European Review for Medical and Pharmacological Sciences 2024; 28: 2237-2249

Causal relationship between circulating inflammatory factors and osteoporosis: a bidirectional Mendelian randomization study

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Abstract. – OBJECTIVE: Osteoporosis (OP), a persistent metabolic bone disorder linked with inflammation, has an undetermined cause. In our research, we employed bidirectional Mendelian randomization (MR) to investigate the interplay between OP and inflammation agents.

MATERIALS AND METHODS: We performed two-way pooled-level MR analyses to characterize the causal relationship between 41 circulating inflammatory modulators and OP. Genetic variation data for the 41 regulatory factors associated with inflammation were obtained from genome-wide association studies (GWASs) of human cytokines. Bone mineral density (BMD) was utilized as a phenotype for OP in our approach. The BMD dataset, sourced from the GEFOS consortium, a large GWAS meta-analysis study and UK Biobank, was classified based on varied sections [whole body (TB), lumbar spine (LS), femoral neck (FN), forearm (FA), and heel] and age brackets (0-15 years, 15-30 years, 30-45 years, 45-60 years, and above 60 years). Primary MR analyses were executed using the inverse variance weighting (IVW) method, and sensitivity analyses were performed using the MR-Egger, weighted median, simple model, and weighted model. Cochran's Q test was utilized to evaluate the existence of heterogeneity. We used MR-Egger regression and MR multiplicity of residuals and outliers (MR-PRESSO) to assess pleiotropy.

RESULTS: After false discovery rate (FDR) correction, elevated levels of circulating interleukin-8 (IL-8) [β = 0.072 (0.031-0.114), $p < 0.01$], macrophage inflammatory protein-1b (MIP-1β) [β = 0.008 (0.003-0.013), $p < 0.01$; β = 0.026 (0.009-0.042), $p < 0.01$], and cutaneous T-cell attracting chemokine (CTACK) [β = 0.037 (0.017-0.056), $p < 0.01$] was associated with a reduced risk of OP. Reduced levels of hepatocyte growth factor (HGF), IL-1ra, IL-10, macrophage colony-stimulating factor (MCSF), and MIP-1α were associated with a reduced risk of OP [β = -0.030 (-0.047 – -0.013), $p < 0.01$; β = -0.025 (-0.041 – -0.010), $p < 0.01$; β = -0.018 (-0.029 – -0.007), $p < 0.01$; β = -0.060 (-0.097 – -0.024), $p < 0.01$; β = -0.118 (-0.190 – -0.047), $p < 0.01$]. We observed a significant causal correlation between FN-BMD and MCP-3 (FDR < 0.05). The occurrence of OP may also lead to elevated levels of MCP3 [β = -0.466 (-0.714 – -0.217), $p < 0.01$]. The reliability of the results was confirmed by sensitivity analyses.

CONCLUSIONS: This study demonstrated the pathogenic role of circulating inflammatory modulators in OP using bidirectional MR analysis. This further deepens the understanding of OP pathogenesis and provides new ideas for therapeutic intervention in OP.

Key Words:
Bidirectional Mendelian randomization, Circulating inflammatory regulators, Osteoporosis, Bone mineral density.

Introduction

Osteoporosis (OP) is a skeletal disorder characterized by diminished bone mineral density (BMD) and elevated fracture hazard[1]. It is a disease that afflicts the elderly population and increases fragility fractures, thus negatively affecting the quality of life. This represents a significant global public health issue, impacting millions of people globally[2]. The loss of BMD and bone mass is associated with excessive apoptosis of osteoblasts[3]. In addition to this, osteoporosis

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is a multifactorial disease in which age, gender, calcium and vitamin D intake, physical activity, and family history of osteoporosis have all been implicated. Its pathogenesis also includes oxidative stress and inflammation. OP frequently complicates chronic inflammatory conditions, with a rise in pro-inflammatory cytokines substantially contributing to bone depletion by enhancing bone resorption and hindering bone formation[4,5]. Minimizing inflammation levels is crucial for osteoporosis prevention.

Inflammatory factors known to be associated with osteoporosis include nuclear factor (NF)-kappaB (NF-κB), interleukin-6 (IL-6), IL-7, tumor necrosis factor-alpha (TNF-α), and TGF-β, which mainly promote the secretion of Receptor activator of nuclear factor kappa beta ligand (RANKL) to increase osteoclast differentiation and promote macrophage colony-stimulating factor (M-CSF) expression[6-10]. Previous literature may not have definitively examined cause and effect and provided an overall perspective, leading to inconsistent findings across different studies. It is well recognized that the inflammatory response is a dynamic process; thus, single-point measurements of high (or low) values may not accurately reflect the overall trend of changes in inflammatory factors. Additionally, observational research frequently lacks regulation for possible disruptors and inverse causality bias.

Mendelian randomization (MR), as an analytical method, a methodical approach employing genetic diversity as an instrumental factor for exposure evaluation, allows reasonable inference about etiology while minimizing confounding variables and measurement errors associated with reverse causation bias. Two-way MR may be utilized to ascertain the causative direction between two interconnected phenotypes.

Therefore, the authors selected 41 systemic inflammatory modulators to investigate their causal relationship with OP[11,12].

Materials and Methods

Data Resource

The schematic representation of the bidirectional Mendelian randomization study is depicted in Figure 1. Initially, we obtained the most

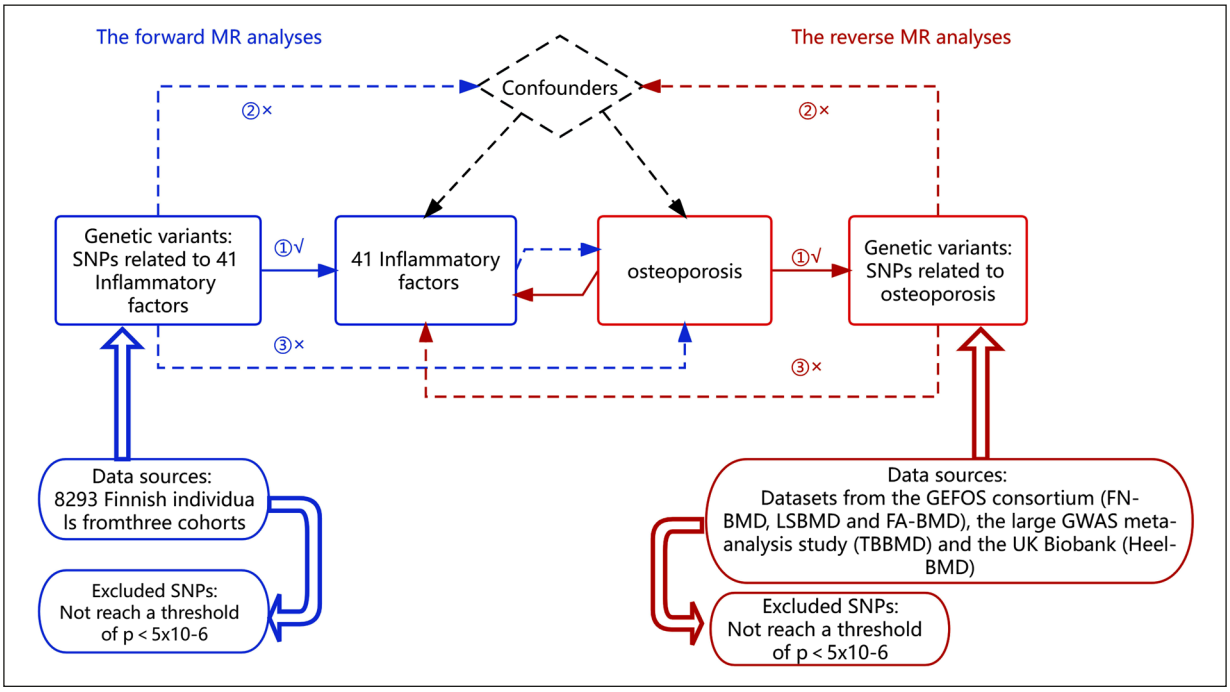

Figure 1. Flow chart. MR analyses depend on three core assumptions: (1) Relevance: G is associated with the X; (2) Independence: G is not related to any confounding factors of the exposure-outcome association; (3) Exclusion restriction: G does not affect Y except through its potential effect on the X. G, genetic variant; X, exposure; Y, outcome. Blue represents forward MR analysis with 41 inflammatory factors as exposure and osteoporosis as the outcome. Red represents reverse MR analysis with osteoporosis as exposure and 41 inflammatory factors as the outcome. MR, Mendelian randomization; SNPs, single nucleotide polymorphisms.

inclusive and extensive dataset on cytokines associated with inflammation from the publicly accessible Genome-Wide Association Study (GWAS) database. Single nucleotide polymorphisms (SNPs) associated with inflammatory factors were obtained from 8,293 Finns in three independent cohorts from FinnGen Biobank (https://www.finngen.fi/en) and included 41 cytokines and growth factors[12]. The summary data for the genetic associations with the results are detailed in Table I. We opted for BMD as the genetic tool, focusing on site and age selection. These tools encompass lumbar spine bone mineral density (LS-BMD), femoral neck bone mineral density (FN-BMD), and forearm bone mineral density (FA-BMD). LS-BMD, FN-BMD, and FA-BMD were determined using dual-energy X-ray bone densitometry (DXA) by the GEFOS Consortium (http://www.gefos.org)[13]. Heel bone mineral density (Heel-BMD) was assessed through ultrasonic measurements conducted by the UK Biobank[14]. Whole-body DXA measurements of bone mineral density (TB-BMD) were obtained from a comprehensive GWAS meta-analysis[15]. TB-BMD is classified into five age brackets: 0-15 years, 15-30 years, 30-45 years, 45-60 years, and above 60 years. **Supplementary Table I** provides further details on the GWAS and datasets used in our study. The GWAS summary information employed in this study was derived from published research where each participant provided written informed consent; thus, no approval from the institutional review board was necessary.

Instrumental Variables Selection

Firstly, we applied a genomics-wide importance threshold of $p < 5\times10^{-6}$ for selecting SNP, tightly linked with inflammation agents, as prospective IVs[16]. Subsequently, to prevent false-positive IVs occurrences, we needed to exclude the interference of linkage disequilibrium (LD), and the aggregation parameters were set to $R^2 < 0.001$ with a window size = 10,000 kb[17]. Furthermore, aiming to nullify potential manifold impacts, we explored the Phenoscanner V2 portal (http://www.PhenoScanner.medschl.cam.ac.uk/) for links between chosen SNP and any disruptors potentially affecting the nexus between inflammation agents and BMD, en-

Table I. The sample sizes for each type of BMD analyzed in this study were obtained from GWAS.

Bone mineral density	Sample size	Ancestry	Consortia	URL of available datasets
Femoral neck bone mineral density	32,735	European	GEFOS Consortium	https://gwas.mrcieu.ac.uk/datasets/ieu-a-980/
Lumbar spine bone mineral density	28,498	European	GEFOS Consortium	https://gwas.mrcieu.ac.uk/datasets/ieu-a-982/
Forearm bone mineral density	8,143	Mixed	GEFOS Consortium	https://gwas.mrcieu.ac.uk/datasets/ieu-a-977/
Heel bone mineral density	265,627	European	UK Biobank	https://gwas.mrcieu.ac.uk/datasets/ukb-b-8875/
Total body bone mineral density	56,284	European	GWAS meta-analysis study	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST005348/
Total body bone mineral density (age 0-15)	11,807	Mixed (more than 86% European)	GWAS meta-analysis study	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST005345/
Total body bone mineral density (age 15-30)	4,180	Mixed (more than 86% European)	GWAS meta-analysis study	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST005344/
Total body bone mineral density (age 30-45)	10,062	Mixed (more than 86% European)	GWAS meta-analysis study	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST005346/
Total body bone mineral density (age 45-60)	18,805	European	GWAS meta-analysis study	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST005350/
Total body bone mineral density (age over 60)	22,504	Mixed (more than 86% European)	GWAS meta-analysis study	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST005349/

Genome-wide association studies (GWASs), bone mineral density (BMD).

compassing diabetes, rheumatoid arthritis, lipid levels, and body mass index (BMI). Weak instrumental variables with F-statistics less than 10 were excluded due to a low significance threshold, which indicates that the study is sufficiently robust in terms of avoiding bias[18]. Inconsistent alleles were excluded after matching the selected SNP with the outcome dataset SNPs and palindromic SNPs. Ultimately, we utilized SNP, encompassing 41 systemic inflammation regulators and having undergone stringent screening, for ensuing MR examination.

Statistical Analysis

In this bidirectional MR study, we mainly used the inverse-variance weighted (IVW) method to estimate the causal relationship between inflammatory cytokine levels and BMD. IVW incorporates the Wald estimator of SNP, which has higher statistical efficacy compared to the other methods and was used as the main analytical method[19]. In addition, to improve the reliability of our findings, MR-Egger regression, weight median estimator (WME), and simple and weighted models were used as complementary methods to IVW. We used a combination of Cochran's Q statistic and *p*-value to determine the presence of heterogeneity ($p < 0.05$ indicates the presence of significant heterogeneity)[20]; in addition, we used the intercepts of the instrumental variables in the MR-Egger regression to test for the presence of horizontal multinomiality in the instrumental variables ($p < 0.05$ indicates the presence of horizontal multinomiality)[21]. The MR-PRESSO method was used to detect and identify potential horizontal multinomiality and to obtain unbiased causal estimates by removing possible outliers[22]. Finally, we assessed overall stability by performing "leave-one-out" analyses to test for the presence of SNPs with biased effects. Due to the inclusion of 41 exposure factors, we used a false discovery rate (FDR) correction to control for false positives in multiple testing[23]. Specific inflammatory factors estimating causal effects were considered statistically significant if their FDR values were lower than 0.05, and the *p*-value ranging from the conventional benchmark ($p = 0.05$) to the FDR-adjusted marker of statistical prominence would serve as indicative proof of a possible causative link. All statistical analyses were performed using the TwoSampleMR package (version 0.5.8, Bristol, UK) in R software version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria) and the MR-PRESSO package (version 1.0, New York, NY, USA).

Results

In this study, a bidirectional association was found between the levels of inflammation-related cytokines and BMD. Multiple genetically predicted inflammatory cytokines were associated with BMD. The IVW method revealed 29 causal associations between inflammatory cytokines and BMD phenotypic features ($p < 0.05$). After FDR correction, we observed 9 inflammatory cytokines with significant causal correlation with BMD (FDR < 0.05). The results are shown in Figure 2. Elevated levels of circulating IL-8 [$\beta = 0.072$ (0.031 - 0.114), $p < 0.01$], MIP-1β [$\beta = 0.008$ (0.003 - 0.013), $p < 0.01$; $\beta = 0.026$ (0.009 - 0.042), $p < 0.01$], and Cutaneous T-cell-attracting chemokine (CTACK) [$\beta = 0.037$ (0.017 - 0.056), $p < 0.01$] were associated with a reduced risk of OP. Reduced levels of HGF, IL-1ra, IL-10, MCSF, MIP-1α were linked with a greater hazard of OP [$\beta = -0.030$ (-0.047 − -0.013), $p < 0.01$; $\beta = -0.025$ (-0.041 − -0.010) , $p < 0.01$; $\beta = -0.018$ (-0.029 − -0.007) , $p < 0.01$; $\beta = -0.060$ (-0.097 − -0.024), $p < 0.01$; $\beta = -0.118$ (-0.190 − -0.047), $p < 0.01$]. As shown in Table II, the MR-Egger intercept, Cochran's Q test, and MR-PRESSO global test analyses, with the exception of MIP-1β, did not reveal heterogeneity or horizontal multiplicity in the main analyses ($p > 0.05$). Moreover, not a single SNP notably influenced the comprehensive impact of cytokines on OP in IVW in leave-one-out sensitivity evaluations. Figure 2 displays a forest diagram of these outcomes. BMD was associated with inflammatory cytokines, and the IVW approach revealed 35 causal associations between BMD and inflammatory cytokine phenotypic profiles ($p < 0.05$). After FDR correction, we observed a significant causal correlation between FN-BMD and MCP-3 (FDR < 0.05). The results are shown in Figure 3. Similarly, Scatter plots of causal relationships between inflammatory factors and BMD at different sites and ages using different MR methods are shown in Figure 4.

Furthermore, sensitivity assessments revealed no notable outcomes, verifying the dependability of the IVW approach. The notable findings of the MR sensitivity evaluations in this study are displayed in Table II. Considering the sig-

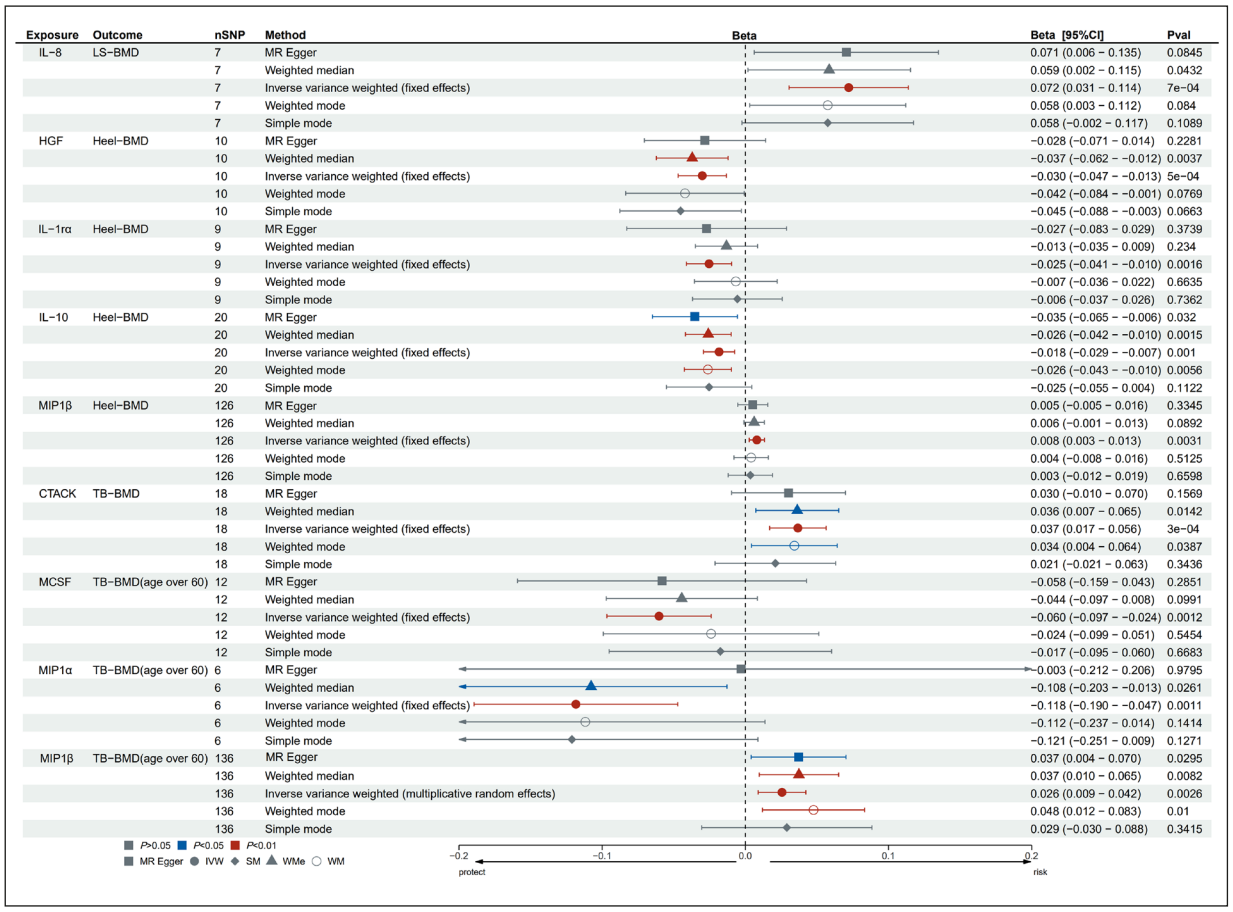

Figure 2. 41 causal effects of circulating inflammatory regulators on BMD at different sites. LS-BMD, lumbar spine bone mineral density; TB-BMD, total body bone mineral density; Heel-BMD, heel bone mineral density; nSNP, number of single nucleotide polymorphisms; CI, confidence interval. IL, interleukin; HGF, hepatocyte growth factor; MIP1α, macrophage inflammatory protein-1a; MIP1β, macrophage inflammatory protein-1b; CTACK, cutaneous T-cell attracting chemokine; M-CSF, macrophage colony-stimulating factor.

nificant causal effect of FN-BMD on MCP-3, we performed a leave-one-out sensitivity analysis. We observed relatively consistent and significant trends across MR tests (Figure 5A), and effect size results for IVW and MR-Egger were consistent with significance (Figure 5B).

Discussion

The link between inflammatory factors and OP has been a focal point in the medical field, and many conjectures have been proposed to elucidate the connection between the two. In the present study, we performed a comprehensive MR analysis to investigate whether circulating inflammatory factors are causally related to OP and *vice versa*. Based on our MR analytical study of 41 cytokines in the largest GWAS dataset, we reached a relatively reliable conclusion that elevated levels of the circulating inflammatory factors IL-8, MIP-1β, and CTACK, as well as reduced levels of HGF, IL-1ra, IL-10, MCSF, and MIP-1α, are associated with a reduced risk of OP. In addition, OP may also lead to increased levels of MCP3.

A tight connection exists between inflammation and reactive oxygen species (ROS), being pro-inflammatory agents generated in the inflammatory procedure. Augmentations in pro-inflammatory cytokines like IL-1, IL-6, and TNF-α consequently activate ROS generation[24,25]. All of this increases or inhibits the function of osteoclasts and osteoblasts, thereby affecting osteoblastic activity and, consequently, bone homeostasis[26]. Therefore, strategies to inhibit pro-inflammatory activities are expected to promote bone regeneration and thus prevent inflammation-induced osteoporosis[3,27]. In addition, chronic inflamma-

Table II. Results of the MR study testing the causal association between systemic inflammatory regulators and risk of BMD.

Exposures	Number of SNPs	*p* for IVW	*p* for FDR	*p* for heterogeneity test	*p* for MR-Egger intercept	*p* for MR-PRESSO (0 outliers)
Cytokines						
Cutaneous T-cell attracting (CCL27)	18	2.71E-04	0.011	0.323	0.708	0.423
Macrophage inflammatory protein-1α (CCL3)	6	0.001	0.024	0.840	0.315	0.874
Macrophage colony-stimulating factor (MCSF)	12	0.001	0.024	0.113	0.963	0.152
Macrophage inflammatory protein-1β (CCL4)	136	0.003	0.035	0.262	0.423	0.258
Interleukin-8 (CXCL8)	7	6.78E-04	0.028	0.557	0.950	0.718
Hepatocyte growth factor (HGF)	10	4.67E-04	0.019	0.106	0.919	0.145
Interleukin-10 (IL-10)	20	9.55E-04	0.020	0.114	0.234	0.141
Interleukin-1 receptor antagonist (IL-1ra)	9	0.002	0.022	0.173	0.952	0.233
Macrophage inflammatory protein-1β (CCL4)	126	0.003	0.032	5.73E-06	0.537	0.326
Bone mineral density						
FN-BMD	55	2.44E-04	0.010	0.243	0.203	0.263

FN-BMD, femoral neck bone mineral density; single nucleotide polymorphisms (SNPs); inverse-variance weighted (IVW).

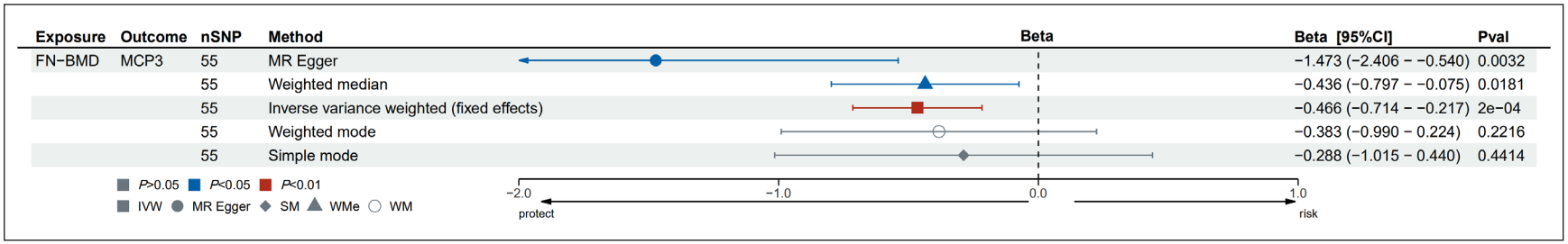

Figure 3. Causal effects of BMD at different sites on 41 circulating inflammatory modulators. FN-BMD, femoral neck bone mineral density. MCP3, monocyte-specific chemokine 3.

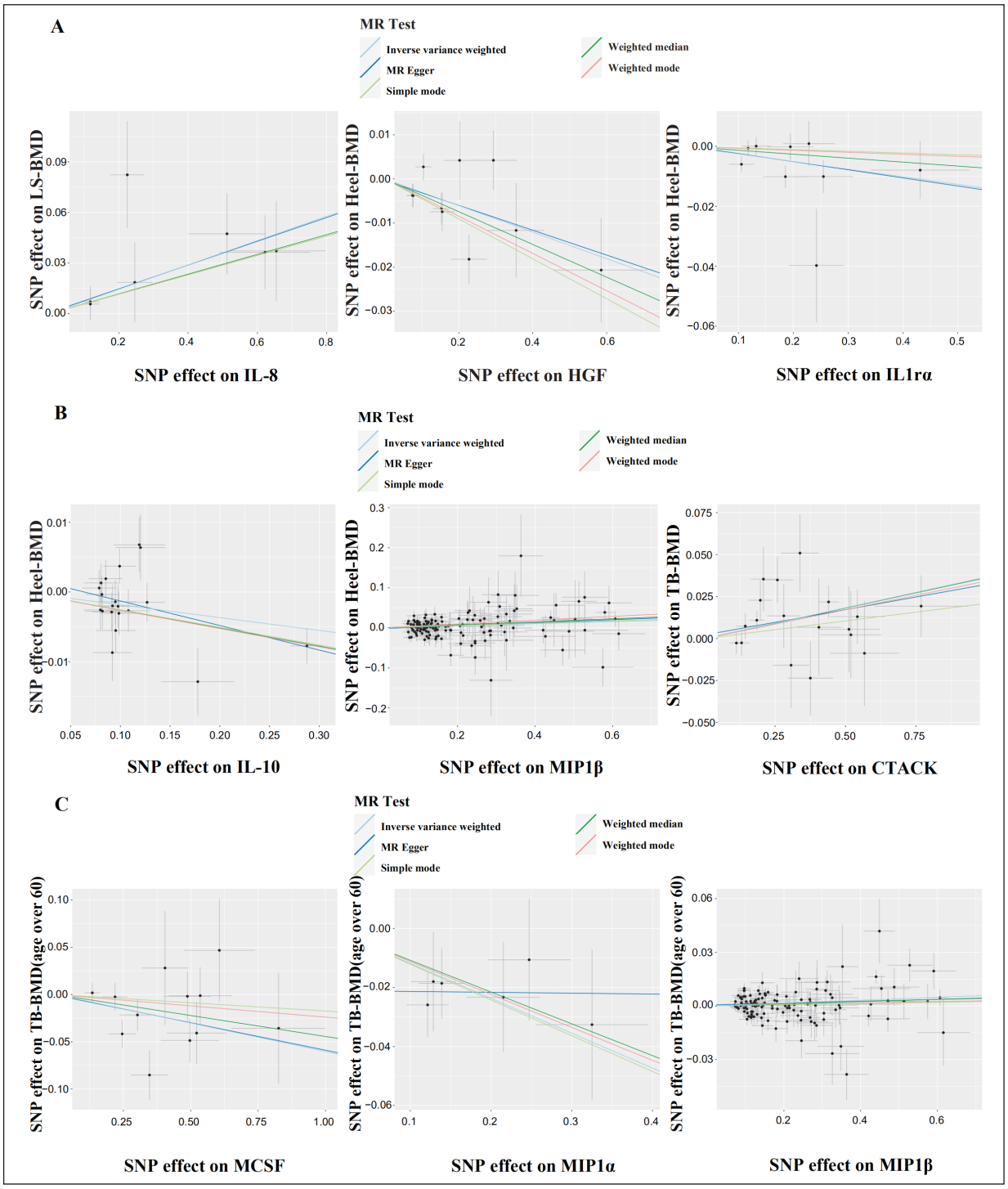

Figure 4. Scatter plots of the causal relationship between inflammatory factors and BMD at different sites and ages using different MR methods. LS-BMD, lumbar spine bone mineral density; TB-BMD, total body bone mineral density; Heel-BMD, heel bone mineral density. IL, interleukin; HGF, hepatocyte growth factor; MIP1α, macrophage inflammatory protein-1a; MIP1β, macrophage inflammatory protein-1b; CTACK, cutaneous T-cell attracting chemokine; MCSF, macrophage colony-stimulating factor.

tion affects the secretion of parathyroid hormone (PTH), which is involved in the regulation of bone metabolism. High levels of PTH increase bone resorption, leading to a decrease in bone mineral density[28,29]. However, the mechanisms regulating the inflammatory response during osteoclast differentiation need to be further investigated. IL-8 is produced by macrophages along with epithelial

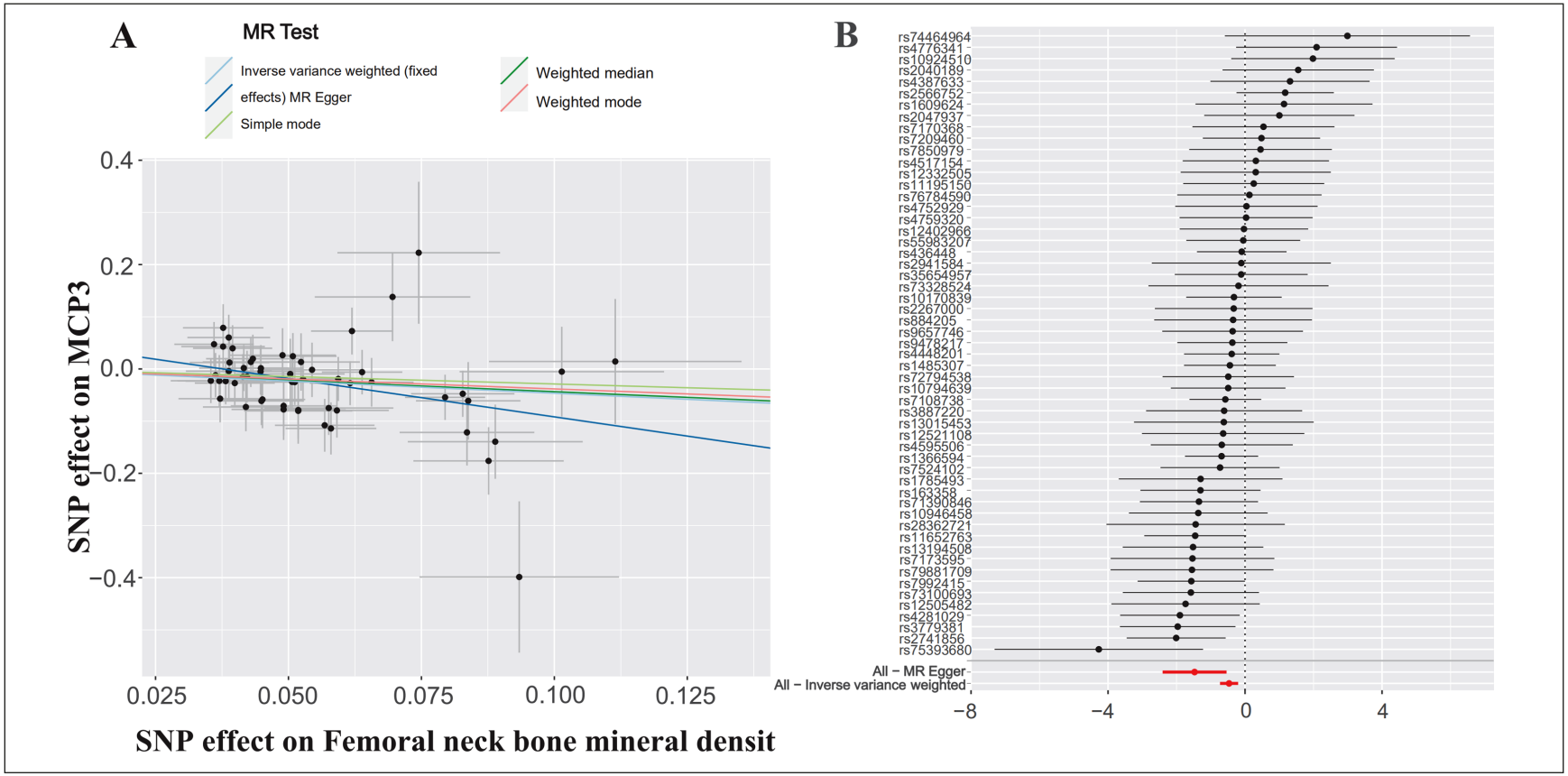

Figure 5. Sensitivity analysis of the causal relationship between BMD and inflammatory factors. **A**, MR effect size of FN-BMD on MCP-3. **B**, Causal estimates for different MR tests. FN-BMD, femoral neck bone mineral density; MCP3, monocyte-specific chemokine 3.

cells, and its principal biological function involves drawing in and energizing neutrophils, part of the CXC group of standard chemokines[30]. In our study, we found that higher levels of IL-8 expression were associated with a lower likelihood of spinal osteoporosis, consistent with a previous study[31] that IL-8 recruits bone marrow mesenchymal stem cells (BMSCs) to repair cartilage defects. In addition, another study[32] also suggested that IL-8 enhances the therapeutic effect of MSC on bone regeneration *via* the CXCR2-mediated PI3k/Akt signaling pathway. CTACK is involved in the migration of keratinocyte precursor cells from the BM to the skin as a major regulator and may contribute to delayed healing[33]. However, the literature is limited on the relevance of CTACK to OP, and our study fills this gap and provides new ideas for the treatment of OP.

Macrophages assume a significant part in inflammation, wound healing, and tissue restoration. Macrophage inflammatory proteins-1α (MIP-1α) along with MIP-1β, closely related constituents of the CC chemokine subgroup, display diverse pro-inflammatory actions *in vitro*, encompassing leukocyte chemotaxis. The release of MIP-1α and MIP-1β is tightly linked with the capability of myeloma cells to intensify osteoclastic bone dissolution both *in vitro* and *in vivo*. Recombinant MIP-1α and MIP-1β prompt stromal cells to produce nuclear factor-κB receptor activator-κB (RANK) ligands, promoting osteoclast precellular diversification[34]. As in our study, previous studies[35] have shown that MIP-1a is the most potent soluble factor leading to osteolysis. M-CSF, initially characterized as a growth element for mononuclear phagocyte lineages, plays a role in immune and inflammatory reactions alongside bone metabolism[36-39]. However, controversy still exists as to whether M-CSF has a protective or destructive effect on bone, with some authors suggesting that M-CSF signaling protects bone by restricting osteoclast formation[40,41], whereas others suggest that M-CSF promotes osteoclast formation[42,43]; however, through our MR analysis study, we found that reduced levels of M-CSF were responsible for increased total BMD in people over 60 years of age.

Hepatocyte growth factor (HGF) is a multifunctional growth factor involved in organ and tissue repair and bone remodelling[44]. HGF is highly abundant in the bone marrow of patients with multiple myeloma and induces the expression of RANKL in osteoblasts and bone marrow stromal cells (BMSCs)[45]. Standal et al[46] found that HGF inhibited bone morphogenetic protein (BMP)-induced osteoclastogenesis *in vitro* and observed a negative correlation between serum HGF concentration and markers of osteoclast activity in the sera of 34 myeloma patients, suggesting that HGF inhibits bone formation in multiple myeloma. Interestingly, Zhen et al[47] found that HGF promotes bone regeneration through the production of bone morphogenic protein-2 (BMP-2)[48]. Furthermore, HGF stimulates the production of vascular endothelial growth factor (VEGF), which fosters bone development *via* its angiogenic characteristics[49]. The release of HGF similarly diminishes in reaction to cellular aging, illness, or the age of the donor[50].

Monocyte chemotactic protein 3 (MCP-3/CCL7) attracts bone marrow stromal cells, developed endothelial cells, and precursor cells, promoting angiogenesis as well as osteogenic diversification[51], and MCP-3 expression is upregulated in the early stages of fracture healing[52].

Studies[53] have shown that MCP-3 is another possible signaling pathway for the recruitment of progenitor cells from the somatic circulation and is a homing factor for MSCs. Alternatively, MCP-3 may act as a physiological signal transducer and a potential therapeutic agent to enhance the homing of circulating progenitor cells to sites of bone repair[54].

Interestingly, we found that elevation of the inflammatory factors MCSF and MIP-1α led to a decrease in TB-BMD in those older than 60 years of age, and no such significant causal relationship was found for TB-BMD in other age groups. Whether MCSF and MIP-1α increase with age has been little studied; therefore, this is our next research direction. In contrast, a decrease in MIP-1β led to a decrease in TB-BMD in people over 60 years of age, which is inconsistent with the results of most studies, and the reason for this difference may be related to our sample size. The neutrophil-to-lymphocyte ratio (NLR), monocyte-to-HDL cholesterol ratio (MHR), and platelet-to-lymphocyte ratio (PLR) are commonly used to assess inflammation and immune system status, and recent results have shown that NLR correlates with early stages of LEAD[55]. Osteoporosis is a disease associated with bone health. While these ratios are not directly linked to osteoporosis, they can provide some indirect information, as inflammation and immune system status may be associated with osteoporosis risk. High NLR, MHR, and PLR may indicate the presence of an inflammatory response in the body, and chronic inflammation is associated with the development of osteoporosis. Chronic inflammation may lead to bone

loss and decreased bone density. It is important to note that while these ratios may provide some indication, the diagnosis and management of osteoporosis usually requires a more comprehensive assessment.

Current osteoporosis treatment consists of calcium, vitamin D, and drugs that have anti-bone resorption or anabolic effects on bone[56]. However, anti-inflammatory drugs are used less in the treatment of OP; therefore, our study provides a new idea for the treatment of osteoporosis and a theoretical basis for the treatment of osteoporosis with anti-inflammatory drugs.

The strength of this study is that the causal relationship between 41 circulating inflammatory factors and OP was explored using a two-sample Mendelian randomization method, which effectively avoids potential confounders and reverses causality from interfering with MR results. Meanwhile, the datasets used for exposure and outcome in this study were obtained from different large public GWAS databases, and the possibility of duplication of samples from different databases is small, and the larger the sample size, the smaller the likelihood of bias, compared with traditional observational studies. However, there are some limitations in this study, as most of our study samples were from European populations, and the existence of causal associations in other ethnic populations needs to be further explored. In addition, the results of this study require further experiments to elucidate the underlying biological mechanisms.

Conclusions

Our findings suggest a bidirectional causal role of circulating inflammatory factors with OP. Elevated levels of the circulating inflammatory factors IL-8, MIP-1β, and CTACK, as well as decreased levels of HGF, IL-1ra, IL-10, MCSF, and MIP-1α, were associated with a reduced risk of OP. In addition, OP may also lead to increased levels of MCP3. These findings provide new ideas for the treatment of osteoporosis and a theoretical basis for the treatment of osteoporosis with anti-inflammatory drugs.

Data Availability

The original contributions presented in the study are included in the article **Supplementary Material**. Further inquiries can be directed to the corresponding author.

Ethics Approval

Not applicable.

Authors' Contributions

Conceptualization: KY and RK; Data collection: KY, RK; Formal analysis: KR and YZ; Methodology: KY and YZ; Validation: KY, YZ; Visualization: QL and YZ; Writing original draft: QL and YZ; Writing-review and editing: QL and YZ; All authors contributed to the article and approved the submitted version.

Funding

None.

Acknowledgments

The author sincerely thanks the researchers and participants of the original biobank for collecting and managing large-scale data resources and those who actively participated in this study.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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