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Inflammatory factors and osteoporosis: a bidirectional Mendelian randomized study

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Abstract. Purpose: Osteoporosis (OP) poses a significant risk to the elderly population, which is rapidly increasing worldwide. Prior research has linked various inflammatory cytokines to the development of OP. This study employs Mendelian randomization (MR) to investigate the causal relationships between 41 inflammatory cytokines and OP, utilizing genetic variants as instrumental variables to clarify direct effects rather than mere associations. **Methods:** Genome-wide association studies summarize data of osteoporosis comprising 399,054 individuals (8,017 cases and 391,037 controls) for OP from Release 10 of FinnGen Biobank. The IEU OpenGWAS offered the GWAS data on 41 factors related to inflammation. MR is a statistical approach to minimize bias when analyzing whole genome sequencing data. This method offers a straightforward yet powerful framework that leverages genetic information to investigate various facets of human biology. **Results:** The results obtained from the inverse variance weighting (IVW) method suggest that lower circulating levels of interleukin-9 and higher levels of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and interleukin-18 are potentially linked to an increased risk of OP. Furthermore, our analysis using reverse Mendelian randomization did not reveal any evidence that osteoporosis influences the levels of these inflammatory cytokines. This finding reinforces the notion that the relationship between these cytokines and osteoporosis may be primarily causal, rather than bidirectional. **Conclusion:** These findings indicate that TRAIL, IL-18, and IL-9 may play an essential role in developing OP. Further investigation is necessary to determine if these biomarkers have the potential to be utilized in the prevention or treatment of OP.

Keywords: Inflammatory factors, Osteoporosis, Mendelian randomization study, Causal effects.

1. Introduction

Osteoporosis (OP) is a chronic metabolic bone disorder characterized by reduced bone mass and impairment of the microarchitecture of bone tissue. This condition leads to diminished bone strength and increased susceptibility to fragility fractures[1]. The diagnosis of osteoporosis primarily relies on the measurement of bone mineral density (BMD), typically assessed using dual-energy x-ray absorptiometry[2]. The World Health Organization (WHO) has established criteria, including T-scores and Z-scores, to evaluate bone health. Specifically, the T-score indicates how many standard deviations a person's BMD is below the average BMD of a young adult; osteoporosis is classified as a T-score of less than -2.5 according to WHO guidelines[3]. OP poses a significant risk to the elderly, a demographic

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that is rapidly expanding globally, as the likelihood of fractures escalates with the aging population[4]. Consequently, explorations of potential causal risk factors for osteoporosis are warranted [5].

The precise mechanisms contributing to osteoporosis and associated fractures remain poorly understood. Chronic inflammation is increasingly recognized as a major component in the development of osteoporosis [6]. Osteoporosis is a principal cause of fragility fractures, with an osteoporotic fracture occurring every three seconds[7]. Literature indicates that there is a notable correlation between interleukin-8 (IL-8) and the occurrence of vertebral osteoporotic fractures [8]. Furthermore, a recent study highlighted that men exhibiting three or more pro-inflammatory markers in the highest quartile were at an increased risk for fractures [9]. Throughout life, bone remodeling takes place as a vital process that repairs microfractures and supports bone mass maintenance. Disruptions in this remodeling process contribute to the pathophysiology of osteoporosis[10]. Cytokines such as IL-6, interleukin-1 (IL-1), and TNF-α are crucial in bone remodeling, with numerous in vitro and animal studies indicating that inflammatory markers are involved in the development of osteoporosis[11].

In addition, a higher incidence of fractures has been found in patients with certain inflammatory factor-related diseases such as rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) [12, 13]. Nevertheless, these investigations focused solely on a restricted set of inflammatory markers and failed to account for the impact of additional physiological variables on changes in inflammatory markers. Osteoporosis is a complex process with all factors, and immune and inflammatory factors are closely related to bone. In normal studies, it is difficult to ignore the influence of confounding factors on osteoporosis, so we carried out a Mendelian randomization study. Due to the uncertain role of inflammatory cytokines in individuals with osteoporosis, further investigation is necessary to ascertain if alterations in these cytokines can serve as indicators for the risk of developing osteoporosis.

Mendelian randomization (MR) is a new technique that explores the causal relationship between exposure and outcomes [14]. There have been previous Mendelian randomization studies on inflammation and osteoporosis, but they only selected several inflammation-related indicators and had a single outcome [15]. Our study, which included a two-way Mendelian randomisation study and looked at 41 inflammatory factors, can help us better explore the relationship between the two.

2. Materials and Methods

2.1. Study Design

Mendelian randomization relies on three assumptions: 1) first, the genetic instrumental variables (IVs) must have a strong connection to the exposure; 2) second, it is imperative that no confounding variables exert an influence on the risk factors and outcomes under investigation. Furthermore, these variables must not be linked to the genetic instruments associated with the aforementioned risk factors and outcomes; 3) third, there should be no alternative routes from the genetic instrument to the outcome aside from through the risk factor of interest [16]. The flowchart of this MR study is depicted in Figure 1. A bidirectional MR analysis was conducted using samples from two separate populations. The forward MR study examined 41 systemic inflammatory cytokines as the exposure and determined OP as the outcome. OP was designated as the independent variable in the reverse multiple regression analysis, with the outcome being the measurement of 41 systemic inflammatory cytokines. The research utilized publicly accessible summary data for examination, without the need for ethical approval.

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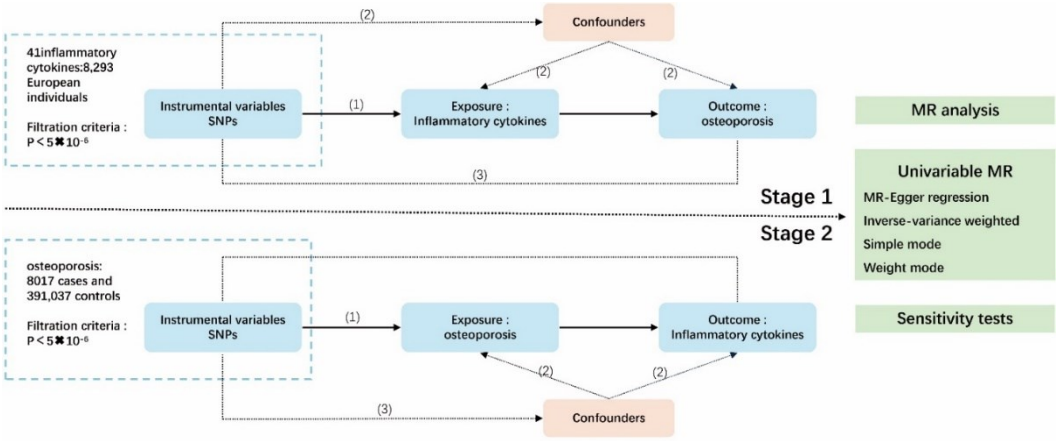

Figure 1. MR assumptions:(1) IVs must show a high correlation with the exposure; (2) there should be no confounding variables that influence both the risk factor and the outcome, and these variables should not be associated with the genetic instrument associated with risk factor and outcome either;(3) lVs should only affect the result by means of exposure.

Stage1: assess the causal influence of inflammatory factors on the risk of developing OP
Stage2: assess the causal influence of OP on the inflammatory cytokines levels
MR, Mendelian Randomization; IVs, genetic instrumental variables; OP, osteoporosis.

2.2. Data Sources

Genome-Wide Association Study (GWAS) database is a publicly available database. SNPs were chosen as instrumental variables (IVs) from GWAS databases for both exposure and outcome variables. In a study of 8,293 individuals, SNPs linked to inflammation were identified, involving 41 cytokines and growth factors [17]. Data from the osteoporosis GWAS were sourced from the FinnGen R10 database, which consists of 8,017 cases and 391,037 controls of European descent. Based on aggregated data from GWAS, we compiled a summary of cytokine details from Supplementary Table 1.

2.3. Instrumental variables selection

Potential instrumental variables (IVs) were identified by us as SNPs substantially linked to inflammatory markers and with genome-wide significance (P-value$<5\times10^{-8}$) [18]. Following that, linkage disequilibrium (LD) must be eliminated by setting the threshold at $r^2<0.001$, kb=10,000. However, so few SNPs have been found, there aren't enough SNPs. Consequently, we chose to employ a higher cut-off ($P<5\times10^{-6}$) as the exposure threshold for 41 inflammatory exposure [19]. Next, we employed SNP clustering, a technique that has been used in previous investigations, to eliminate LD with a 10,000 kb window size and a $r^2<0.001$ [20]. In reverse MR, we set a P-value<5×10-6 threshold for osteoporosis, LD, and an r2 < 0.001 threshold within a 10,000 kb range. We excluded palindromic SNPs with ambiguous results. Each SNP was individually assessed for its F-value, and only those with F-values exceeding 10 were selected as instrumental variables for this study [18]. The formula for calculating the F-value is as follows:

$$F = \frac{R^2(N-1-K)}{(1-R^2)K}$$

R^2 is the percentage of exposure variance that the IVs can account for, with N denoting the sample size of the GWAS and K is the number of instrumental variables [21]. To avoid reverse causation, we first conducted the Steiger test before conducting each MR analysis. Additionally, we utilized the MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO) method to detect and remove any outliers [22]. To prevent bias, we excluded SNPs which were linked to confounding factors. The eventually selected SNPS will be used as instrumental variables (IVs) in subsequent MR Studies.

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3. Statistical Analyses and sensitivity analyses

As shown in Figure 3, five different MR Analysis techniques were used in this study. Among these, the IVW methodology is the primary MR analysis technique and is widely regarded as the most effective for evaluating causal effects [23,24]. The IVW method operates on the premise that all genetic variations can function as valid instrumental variables; however, this assumption may not always hold in practice [25]. The WM method yields a robust effect estimate when over half of the SNPs are valid, while MR Egger offers dependable estimates even in cases where all SNPs are inaccurate [18]. To determine whether instrumental variables show unbalanced pleiotropic effects that can create bias, we performed the MR-PRESSO technique and the MR-Egger regression intercept [26]. The Cochran Q test was used to assess SNP heterogeneity. When heterogeneity (P-value<0.05) was present, the MR effect had to be assessed using a random-effects model or by excluding certain SNPs with low p-values. Finally, we performed a "leave-one-out" analysis to evaluate the findings' dependability. All analyses were performed using the "TwoSampleMR" package in R version 4.3.3, with a significance threshold set at $p < 0.05$.

4. Results

It proved impossible to remove a sufficient number of SNPs when the genome-wide significance threshold was set at 5×10^{-8}, so we set at $P < 5 \times 10^{-6}$. However, the extraction of monocyte-specific chemokine 3 (MCP3) as a valid instrumental variable was unsuccessful. Each inflammatory cytokine's F-statistic value was greater than 10, indicating a low level of instrumental bias. The SNPs that were used as valid instrumental variables are shown in Supplementary Table 2. Figures 2 show roughly the outcomes of two-sample MR between 41 inflammatory cytokines and OP. Using the IVW approach, it was discovered that elevated levels of TNF-related apoptosis-inducing ligand (TRAIL) (IVW-OR=1.074, 95% CI=1.018–1.134, P=0.009) and Interleukin-18 (IL-18) (IVW-OR=1.083, 95% CI=1.010–1.161, P=0.025) levels are associated with an increased risk of OP. We also found higher interleukin-9 (IL-9) levels can reduce the risk of osteoporosis (IVW-OR=0.878, 95% CI=0.783–0.985). This information is presented in Figure 3. The findings did not show any diversity or horizontal pleiotropy (P-value>0.05). Additionally, MR-Egger and IVW tests for heterogeneity indicated the absence of significant heterogeneity (P-value>0.05), Supplementary Table 3. Leave-one-out analyses were conducted as part of the sensitivity analysis, and the results indicated no significant influence from any individual SNP on the overall findings, Supplementary Figures 1-3. In reverse magnetic resonance, we found that osteoporosis did not affect these 3 inflammatory factors which with positive outcome in forward MR.

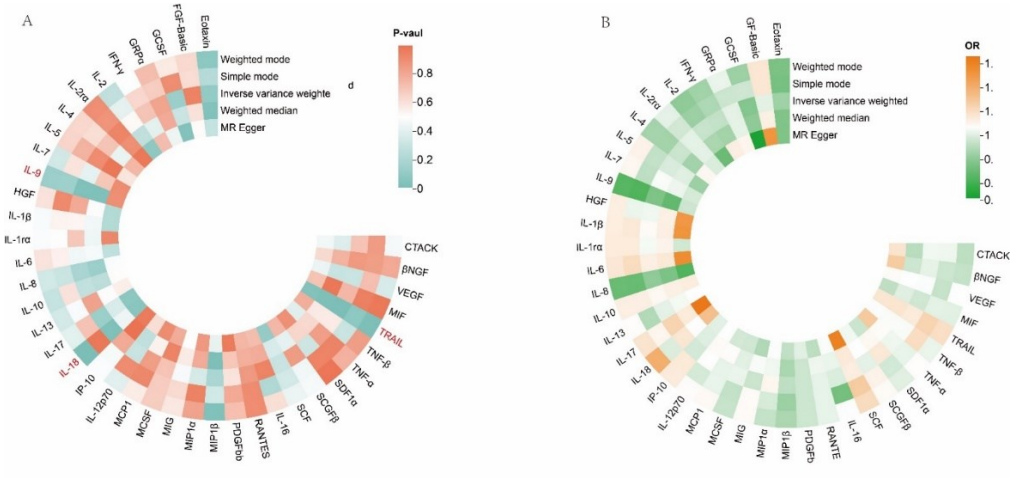

Figure 2. Ring heat map Figure A presents the P-value and Figure B presents the OR value

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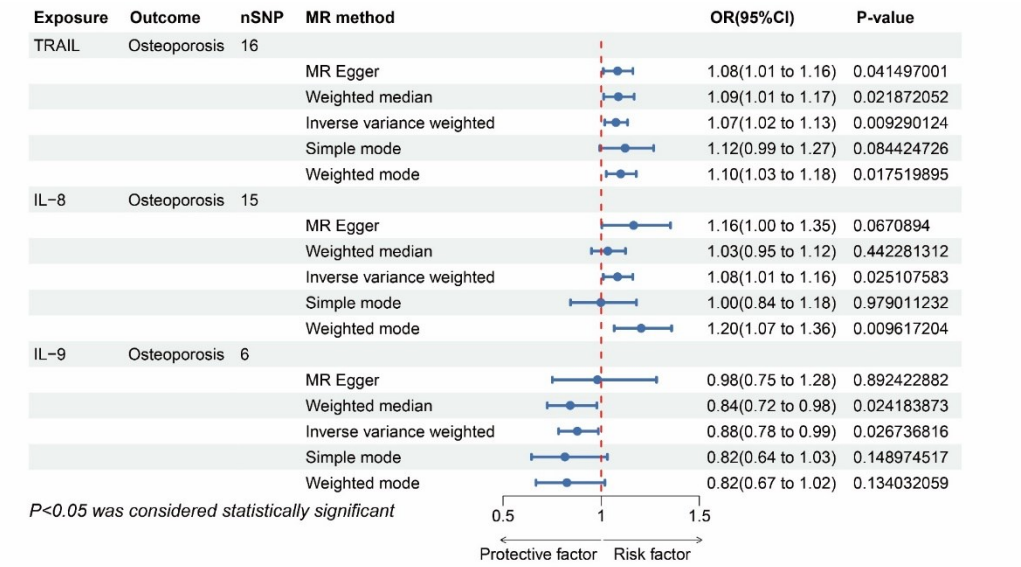

Figure 3. Forest plot of Mendelian randomized analvsis of causal effects of infammatory cvtokines on osteoporosis

5. Discussion

Osteoporosis (OP) is a condition affecting the entire skeletal system, resulting in decreased bone density and structural integrity, which can increase the likelihood of bone fracture [3, 27].

A growing amount of evidence backs up the idea of a mysterious connection between the immune and skeletal systems, marked by the clustering of common cell types and cytokine mediators, known as the "immuno-skeletal interface" [28]. Research has indicated that T cells and associated cytokines are crucial in controlling bone metabolism, contributing directly to the formation of osteoclasts or indirectly causing osteoclast formation and bone loss by producing different inflammatory factors [29]. Hence, inflammatory elements are crucial in the onset and progression of osteoporosis. TNF-α stimulates the development of osteoclast precursors and, in conjunction with other inflammatory cells, results in reduced osteoblast proliferation [30]. Osteoporosis is a systematic model that integrates synergistic signaling pathways and cytokines, and TNF-α is an effective trigger for bone resorption [31]. In addition, TNF-α has been shown to decrease osteoblast activity by increasing osteoblast apoptosis and inhibiting genes involved in bone [32]. M-CSF has many pro-inflammatory functions, and it is also essential in the continuous process of osteoclast formation. Preinduction of high-concentration M-CSF can promote the formation of osteoclasts and enhance the absorption function of osteoclasts [33]. IL-6 promotes the inflammatory bone microenvironment and participates in the direct activation of osteoclasts during bone resorption, leading to bone destruction and osteopenia [34]. In summary, we listed some inflammatory factors that have been supported by relevant studies to prove their important role in the risk of osteoporosis. In the occurrence of osteoporosis, there is a close relationship between immune, inflammatory factors and bone. Nevertheless, reverse causation and lingering confounding are prevalent sources of bias in such conventional observational research. Investigation is needed to determine if these alterations in inflammatory mediators are the cause of osteoporosis or a reaction to osteoporosis. Therefore, we conducted a Mendelian randomized study.

The findings indicated that a reduction in IL-9 levels in the peripheral blood was associated with an elevated risk of osteoporosis. An elevated level of TRAIL and IL-18 in the bloodstream is significantly correlated with an increased risk of osteoporosis. The discovery provides novel insights into the role of inflammatory cytokines in OP progression and offers valuable insights for the prevention and treatment of OP.

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), a well-characterized member of the TNF superfamily, has been demonstrated to induce cell death by binding to its receptors. TRAIL

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interacts with a number of receptors, including osteoprotegerin (OPG) [35]. OPG was initially recognized as a decoy receptor for RANKL; however, subsequent studies revealed that OPG can also interact with TRAIL [36]. OPG plays a pivotal role in the regulation of bone remodeling through its function as a signaling molecule. OPG binds to RANKL to inhibit osteoclast differentiation and bone resorption[37]. TRAIL blocks the OPG-induced suppression of RANKL-controlled osteoclast development [38]. TRAIL affects the process of osteoporosis through the above mechanism. Meanwhile, in our MR study, we found that high levels of TRAIL were associated with a high risk of osteoporosis. This finding is consistent with previous results of related molecular mechanisms. Studies have shown that IL-18 enhances the formation of osteoclasts by activating various pathways, such as stimulating the release of interferon-γ (IFN-γ) and influencing T lymphocytes [39]. Additionally, T lymphocytes are crucial in the development of osteoporosis in women after menopaus [40]. Similarly, we observed high levels of IL-18 in women with osteoporosis [41]. IL-18 can speed up the formation of osteoclasts by increasing the inflammatory reaction, while also blocking the production of proteins or transcription factors related to bone formation [42]. In our study, we also found the higher levels of IL-18 are associated with an increased risk of developing OP. The findings back the significance of IL-18 in the development of osteoporosis. It also emphasizes the importance of the treatment of osteoporosis. Interleukin-9(IL-9) is a multifunctional cytokine secreted by TH2 lymphocytes [43]. Research has indicated that IL-9 has regulatory effects on arthritis by reducing inflammation and resolving joint swelling. Additionally, studies have found that IL-9 has anti-osteoclastogenic properties, which help decrease bone resorption and protect bone [44]. Currently, research has indicated the significant involvement of IL-9 in the development of inflammatory arthritis, rheumatoid arthritis, and different allergic responses [45-49], yet there is a lack of studies on its impact on osteoporosis. We discovered by this MR that increased IL-9 levels can lower the incidence of osteoporosis. In reverse magnetic resonance, we found that osteoporosis did not affect these three positive inflammatory factors, which further proves the causal relationship between these three positive factors and osteoporosis. This finding offers a fresh approach for future studies on the prevention and treatment of osteoporosis.

6. Conclusion

We used two-sample two-way MR Analysis to investigate the relationship between inflammatory proteins and osteoporosis. To achieve this, we employed a two-sample MR analysis method. According to the study's findings, there may be a correlation between a lower blood level of IL-9 and a higher risk of OP. while elevated levels of TRAIL and IL-18 in the bloodstream may be linked to a higher risk of OP. Moreover, an understanding of the underlying causal relationships can inform the development of preventative strategies and enhance the development of treatment methods. It is our contention that our study can provide a reference point for subsequent research. Further studies are required to ascertain whether these cytokines can be employed as novel targets for the prevention and treatment of OP.

Data availability statement

The GWAS data pertaining to the original publication (OP) was sourced from the FinnGen Biobank. The IEU OpenGWAS Knowledge Baseprovides summary statistics on inflammatory factors. The study presents the original findings that are discussed in the article and its supplementary material. Should further clarification be required, please direct your enquiry to the authors responsible for the content.

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