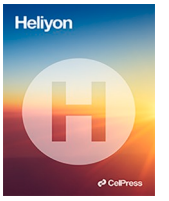
Heliyon 10 (2024) e34494

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Repurposing anti-osteoporosis drugs for autoimmune diseases: A two-sample Mendelian randomization study

Pan Xiang [a,1], Chengyuan Yang [a,1], Ruoyi Shen [b,1], Xiaoxiong Huang [c], Xuerong Huang [d], Qi Cheng [a], Zongping Luo [a,e,**], Qin Zhang [a,*]

[a] Department of Orthopaedics, First Affiliated Hospital of Soochow University, Soochow University, Suzhou, 215000, Jiangsu, China
[b] Department of Pulmonary and Critical Care Medicine, the First Affiliated Hospital of Soochow University, Suzhou, 215000, China
[c] Department of Orthopaedics, Ningbo No. 2 Hospital, Ningbo, 315010, Zhejiang, China
[d] Department of Neonatology, Women and Children, s Hospital, School of Medicine, Xiamen University, Xiamen, Fujian, 361003, China
[e] Orthopaedics Institute, Medical College, Soochow University, China

ARTICLE INFO

Keywords:
Bone mineral density
Autoimmune diseases
Drug re-purposing
Mendelian randomization
ESR1

ABSTRACT

Background: Despite the increasing availability of therapeutic drugs for autoimmune diseases, many patients still struggle to achieve their treatment goals. Our aim was to identify whether drugs originally used to treat bone density could be applied to the treatment of autoimmune diseases through Mendelian randomization (MR).
Methods: Using summary statistics from genome-wide association studies, we used a two-sample MR design to estimate the correlation between autoimmune diseases and BMD-related drug targets. Data from the DrugBank and ChEMBL databases were used to identify the drug targets of anti-osteoporosis medications. The Wald ratio test or inverse-variance weighting method was used to assess the impact of genetic variation in drug target(s) on autoimmune disease therapy.
Results: Through our analysis, we discovered a negative correlation between genetic variability in a specific gene (*ESR1*) in raloxifene/colecalciferol and various autoimmune disorders such as ankylosing spondylitis, endometriosis, IgA nephropathy, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, and type 1 diabetes.
Conclusion: These results indicate a possible link between genetic differences in the drug targeting *ESR1* and susceptibility to autoimmune disorders. Hence, our study offers significant support for the possible use of drugs targeting *ESR1* for the management of autoimmune disorders. MR and drug repurposing are utilized to investigate the relationship between autoimmune diseases and bone mineral density, with a focus on *ESR1*.

1. Introduction

Autoimmune disorders encompass a wide array of conditions marked by chronic inflammation and tissue harm caused by the immune system attacking one's own bodily tissues. It is now widely accepted that the causes of ADs include environmental factors [1],

* Corresponding author.
** Corresponding author. Department of Orthopaedics, First Affiliated Hospital of Soochow University, Soochow University, Suzhou, 215000, Jiangsu, China.
E-mail addresses: zongping_luo@yahoo.com (Z. Luo), orthozq@outlook.com (Q. Zhang).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2024.e34494
Received 30 November 2023; Received in revised form 30 May 2024; Accepted 10 July 2024
Available online 11 July 2024

genetic susceptibility [2] and immune dysregulation [3,4]. Nevertheless, extensive epidemiological research has now proven that these illnesses impact around 3–5% of the populace [5]. Autoimmune thyroid disease and type 1 diabetes (T1D) are the prevailing ailments among them [6]. Over the past few years, nearly 100 autoimmune disorders have been recognized, with systemic lupus erythematosus, rheumatoid arthritis (RA), and type 1 diabetes (T1D) emerging as the most common ones. The treatment of autoimmune disorders is difficult because they are characterized by their intricate and varied nature as well as their underlying causes [7].

New drug development requires significant amounts of time and resources. Another method is drug repositioning, in which approved medications with extensively studied safety and pharmacokinetic characteristics are employed for different purposes. Off-target effects are a major challenge in drug development and gene editing, primarily caused by nonspecific binding of drugs, nonspecific cleavage by gene editing tools, and complex metabolic processes [8]. Mitigation strategies include enhancing target specificity, improving gene editing tools, systems biology analyses, and in vitro and in vivo validations. Employing systems biology and multi-omics technologies can serve as an effective approach to mitigate off-target effects [9].

According to the World Health Organization (WHO), osteoporosis is identified by a T-score $<$ -2.5 for bone mineral density (BMD), which is measured using dual-emission X-ray absorptiometry (DXA) [10,11]. The T-score is a standardized score that compares an individual's bone density to the average peak bone density of a healthy young adult of the same sex. It is a crucial measure used in the diagnosis of osteoporosis and assessment of fracture risk [12]. This is a common ailment that affects more than 30 % of females and 12 % of males during certain periods of their lifetime. The primary medications prescribed for osteoporosis treatment are anti-resorptive drugs [13], which encompass bisphosphonates (BPs) such as alendronate [14], risedronate [15], zoledronic acid [16], ibandronate [17], and etidronate [18], selective estrogen receptor modulators (SERMs) such as raloxifene [19], and the RANK-ligand inhibitor denosumab [20,21].

Estrogen receptors (ER) play a crucial role in regulating inflammatory responses through multiple pathways. First, estrogen agonist can inhibit the NF-κB signaling pathway, thereby reducing the production of pro-inflammatory cytokines and mitigating inflammation [22]. Secondly, ER antagonist activates the Nrf2 signaling pathway, promoting the expression of antioxidant genes and alleviating inflammation and oxidative stress [23]. Additionally, ER affects the function of immune cells by regulating the activity of T cells and B cells. For example, estrogen regulates the proliferation and differentiation of T cells through ERα and influences antibody production by B cells, thereby modulating immune responses [24]. Furthermore, ER directly or indirectly regulates the expression of various inflammatory mediators, including inhibiting the production of pro-inflammatory cytokines such as IL-6 and TNF-α, and promoting the expression of anti-inflammatory cytokines like IL-10.

Autoimmune diseases are closely associated with osteoporosis [25]. Chronic inflammatory responses in diseases such as rheumatoid arthritis and systemic lupus erythematosus activate osteoclasts, accelerating bone resorption and leading to decreased bone density. Additionally, cytokines released by immune cells affect bone metabolism, promoting the development of osteoporosis [26]. Commonly used treatments, such as glucocorticoids, suppress osteoblast activity, increasing the risk of osteoporosis. Moreover, pain and limited mobility caused by these diseases reduce patients' physical activity, further impacting bone health. Therefore, we aim to investigate whether certain drugs that have anti-osteoporotic effects also possess therapeutic potential against autoimmune diseases.

Mendelian randomization (MR) shows promise for evaluating the possibility of repurposing drugs. In MR, genetic variations, commonly known as single nucleotide polymorphisms (SNPs), are used as instrumental variables to calculate the unbiased impact of exposure on the outcome. The presence of genetic variations in the gene locus responsible for encoding a drug target protein is expected to affect the protein expression or function. Using these different forms as genetic tools, we replicated the regulatory influence of the medication on its intended protein, enabling us to assess the influence of genetic diversity on the target of the medication based on a novel indication, similar to a randomized controlled experiment. This study aimed to evaluate the possibility of using BMD-related medications in the management of ADs using an MR approach by utilizing genetic variations found in the gene loci that encode the targets of different medications. Finally, our results show that targeting the estrogen receptor ESR1, which is involved in osteoporosis treatment, can reduce the risk of certain autoimmune diseases. This finding provides a theoretical basis for the potential use of osteoporosis medications in the treatment of autoimmune diseases.

2. Methods

2.1. Identification of drug targets and related drugs

Data from the DrugBank and ChEMBL databases were utilized to identify the drug targets of anti-osteoporosis medications. These databases provide comprehensive information on drug targets.

2.2. GWAS data

Associations between IV exposure and BMD were obtained by analyzing a GWAS conducted on individuals of European descent from UK Biobank (UKB) and FinnGen. People who have been diagnosed with osteoporosis, which is classified as M81 in ICD-10 and 733 in ICD-9. The association testing utilized a method based on mixed linear models to manage population stratification through principle components and relatedness through a genetic relationship matrix. In the end, a total of 326,885 individuals were examined. Table S2 contains information regarding the GWAS. Table S2 also contained the comprehensive details of GWAS Data for autoimmune diseases.

2.3. MR anlaysis

The MR results were estimated using the R software by applying the 'TwoSampleMR' packages. Effect estimates were reported in odds ratios (ORs) values when the outcome was dichotomous. The Phenoscanner tool was utilized for the identification and elimination of cofounder SNPs linked to the study. The use of inverse-variance weighted (IVW) served as the main measure, with MR-Egger, weighted mode, weighted median, and Simple mode improving the IVW estimates to provide stronger and more reliable results across various situations. To evaluate the pleiotropy effect, the MR Egger test was utilized, while heterogeneity was identified using Cochran's Q test [27].

2.4. Genetic instruments for anti-osteoporosis drugs

Major anti-osteoporosis drugs included alendronate, risedronate, zoledronic acid, ibandronate, and etidronate, selective estrogen receptor modulators (SERMs) such as raloxifen, and the RANK-ligand inhibitor denosumab. Genes encoding the target proteins of these antidiabetic drugs were identified from Drugbank and ChEMBL databases.

Palindromic variants were included if their minor allele frequency was below 0.3. For variants not present in the autoimmune disease GWAS, we used the European panel from the 1000 Genomes Project Phase 3 as a reference and selected the variant in high LD ($r^2 > 0.8$) with the drug-target-associated variant as a proxy. We extracted genetic variants from the target gene region and its adjacent 2.5 kb window for each drug class, retaining those associated with autoimmune disease prevalence with a false discovery rate below 0.05. We then conducted linkage disequilibrium (LD) clumping ($r^2 < 0.001$) to select nearly independent variants as genetic instruments. To determine if these genetic instruments might influence autoimmune disease risk through pathways other than the intended drug target, we also searched for traits associated with these instruments in the GWAS Catalog [28].

2.5. Phewas analysis

The Phewas analysis was conducted on the atlas GWAS data source website at (https//atlas.ctglab.nl/PheWAS). The top six *ESR1*-related factors was presented.

3. Results

3.1. Instrument Selection

Various significant categories of drugs related to BMD were identified and are presented in Table 1. Data on protein targets with pharmacological activities and their corresponding encoding genes were obtained from the DrugBank and ChEMBL databases. Subsequently, *cis*-variants in each encoding gene were detected (±2500 base pairs from the gene location), and the variants linked to BMD with a false discovery rate of <0.05 were retained. Subsequently, we used linkage disequilibrium (LD) clumping (r 2 less than 0.01) to select nearly independent variants as genetic instruments (Table S3). A flowchart of the instrument selection process is shown in Fig. 1.

3.2. Positive control analysis

To evaluate the effectiveness of the chosen tools in preventing osteoporosis, we conducted a positive control MR analysis using two separate groups from the UK Biobank and FinnGen (Fig. 2, Table S4). The results of our study indicate a possible link between particular genetic mutations in drug targets and the likelihood of developing osteoporosis. The findings from the UK Biobank cohort indicate that there is a decreased likelihood of developing osteoporosis when there are genetic variations in CASR (OR = 0.99, 95 % CI 0.98–0.99), CTSB (OR = 0.99, 95 % CI 0.98–1.00), ESR1 (OR = 0.98, 95 % CI 0.87–0.98), SOST (OR = 0.98, 95 % CI 0.97–0.99), OPN (OR = 0.97, 95 % CI 0.96–0.98), and RANKL (OR = 0.99, 95 % CI 0.99–1.00), surpassing the threshold adjusted for Bonferroni correction. Conversely, within the FinnGen cohort, only ESR1 (OR = 0.36, 95 % CI 0.32–0.41) and PTH1R (OR = 0.52, 95 % CI

Table 1
Information of target genes of anti-osteoporosis drugs.

Drug	Effect	Target Gene	Chr	GRch37_start	GRch37_end
MIV-711	inhibitor	CTSK	1	150768684	150780736
Evocalcet	activator	CASR	3	121902515	122010476
Teriparatide	activator	PTH1R	3	46919211	46945289
IPS-02001	Antagonist	OPN	4	88896866	88904563
Raloxifene	activator	ESR1	6	151977807	152450754
Calcitonin	activator	CALCR	7	93053798	93204036
Aoxistatin	inhibitor	CTSB	8	11842524	11868087
Trimegestone	activator	PR	11	100900355	101000544
Eldecalcitol	activator	VDR	12	48235320	48298777
Denosumab	inhibitor	RANKL	13	43136872	43182149
Romosozumab-AQQG	inhibitor	SOST	17	41831106	41836159

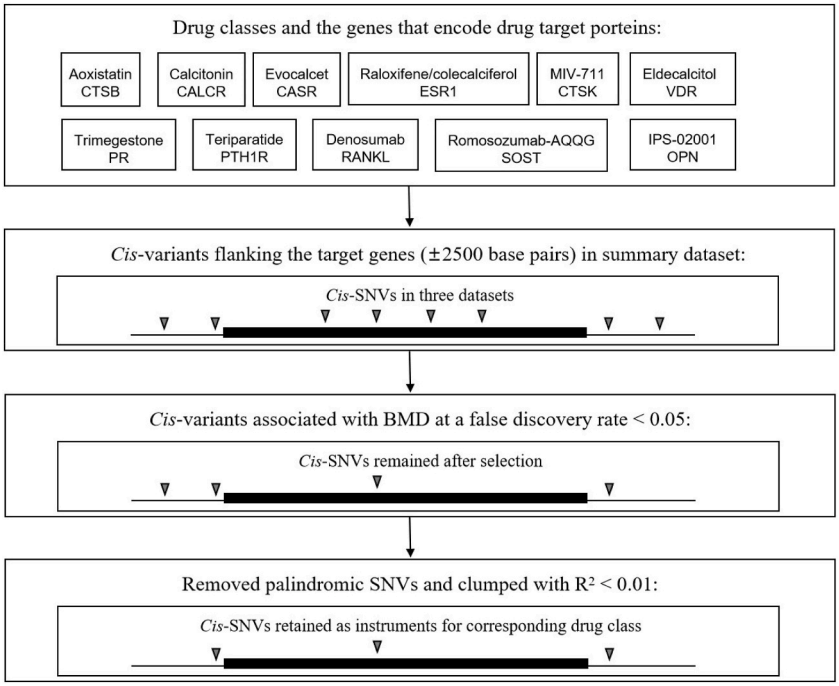


Fig. 1. Instrument Selection for BMD-related drugs.

exposure	outcome	method	nsnp	pval	or(95%CI)
CASR	Osteoporosis (UKB)	Inverse variance weighted	18	7.7e−07	0.99(0.98 to 0.99)
	Osteoporosis (FinnGen)	Inverse variance weighted	23	8.6e−01	1.05(0.64 to 1.71)
CTSB	Osteoporosis (UKB)	Inverse variance weighted	6	2.5e−02	0.99(0.98 to 1.00)
	Osteoporosis (FinnGen)	Inverse variance weighted	5	7.1e−02	0.35(0.11 to 1.10)
ESR1	Osteoporosis (UKB)	Inverse variance weighted	113	7.1e−168	0.98(0.97 to 0.98)
	Osteoporosis (FinnGen)	Inverse variance weighted	135	7.2e−54	0.36(0.32 to 0.41)
PTH1R	Osteoporosis (UKB)	Wald ratio	1	8.3e−01	1.00(0.98 to 1.01)
	Osteoporosis (FinnGen)	Inverse variance weighted	8	3.3e−03	0.52(0.34 to 0.81)
SOST	Osteoporosis (UKB)	Inverse variance weighted	4	4.5e−07	0.98(0.97 to 0.99)
	Osteoporosis (FinnGen)	Inverse variance weighted	4	1.1e−01	0.53(0.25 to 1.14)
OPN	Osteoporosis (UKB)	Inverse variance weighted	3	4.1e−05	0.97(0.96 to 0.98)
	Osteoporosis (FinnGen)	Inverse variance weighted	3	3.2e−01	0.48(0.11 to 2.06)
RANKL	Osteoporosis (UKB)	Inverse variance weighted	36	3.4e−03	0.99(0.99 to 1.00)
	Osteoporosis (FinnGen)	Inverse variance weighted	55	3.6e−01	0.88(0.66 to 1.16)
VDR	Osteoporosis (UKB)	Inverse variance weighted	3	7.3e−01	1.00(0.99 to 1.01)
	Osteoporosis (FinnGen)	Inverse variance weighted	3	1.6e−01	2.53(0.69 to 9.34)

P<0.05 was considered statistically significant

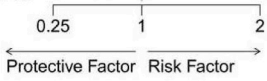


Fig. 2. Estimated effects of genetic variation in drug targets of BMD on osteoporosis from two cohorts.

0.34–0.81) demonstrate a correlation indicating a decreased likelihood of developing osteoporosis. By merging the findings of both groups, it became evident that only the genetic diversity in ESR1 was consistently correlated with a decreased likelihood of osteoporosis, and this correlation was statistically significant ($p < 0.05$).

3.3. Estimated effects of genetic variation in ESR1 on autoimmune diseases

ESR1 receptor plays a crucial role in physiological processes, particularly in estrogen signaling, reproductive tissue development, bone health, and cardiovascular protection. It is also closely associated with the onset and progression of diseases like breast cancer and endometrial cancer [39]. As a therapeutic target, *ESR1* is pivotal in the treatment of conditions such as breast cancer and osteoporosis, providing crucial direction for researchers and clinicians. To examine the potential influence of *ESR1* on ADs, we selected 11

ADs as outcomes and performed a two-sample MR analysis. Surprisingly, our analysis revealed the therapeutic potential of *ESR1* in seven ADs. According to Fig. 3 and Table S5, *ESR1* was found to be associated with a decreased risk of ankylosing spondylitis (OR = 0.87, 95 % CI 0.78–0.97), IgA nephropathy (OR = 0.27, 95 % CI 0.11–0.63), rheumatoid arthritis (OR = 0.78, 95 % CI 0.73–0.84), sarcoidosis (OR = 0.80, 95 % CI 0.68–0.94), Systemic lupus erythematosus (OR = 0.78, 95 % CI 0.65–0.94), and T1D (OR = 0.49, 95 % CI 0.44–0.55) ($p < 0.05$). These results indicate that genetic elements within *ESR1* may play a role in the control of bone mineral density and the emergence of ADs. Additional research is necessary to clarify the fundamental processes by which these genetic differences impact bone mineral density and contribute to the development of ADs.

3.4. Phewas analysis

Phenome-wide association study (PheWAS) is a research method used to explore the associations between genetic variations and a variety of phenotypes (i.e., diseases or traits) [29]. In order to evaluate the possible effects of *ESR1* inhibitors on other traits, we performed an PheWAS analysis for ESR1. The result revealed a robust correlation between *ESR1* and bone density and height ($p < 5e^{-30}$) while indicating minimal associations with other traits related to cardiovascular system or hepatorenal function (Fig. 4). Consequently, we can confidently conclude that drugs targeting *ESR1* have remarkable levels of safety and reliability.

4. Discussion

The present study was an initial MR study that examined the possible link between genetic variations in drug targets for osteoporosis and susceptibility to ADs. Our genetic analysis suggests that genetic variations in *ESR1* may provide a safeguard against ADs, as we utilized abundant genetic association data on the risk of these conditions. However, similar associations were not observed with other drug targets related to bone mineral density (BMD).

The precise mechanisms responsible for the preventive effects of *ESR1* on ADs are still unknown. Nevertheless, the observed impacts on pertinent gene targets provide significant understanding. In women who have gone through menopause and have rheumatoid arthritis and osteoporosis, the combined use of methotrexate (MTX) and Raloxifene showed that Raloxifene can hinder the function of aldehyde oxidase (EC 7.7.1.2) (AOX), resulting in decreased production of 7-OH MTX [30–32]. This inhibition of aldehyde oxidase enhances MTX levels and improves its efficacy. In addition, LNP023, a reversible binding inhibitor, was found through network pharmacology screening to target AKT (Protein Kinase B) , TNF-α (Tumor Necrosis Factor Alpha), MDM2 (MDM2 Proto-Oncogene), UBC (Ubiquitin C), STST3 (Signal Transducer and Activator of Transcription 3), ESR1, and TP53 (Tumor Protein P53), which are considered core targets for treating Lupus nephritis (LN) [33]. The advancement of lupus nephritis is expedited by estrogen-stimulated tumor necrosis factor-like weak inducer of apoptosis (TWEAK) via the expression of ERα [34,35]. Estrogen significantly promotes pulmonary fibrosis development. Nevertheless, the attachment of ESR1 to the STAT3 promoter causes a transition in fibrotic cytokine expression, changing it from an IL-17A-induced inflammatory characteristic to a TGF-β1-induced immune-suppressing characteristic [36]. Earlier research indicates that estradiol could potentially be involved in the management of ankylosing spondylitis (AS) through the suppression of inflammatory elements, highlighting the significance of *ESR1* as a crucial focus of attention [37]. Through bioinformatics analysis, a noteworthy correlation between T1DM30 and *ESR1* was discovered, with the objective of identifying potential biomarkers for type 1 diabetes T1DM [38]. Nevertheless, the uncertainty persists regarding the origin of this connection, whether it is solely influenced by the natural progression of the autoimmune disease or other variables. Hence, our discoveries underscore the possible involvement of *ESR1* in the development and advancement of autoimmune disorders, underscoring the necessity for additional focused investigation in this domain.

As far as we know, there is a lack of prior studies investigating the impact of drug targets linked to bone mineral density (BMD) on the susceptibility to autoimmune disorders. The objective of this article is to establish a correlation between genetic mutations in drug targets associated with BMD and the susceptibility to autoimmune disorders. This study possesses several notable strengths. Causal inference is facilitated by implementing a Mendelian randomization (MR) design, which helps to reduce bias from confounding and

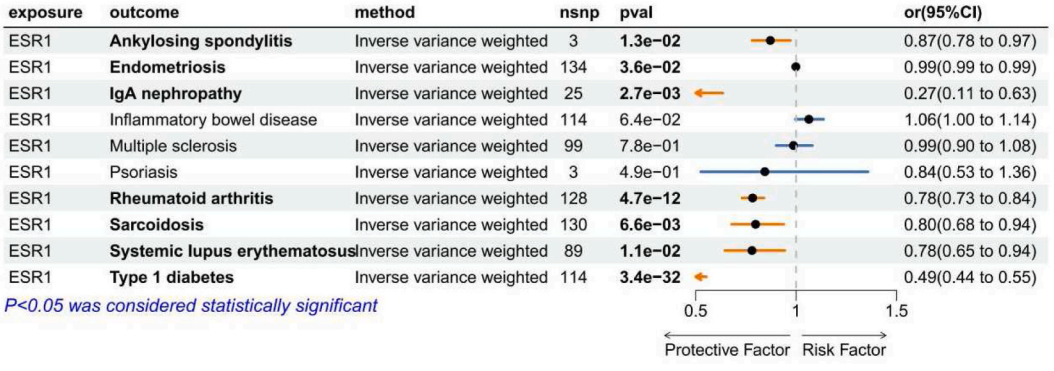


Fig. 3. Estimated effects of genetic variation in ESR1 of BMD on autoimmune diseases.

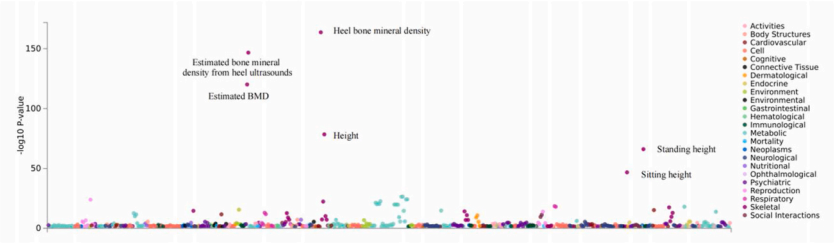


Fig. 4. The PheWAS result of ESR1. The significance of the association between ESR1 and other traits was represented by - log10 $^{p\text{-value}}$. The result of PheWAS result showed that ESR1 was obviously associated to BMD or height, however indicating minimal associations between ESR1 and other traits related to cardiovascular system or hepatorenal function.

reverse causation. Secondly, the analyses were limited to two specific cohorts, reducing the likelihood of spurious associations. In addition, the instruments potentially associated with gene function or expression were carefully chosen from a limited range (2.5 kb) of the encoding gene. In addition, to validate the selected genetic instruments and predict the impact of antidiabetic medications on the intended indication and established outcomes, positive control analyses were performed. In conclusion, the significant F statistic suggests a low likelihood of weak instrument bias.

ESR1 is associated with various autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and Hashimoto's thyroiditis. *ESR1* encodes the estrogen receptor, which plays a crucial role in modulating the immune system and inflammatory responses involved in these diseases. Studies indicate that variations in the *ESR1* and its expression levels influence disease susceptibility and severity [40]. Understanding the specific mechanisms of *ESR1* in autoimmune diseases can aid in developing new diagnostic and therapeutic approaches, advancing personalized medicine.

Variants of the E*SR1* gene significantly affect patient responses to hormone-related therapies, providing opportunities for drug repurposing. Specific *ESR1* gene variants, such as rs9340799, rs2234693, and rs1801132, influence the efficacy and suitability of drugs like selective estrogen receptor modulators (SERMs) and aromatase inhibitors [41]. These variants are associated with the susceptibility and progression of diseases such as breast cancer, osteoporosis, cardiovascular diseases, and autoimmune disorders. By understanding how these genetic variations impact drug responses, existing medications can be re-evaluated and repurposed to treat a broader range of conditions, enhancing the precision and effectiveness of personalized medicine. For example, variants such as *ESR1* rs2234693 can guide the use of osteoporosis treatments. Patients with particular genotypes may respond better to specific therapies, enabling the repurposing of osteoporosis drugs for those with a genetic predisposition to bone density issues.

Nevertheless, it is crucial to recognize specific constraints of this research. Our predictions about the influence of the medication on the likelihood of autoimmune disorders are exclusively founded on disruptions of established proteins (on-target effects). The potential for drugs to modify autoimmune disease risk through interactions with other proteins (off-target effects) cannot be definitively ruled out. Furthermore, it is important to mention that estimates from Mendelian randomization could be influenced by bias caused by horizontal pleiotropy. Nonetheless, we have implemented preventive measures by choosing alternatives in immediate vicinity to the genetic site, reducing the chances of pleiotropic consequences caused by other genes.

5. Conclusion

In summary, this study aimed to investigate the possibility of using anti-osteoporosis medications for the management of ADs. Through the implementation of MR analysis, we unveiled noteworthy connections between genetic alterations in the pharmaceutical objective *ESR1* and susceptibility to ADs. These results provide significant support for the possible use of drugs targeting *ESR1* for the treatment of ADs.

Ethics approval and consent to participate

All data used in this study are in the public domain. All participants provided informed consent and study protocols were approved by their respective local ethical committees. This project was approved by the First Affiliated Hospital of Soochow University.

Consent for publication

Not applicable.

Funding

This project is funded by the National Natural Science Foundation of China (32071307).

Data availability

The UKB data and FinnGen data are available through application. All data in this work are available on personal request (email: orthozq@outlook.com). The analysis software is R (version 4.2.1) downloaded from https://www.r-project.org/.

CRediT authorship contribution statement

Pan Xiang: Writing – review & editing, Writing – original draft, Data curation. **Chengyuan Yang:** Formal analysis, Data curation. **Ruoyi Shen:** Formal analysis, Data curation. **Xiaoxiong Huang:** Data curation. **Xuerong Huang:** Data curation. **Qi Cheng:** Data curation. **Zongping Luo:** Writing – review & editing, Writing – original draft, Funding acquisition. **Qin Zhang:** Writing – review & editing, Writing – original draft, Software.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to thank all study participants as well as all investigators of the studies that were used throughout the course of this investigation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e34494.

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