stem cells on BV/TV in osteoporotic animals compared to stem cells alone [24–26, 29–33, 35, 36, 38]. There was high heterogeneity between the results of the studies

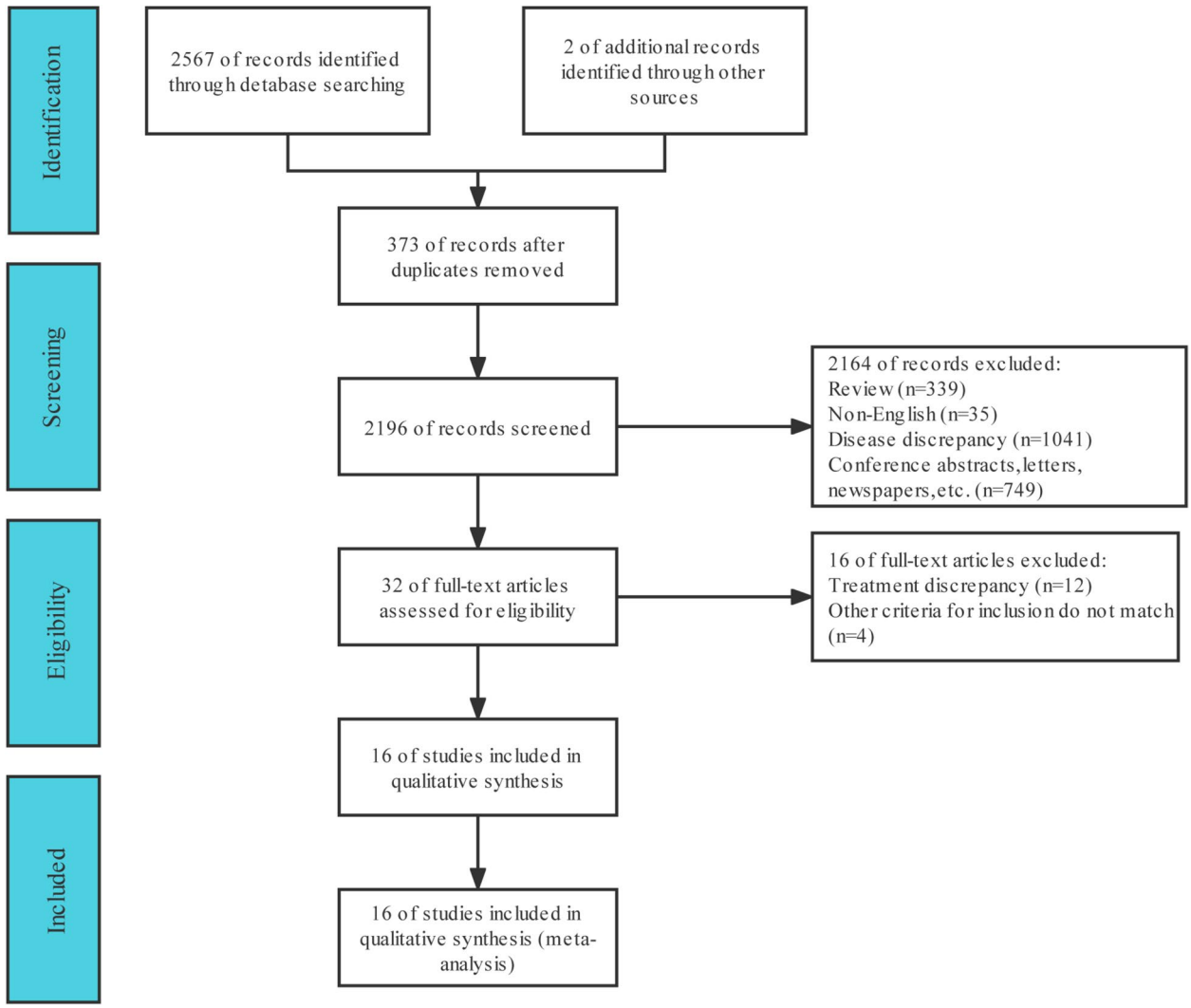

Fig. 1 Flowchart of study selection. A total of 2569 records were retrieved; after application of the inclusion criteria, 16 studies remained

($I^2 = 78\%$ and $P < 0.01$), and the random effects model was chosen to show that BV/TV was higher in the experimental group than in the control group (SMD = 2.11, 95% CI: 1.10–3.12), see Fig. 3B.

Subgroup analysis

We analyzed the source of heterogeneity by evaluating BMD and BV/TV in a subgroup analysis. All participating subjects underwent stem cell transplantation; stem cells in the control group were unmodified and those in the comparison group were genetically modified. We focused on stem cell types, transplantation pathways, and modifier genes, which were reported in Table 2 and Figs. 4– 5, respectively. Stem cells in the experiment included bone marrow stem cell (BMSC), adipose-derived stem cell (ADSC), and dental pulp-derived stem cell (DPSC). A similar effectiveness was observed between BMSC and ADSC. Transplantation of BMSC (SMD = 1.44, 95% CI: 0.60, 2.29), ADSC (SMD = 3.34, 95% CI: 1.13, 5.55), and DPSC (SMD = 1.90, 95% CI: 0.27, 3.54) were all associated with significantly improved BMD as compared to that observed in controls. The effect of stem cell type on BV/TV is similar to the BMD situation. The transplantation routes are divided into Tail vein injection, Local injectable fillers, and Peritoneal cavity intraperitoneal injection. Although the different routes of transplantation did not make a significant difference to BMD outcomes, in terms of BV/TV we could see no significant difference between the experimental and control groups for Peritoneal cavity intraperitoneal injection ($P = 0.19$), and we found relatively low heterogeneity in both BMD and BV/TV in the Peritoneal cavity intraperitoneal injection group ($I^2 < 50\%$). The modifier genes are divided into CXCR4, BMP2, and others. When the number of papers

Table 1 Characteristics of the included studies

Author (year)	Subject animal	Disease model	Ages(weeks)	Grouping	Sample size(n)	Type of cells	Genetic Modification	Modified carriers	Transplantation route	Modeling Duration (weeks)	Outcomes
Kim et al. 2006 [27]	Female C57Bl/6 mice	OVX	5 ~ 6	BMSC-GFP / BMSC-(RANK-Fc + GFP)	7/8	BMSC	Rank-fc	Reverse transcription virus	Peritoneal cavity Intraperitoneal injection	4,8	Cranial BMD
Cho et al. 2009 [28]	Female C57Bl/6 mice	OVX	10	BMCS-(RED + GFP)/ BMCS-(RANK-Fc + CXCR4)/ BMCS-(RANK-Fc + GFP) /BMCS-(CXCR4 + RED)	6/6/6/9	BMSC	CXCR4 or Rank-fc	Reverse transcription virus	Tail vein injection	4,9	Cranial BMD
Lien et al. 2009 [39]	Female C3H/HeN mice	Glucocorticoid-induced osteoporosis	5	BMSC/BMSC-Cbfa1/BMSC-CXCR4/ BMSC-Cbfa1-CXCR4	5/5/5/5	BMSC	CXCR4 or Cbfa-1	Adenovirus	Peritoneal cavity Intraperitoneal injection	4	Tibial BMD
You et al. 2012 [38]	Female ddY mice	OVX	8	ADSC/ADSC-Zfp467	6/6	ADSC	Zfp467	lentiviral	Tail vein injection	4	Tibial BMD, BV/TV, Tb.N
Zhao et al. 2013 [31]	Female SD rats	OVX	24	BMCS/BMCS-BMP2	7/7	BMSC	BMP2	lentiviral	Local injectable fillers	12	Femur BMD,BV/TV, Tb.N, Tb.Sp, Tb.Th
Yin et al. 2015 [32]	Female SD rats	OVX Femoral Defects	28	BMSC/BMSC-OPG	12/12	BMSC	OPG	Adenovirus	Local injectable fillers	1,4	Femur BV/TV. Tb.N, Tb.Sp, Tb.Th
Liu et al.2016 [34]	Female SD rats	OVX Mandibular Defects	Unclear	BMSC/BMSC-OPG	12/12	BMSC	OPG	Adenovirus	Local injectable fillers	4,6,8	Mandibular BMD
Li et al. 2016 [35, 43]	Female SD rats	OVX Femoral Defects	8	BMSC/BMSC-BMP2	6/8	BMSC	BMP2	Plasmids	Local injectable fillers	2,4	Tibial BMD, BV/TV, Tb.N,Tb.Sp,Tb.Th
Akbar et al. 2017 [30]	Female C57Bl/6 mice	OVX	7	ADSC/AAT/ ADSC + AAT	10/9/10	ADSC	AAT	lentiviral	Peritoneal cavity Intraperitoneal injection	2,8	Lumbar spine BMD, BV/TV, Tb.N,Tb.Th
Li et al.2017 [36]	Female SD rats	OVX Femoral Defects	8	ADSC/ADSC-BMP2	12/12	ADSC	BMP2	Plasmids	Local injectable fillers	2,5	Tibial BMD, BV/TV, Tb.N, Tb.Sp, Tb.Th
Kong et al. 2018 [26]	Female C57Bl/6 mice	OVX	9	DPSC-Ad / DPSC-HGF	10/10	DPSC	HGF	Adenovirus	Tail vein injection	4,6	Femur BMD,BV/TV, Tb.N, Tb.Sp, Tb.Th

Table 1 (continued)

Author (year)	Subject animal	Disease model	Ages(weeks)	Grouping	Sample size(n)	Type of cells	Genetic Modification	Modified carriers	Transplantation route	Modeling Duration (weeks)	Outcomes
Sanghani et al. 2018 [37]	Female Wistar rats	OVX	24–36	OVXBMSC/ OVXBMSC-CXCR4/ YoungBMSC-CXCR4	6/6/6	BMSC	CXCR4	Adenovirus	Tail vein injection	11	Femur BMD
Wu et al. 2018 [33]	Female SD rats	OVX	12	BMSC/BMCS-(LV-SATB2)	3/3	BMSC	SATB2	lentiviral	Tail vein injection	12	Femur BMD,BV/TV, Tb.N, Tb.Sp
Chen et al. 2020 [29]	Female C57Bl/6 mice	OVX	6 ~ 8	Sca1/Sca1-PDGFB/Sca1-PDGFB-DSS6	6/7/7	BMSC	PDGF	lentiviral	Tail vein injection	10	Femur BV/TV Tb.Th, blood BALP
LIU et al. 2021 [24, 25]	Male optn/- C57Bl/6 mice	Osteoporosis in old age	64	BMSC-PBS/ BMSC-OPTN/ BMSC-FABP3	10/10/10	BMSC	OPTN or Fabp3	lentiviral	Tail vein injection	8	Femur BV/TV, Tb.N, Tb.Sp, Tb.Th
LIU et al. 2021 [24, 25]	Female C57Bl/6 mice	OVX	24	BMSC /BMSC-LRRc17	7/7	BMSC	LRRc17	lentiviral	Local injectable fillers	4	Femur BMD,BV/TV, Tb.N, Tb.Sp, Tb.Th

Abbreviations: *OVX* Ovariectomized, *BMSC* Bone Marrow Stem Cells, *ADSC* Adipose-Derived Stem Cells, *GFP* Green Fluorescent Protein, *RANK-Fc* Receptor Activator of Nuclear Factor Kappa-B Ligand, *Cbfa1* Core-binding factor alpha 1, *CXCR4* C-X-C Chemokine Receptor Type 4, *Zfp467* Zinc Finger Protein 467, *BMP2* Bone Morphogenetic Protein 2, *OPG* Osteoprotegerin, *AAT* Alpha-1 Antitrypsin, *DPSC* Dental Pulp Stem Cells, *HGF* Hepatocyte Growth Factor, *SATB2* Special AT-rich Sequence-binding Protein 2, *PDGF* Platelet-derived Growth Factor, *OPTN* Optineurin, *FABP3* Fatty Acid-binding Protein 3, *LRRc17* Leucine Rich Repeat Containing 17, *BMD* Bone Mineral Density, *BV/TV* Bone Volume to Total Volume Ratio, *Tb.N* Trabecular Number, *Tb.Sp* Trabecular Separation, *Tb.Th* Trabecular Thickness, *BALP* Bone Alkaline Phosphatase

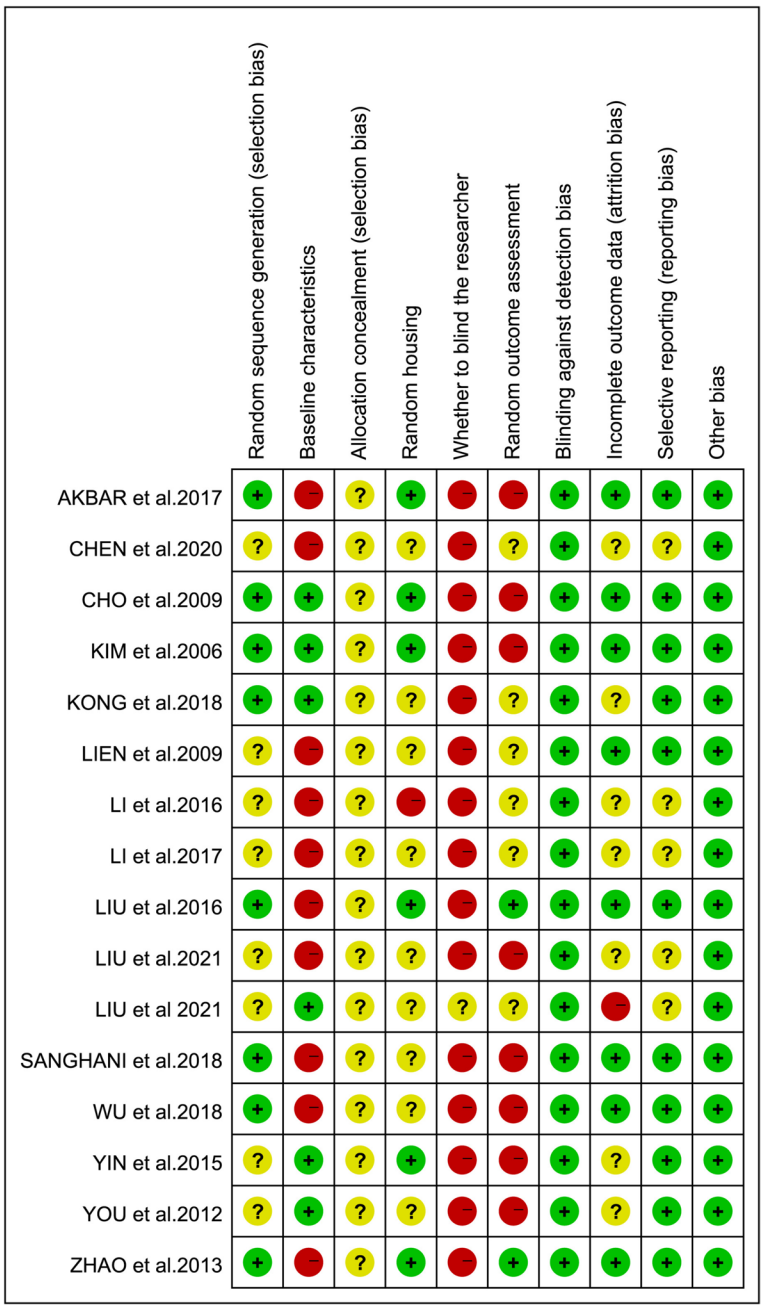

Fig. 2 Risk of bias assessment using the SYRCLE tool

for a given modifier gene was only one, it was grouped into other groups. Although there was no heterogeneity between the experimental and control groups ($I^2 = 0\%$, $p > 0.05$), there was no significant difference in BMD (SMD = 0.43,95% CI: −0.24, 1.11).

Sensitivity analyses and publication bias

Sensitivity analyses were conducted by sequentially excluding one comparison from the analysis and comparing the effects of the fixed effects model and the random effects model on the total effect volume, which were found to have no significant effect on the results of the meta-analysis (Appendix C: Fig. 1A). The funnel plots of BMD and BV/TV for the meta-analysis were asymmetrical on visual inspection, suggesting that possible publication bias may have existed among the included studies (Fig. 6).

Table 2 The study of correlation grouping and heterogeneity between BMD and BV/TV

Subground	Standardized mean difference (95% CI)	I^2	*P*
BMD			
Type of cells			
BMSC	1.44 [0.60, 2.29]	66%	< 0.05
ADSC	3.34 [1.13, 5.55]	72%	< 0.05
DPSC	1.90 [0.27, 3.54]	-	< 0.05
Transplantation pathways			
Tail vein injection	1.86 [0.17, 3.56]	78%	< 0.05
Local injectable fillers	2.41 [1.37, 3.44]	51%	< 0.05
Peritoneal cavity Intraperitoneal injection	1.17 [0.09, 2.24]	47%	< 0.05
Modifier genes			
CXCR4	0.43 [−0.24, 1.11]	0%	0.21
BMP2	0.43 [−0.24, 1.11]	59%	< 0.05
Others	2.63 [1.23, 4.03]	72%	< 0.05
BV/TV			
Type of cells			
BMSC	2.80 [1.20, 4.41]	82%	< 0.05
ADSC	3.34 [1.13, 5.55]	72%	< 0.05
DPSC	1.90 [0.27, 3.54]	-	< 0.05
Transplantation pathways			
Tail vein injection	2.26 [0.36, 4.16]	84%	< 0.05
Local injectable fillers	2.39 [0.81, 3.98]	80%	< 0.05
Peritoneal cavity Intraperitoneal injection	0.91 [−0.45, 2.27]	47%	0.19
Modifier genes			
CXCR4	-	-	-
BMP2	2.12 [0.83, 3.40]	59%	< 0.05
Others	3.03 [1.41, 4.64]	79%	< 0.05

Discussion

BMD and BV/TV were selected as primary metrics. BMD ascertained using quantitative CT techniques, is a crucial indicator of osteoporosis severity [40]. Similarly, BV/TV is vital for assessing bone strength and quality [41]. Our meta-analysis of controlled preclinical studies suggests that genetically modified stem cell transplantation significantly improves BMD and BV/TV in osteoporotic animal models. These results highlight the potential of gene-modified stem cell therapy as an effective approach to osteoporosis treatment.

Based on the 16 papers included in the article, stem cells in the literature are classified as BMSC, ADSC, and DPSC. Different sources of stem cells have different differentiation potentials and it has not yet been determined which stem cells have a unique advantage in targeting a particular disease, which may be a worthwhile direction for future research [42]. The transplantation route is divided into Tail vein injection, Local injectable fillers, and Peritoneal cavity intraperitoneal injection. There is relatively little research in the direction of transplantation pathways. The targets for genetic modification of stem cells for the treatment of osteoporosis were classified into seven types: Osteogenesis-related genes: Cbfa-1, BMP2, and SATB2; Broken Bones Related genes: OPG and RANK; Lipogenic related genes: Zfp467 and Fabp3; Enzyme-related genes: AAT; Stem cell migration-associated genes: CXCR4; Proliferation-related genes: HGF and PDGF; Autophagy-related genes: OPTN and LRRc17.

A subgroup analysis of the above two outcome indicators was conducted to look for sources of heterogeneity and found that stem cell types, transplantation routes, and modifier genes were all possible factors influencing heterogeneity. Although there was high heterogeneity in all stem cell groups, except for the DPSC group, probably related to its small sample size, there were significant differences in BMD and BV/TV results between the experimental and control groups, regardless of the type of stem cells. The results of the subgroup analysis of the transplantation route showed no significant difference between the experimental and control groups for intraperitoneal injection in the BV/TV assessment, because the small sample size for this subgroup analysis may have led to false positive or false negative findings.

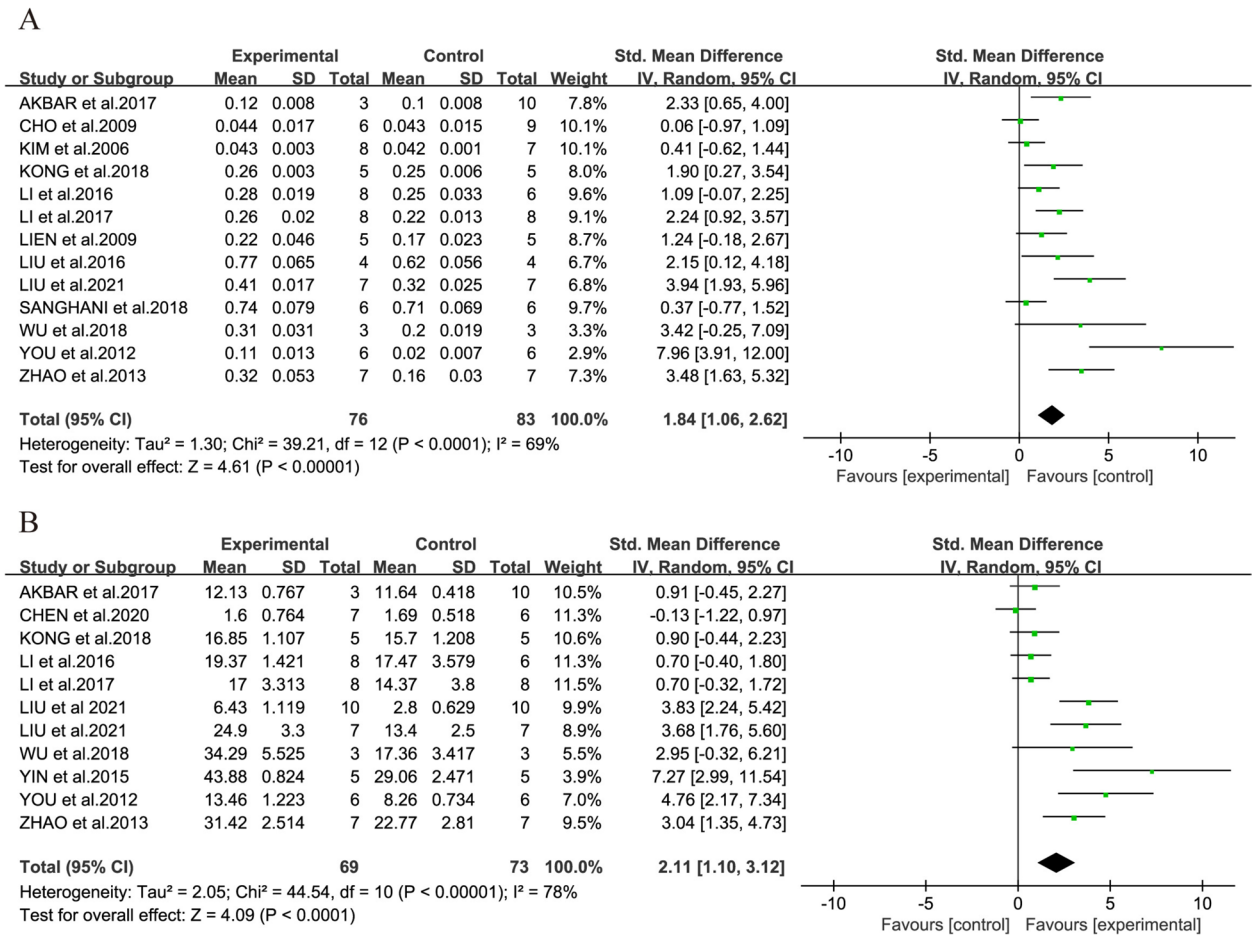

Fig. 3 **A** Forest plot showing the impact of genetically stem cells therapy on BMD. **B** Forest plot showing the impact of genetically stem cells therapy on BV/TV. Compared with controls. 95% CI, 95% confidence interval

In the subgroup of modified genes in BMD, all modifier genes except BMP2 and CXCR4 were grouped into the same category, as the literature was insufficient and the results of the analysis were less convincing. There was no heterogeneity and no significant difference between the experimental and control groups for the modified gene CXCR4. This result may be related to the insufficient number of studies in the subgroup, and additional evidence is needed from a larger sample of studies. In addition, there may be greater heterogeneity between groups due to subject animals, grafts, osteoporosis models, gene transfection vectors, etc., but there are relatively few targeted studies.

Our meta-analysis has several advantages. First, this study is the first to assess the effects of genetically modified stem cells for preclinical studies. While previous meta-analyses have assessed the benefits of stem cells in animal models of osteoporosis [43, 44], the meta-analysis reported here includes stem cells with different genetic modifications and recently published studies. Secondly, we conducted a systematic literature search, comprehensive data collection, and subgroup analysis by stem cell type, transplantation pathway, and modification gene, which improved the accuracy of our findings. Thirdly, the main results on BMD and BV/TV could provide important insights for future studies.

Our study has several limitations. Funnel plots and Egger regression tests highlighted publication bias in our meta-analysis. Notably, studies with positive findings are often more favored for publication, especially in animal research. We confined our analysis to published works, and the emergence of unpublished data could potentially modify our conclusions. Additionally, the quality of several included studies was less than ideal. There's no well-defined, standardized system for quality evaluation in meta-analyses of animal experiments, leading to non-uniform assessments across the literature. Many studies lack detailed descriptions about the randomized assignment of animals, hampering consistent subsequent analyses. We also noted substantial heterogeneity in the

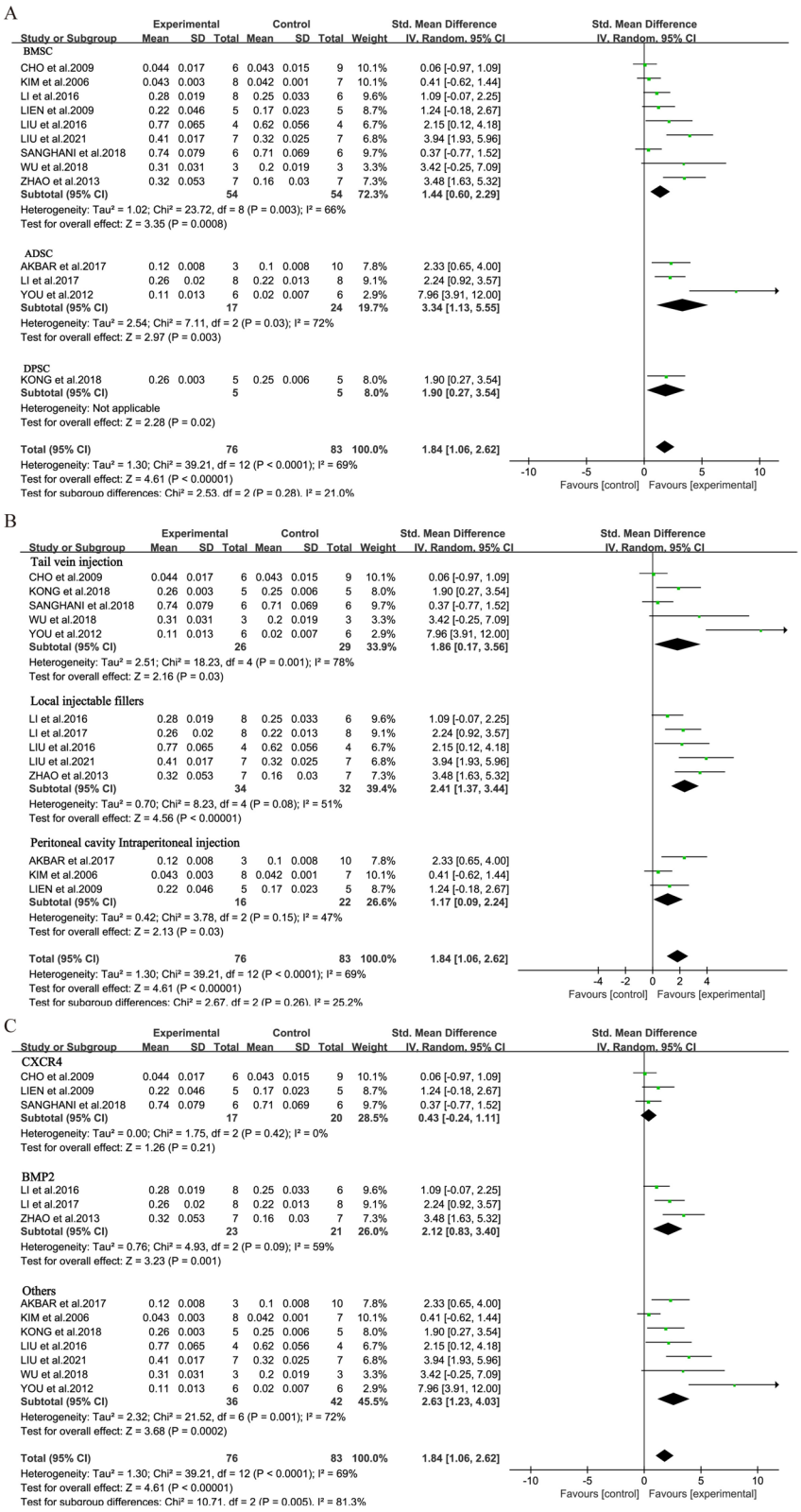

Fig. 4 Subgroup analyses on the effect of various factors on BMD. **A** Effect of stem cell type on BMD. **B** Effect of different transplantation routes on BMD. **C** Effect of gene modification type on BMD

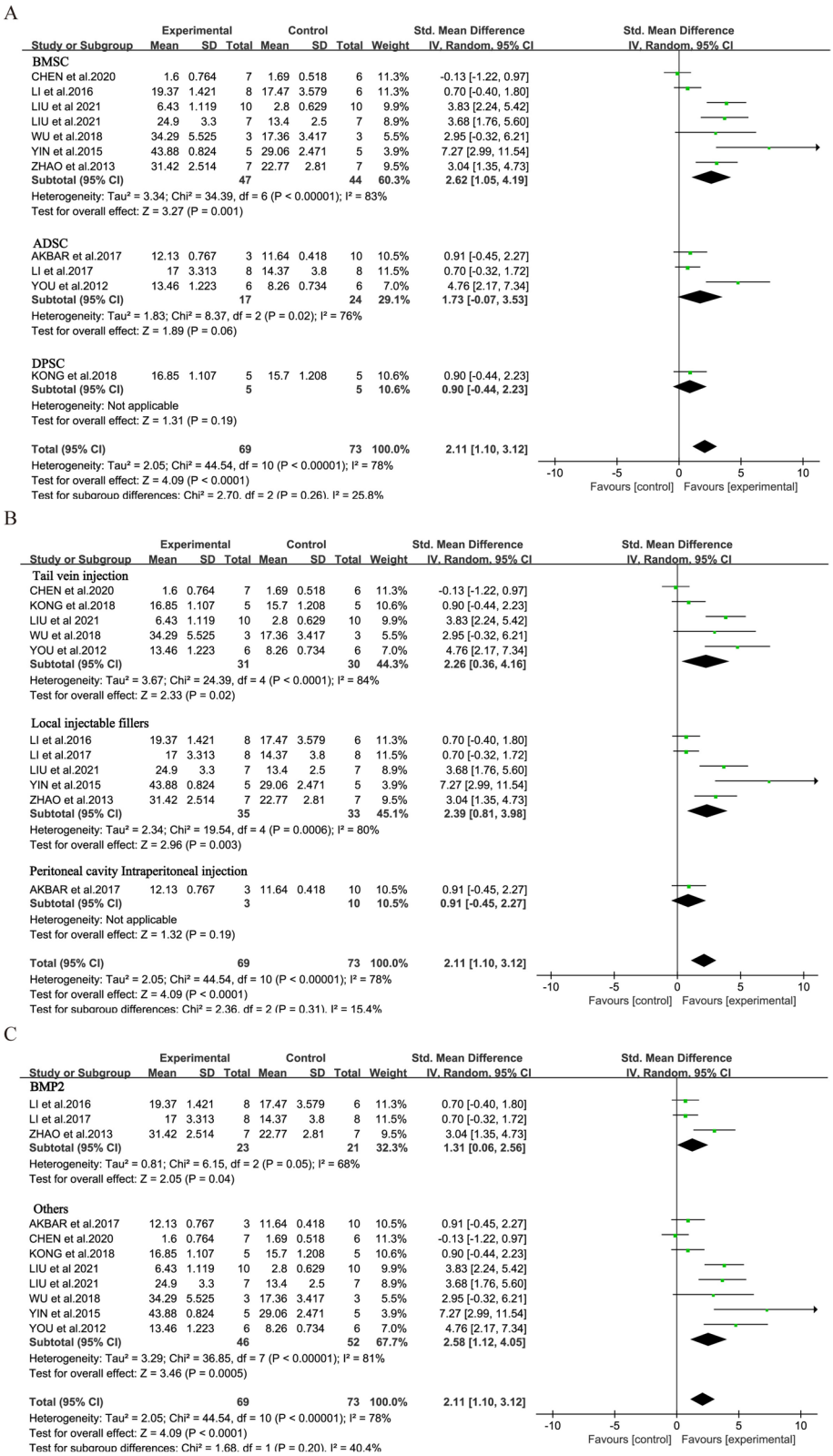

Fig. 5 Subgroup analyses on the effect of various factors on BV/TV. **A** Effect of stem cell type on BV/TV. **B** Effect of different transplantation routes on BV/TV. **C** Effect of gene modification type on BV/TV

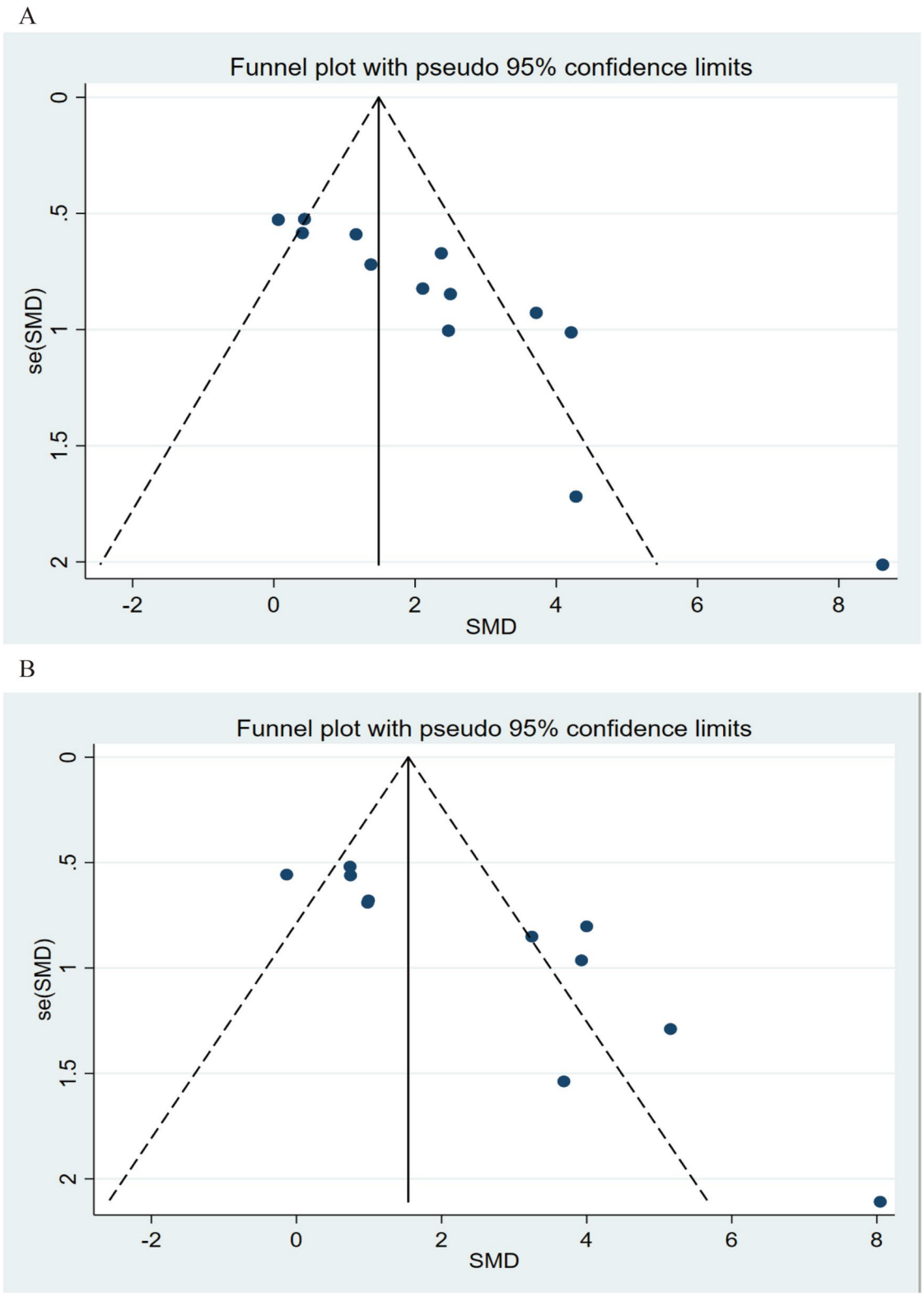

Fig. 6 Funnel plot of included studies for a BMD and b BV/TV

results for BMD and BV/TV between experimental and control groups, albeit this is frequently seen in animal research.

Conclusion

Gene-modified stem cell therapy shows significant promise in enhancing bone mineral density and bone volume fraction in osteoporotic animal models, which provides an important basis for future translational clinical studies. Due to the poor methodological quality, large sample, prospective, double-blind, randomized controlled trials are needed to demonstrate the safety and efficacy of gene-modified stem cell therapy in osteoporotic animals.

Abbreviations

BMD	Bone mineral density
BV/TV	Bone volume fraction
ADSC	Adipose-derived stem cell
BMSC	Bone marrow stem cell
DPSC	Dental pulp-derived stem cell
CI	Confidence interval
SMD	Standard mean difference

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12891-025-08507-0.

Supplementary Material 1.

Authors' contributions

All of the authors have contributed extensively to the work presented in this article. MH designed the study. MH and NX collected the data and performed all analysis. MH, PL wrote the manuscript. MH and NX resolved any differences through discussions. The authors read and approved the final manuscript.

Funding

Gannan Medical University Postgraduate Innovation Special Fund (Grant No. YC2022-X015).

Data availability

Further details on the data processing can be obtained by contacting the corresponding author.

Declarations

Ethics approval and consent to participate

This study is a meta-analysis that synthesizes data from previously published research. As such, it did not involve direct interaction with human or animal subjects. All studies included in our analysis received ethical approval and informed consent as per their original publications.

Competing interests

The authors declare no competing interests.

Received: 28 October 2023 Accepted: 6 March 2025
Published online: 14 March 2025

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