

Original Article

Open Access



The causal relationship between epigenetic aging and osteoporosis: a bi-directional Mendelian randomization study

Chuanxin Wang^{1,2,#}, Wenfei Wu^{4,#}, Bingyang Yan^{4,#}, Di Luo¹, Yanbo Guo¹, Haisheng Yu¹, Wenzhao Wang³ , Liang Ma¹

¹Department of Orthopedics, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan 250014, Shandong, China.

²Department of Orthopedics, Linyi Traditional Chinese Medicine Hospital, Linyi 276037, Shandong, China.

³Department of Orthopedics, Qilu Hospital of Shandong University, Jinan 250012, Shandong, China.

⁴First Clinical Medical School, Shandong University of Traditional Chinese Medicine, Jinan 250011, Shandong, China.

#Authors contributed equally.

Correspondence to: Prof. Wenzhao Wang, Department of Orthopedics, Qilu Hospital of Shandong University, No. 107, Wenhua West Road, Jinan 250012, Shandong, China. E-mail: wayne1898@163.com; Prof. Liang Ma, Department of Orthopedics, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, No. 16369, Jingshi Road, Jinan 250014, Shandong, China. E-mail: 71002106@sduatcm.edu.cn

How to cite this article: Wang C, Wu W, Yan B, Luo D, Guo Y, Yu H, Wang W, Ma L. The causal relationship between epigenetic aging and osteoporosis: a bi-directional Mendelian randomization study. *J Transl Genet Genom.* 2025;9:90-99. <https://dx.doi.org/10.20517/jtgg.2024.94>

Received: 11 Nov 2024 **First Decision:** 23 Apr 2025 **Revised:** 12 May 2025 **Accepted:** 23 May 2025 **Published:** 28 May 2025

Academic Editor: Sheng-Ying Qin **Copy Editor:** Ping Zhang **Production Editor:** Ping Zhang

Abstract

Aim: Osteoporosis (OP) is the most common of the musculoskeletal disorders, with decreased bone mineral density (BMD) being the main manifestation and exacerbating fracture susceptibility. OP was once thought to be an inevitable consequence of aging. We conducted a bi-directional Mendelian randomization (MR) for epigenetic age acceleration (EAA) and osteoporosis to accurately assess the interaction between aging and osteoporosis.

Methods: This study collected data from genome-wide association studies of EAA and OP and assessed significant genetic variables. Bi-directional MR analyses were performed using random-effects inverse-variance weighting as the primary method, and the interaction of epigenetic age acceleration with OP was assessed using other MRI methods and multiple sensitivity analyses.

Results: Inverse-variance weighted (IVW) results suggest that GrimAge acceleration accelerates bone loss in total



© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, sharing, adaptation, distribution and reproduction in any medium or format, for any purpose, even commercially, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.



body bone mineral density [odds ratio (OR) = 1.035, 95% confidence interval (95%CI) = (1.003, 1.069), $P = 0.033$]. The effect of BMD on EAA was investigated, and a causal relationship was found between forearm bone mineral density and GrimAge acceleration [OR = 0.682, (95%CI) = (0.508, 0.916), $P = 0.011$]. There was a causal relationship between femoral neck bone mineral density and PhenoAge acceleration [OR = 1.452, (95%CI) = (1.007, 2.096), $P = 0.046$].

Conclusions: Epigenetic age acceleration was bi-directionally causally associated with osteoporosis. GrimAge acceleration increased the risk of decreased total body bone mineral density. Forearm bone mineral density accelerated GrimAge and femoral neck bone mineral density accelerated PhenoAge acceleration.

Keywords: Osteoporosis, epigenetic age acceleration, Mendelian randomization

INTRODUCTION

Osteoporosis (OP) is the most common of the musculoskeletal disorders, with decreased bone mineral density (BMD) being the main manifestation and exacerbating fracture susceptibility^[1,2]. OP predominantly affects postmenopausal women due to estrogen deficiency accelerating bone loss. While less prevalent in men, they experience more severe fracture outcomes, reflecting gender-specific pathophysiological mechanisms^[3]. Individuals with modifiable risk factors-including tobacco use, excessive alcohol consumption, vitamin D deficiency, and poor nutritional status-demonstrate significantly higher susceptibility to osteoporosis development. OP was once thought to be an inevitable consequence of aging^[4]. As a major global human health problem, the social and economic burden of OP is steadily rising as the population ages more and more^[5]. It is estimated that nearly 20 percent of American women aged 50 and older had osteoporosis in 2018, up from 14 percent a decade earlier^[6].

Epigenetic modifications are strongly associated with several metabolic diseases, including OP^[7-9]. Epigenetic clocks measure biological aging through multiple epigenetic mechanisms, primarily DNA methylation^[10-12], while newer models integrate histone modifications, non-coding RNAs, and chromatin states for enhanced aging assessment. These multi-feature clocks outperform traditional biomarkers in predicting age and mortality by capturing epigenetic aging complexity. When epigenetic age exceeds chronological age, this condition is known as epigenetic age acceleration (EAA), which is associated with various age-related diseases^[10]. Commonly used EAA measurements include: intrinsic EAA (IEAA)^[13] and Hannum Age acceleration (HannumAA)^[14], which better predict chronological age; “second-generation” epigenetic age acceleration, PhenoAge acceleration (PhenoAA)^[15], and GrimAge acceleration (GrimAA)^[16], which integrates nine clinical biomarkers and 513 CpGs associated with mortality, can effectively predict incidence and death rates^[17]. Although DNA methylation has been shown to regulate osteoblast differentiation and bone remodeling, epigenetic modifications are providing new ideas for osteoporosis treatment^[18]. Aging and osteoporosis go hand in hand. However, the relationship between aging and osteoporosis in EAA has not been recognized^[19].

Mendelian randomization (MR) uses genetic variants as instrumental variables (IVs) to support causal inference while minimizing confounding biases inherent in observational studies^[20]. The approach adheres to Mendel’s law of independent assortment, whereby genotypes are randomly allocated during gamete formation, thereby mimicking the design of randomized controlled trials (RCTs)^[21]. In the last few years, a growing number of scholars have analyzed EAA in relation to aging-related diseases, such as COVID-19^[22], heart failure^[23], and kidney function^[24] by MR. In addition, no study has examined MR between EAA and OP. Therefore, we investigated whether there is an association between epigenetic age acceleration and osteoporosis by a bi-directional MR analysis.

RESEARCH DESIGN AND METHODS

Study design

In this analysis, four EAAs (IEAA, HannumAA, PhenoAA, GrimAA) were used as “exposures”. OP Measurement and prediction can be done by BMD^[25]. Therefore, total body bone mineral density (TB BMD), forearm bone mineral density (FA BMD), lumbar spine bone mineral density (LS BMD), femoral neck bone mineral density (FN BMD), and heel bone mineral density (eBMD) were used as “outcomes” to screen the instruments for MR analysis^[26]. We then performed reverse MR analysis with BMD selected as the “exposure” and epigenetic age acceleration as the “outcome”. Three assumptions are met in order to conduct an MR analysis: (1) the instrumental variable is pragmatically related to the exposure factor; (2) the instrumental variable cannot be correlated with exposure and outcome factor-related confounders; and (3) the instrumental variable cannot affect the outcome through factors besides the exposure factor. The study design flow chart of MR is shown in [Figure 1](#).

Data source

GWAS summary statistics for EAA are all available from the IEU GWAS database (IEU <https://gwas.mrcieu.ac.uk/>); we downloaded GWAS summary statistics for BMD from the Osteoporosis Consortium website (GEFOS <http://www.gefos.org/>). The study data were all from Europe. Information on the data are presented in [Table 1](#).

Selection of genetic instrumental variables

Rigorous criteria were used to screen single nucleotide polymorphisms (SNPs) from GWAS pooled data from EAA and BMD. SNPs with threshold significance ($P < 5.0 \times 10^{-8}$), according to the three hypotheses and genome-wide significance, were validated for the linkage disequilibrium parameter r^2 ($r^2 < 0.001$) and kilobase pair kb ($kb > 10,000$). The final SNPs obtained that were significantly associated with exposure were termed instrumental variables (IV). F value ($F = \beta^2 \text{exposure} / \text{SE}^2 \text{exposure}$) was calculated in this study and SNPs with $F < 10$ were removed^[27]. F values > 10 were considered weak instrumental pairs that are effective in reducing the bias caused by MR results.

Statistical analysis

In the analysis of the relationship between EAA and OP, we mainly use the inverse-variance weighted (IVW) statistic. IVW is considered to be the most accurate method for assessing causality if all SNPs fulfill the requirements of the three hypotheses of valid instrumental variables^[28]. In addition, MR-Egger, weighted median method, and simple and weighted model calculations were performed to ensure that the results were not biased^[29].

To ensure the accuracy of the results, heterogeneity among SNPs was tested using Cochran's Q test; $P > 0.05$ indicated no heterogeneity, while a random effect model was applied when $P < 0.05$. Horizontal pleiotropy was evaluated using MR-Egger analysis, with $P > 0.05$ suggesting no evidence of pleiotropy. A leave-one-out analysis was then conducted to validate the culling of IVs that could have a large impact on the MR results. This analysis also helped address issues related to inconsistent SNP annotations, and supported the re-implementation of MR analysis after eliminating all chain fuzzy SNPs. All final statistical analyses were done with the TwoSample MR package in R software (4.3.1).

RESULTS

Extraction of instrumental variables

After removing SNPs from incompatible alleles, information on all exposure-associated SNPs is shown in [Supplementary Table 1](#). None of the F-statistics of the IVs obtained by screening were less than 10, so no weak instrumental variable bias was found.

Table 1. Data and sources of epigenetic age acceleration and osteoporosis

Type	Phenotype	Population	SNP	Sample size	Datasets in the GWAS
EAA	IEAA	European	7,544,289	34,461	ebi-a-GCST90014290
	HannumAA	European	7,541,726	34,449	ebi-a-GCST90014289
	PhenoAA	European	7,545,555	34,463	ebi-a-GCST90014292
	GrimAA	European	7,544,493	34,467	ebi-a-GCST90014288
BMD	FN BMD	European	10,586,900	32,735	ieu-a-980
	LS BMD	European	10,582,867	28,498	ieu-a-982
	FA BMD	European	9,955,366	8,143	ieu-a-977
	eBMD	European	9,851,867	265,627	ukb-b-8875
	TB BMD	European	16,162,733	56,284	ebi-a-GCST005348

SNP: The label of single-nucleotide polymorphism; EAA: epigenetic age acceleration; IEAA: intrinsic epigenetic age acceleration; HannumAA: Hannum Age acceleration; PhenoAA: PhenoAge acceleration; GrimAA: GrimAge acceleration; BMD: bone mineral density; FN BMD: femoral neck BMD; LS BMD: lumbar spine BMD; FA BMD: forearm BMD; eBMD: heel-BMD; TB BMD: total body BMD.

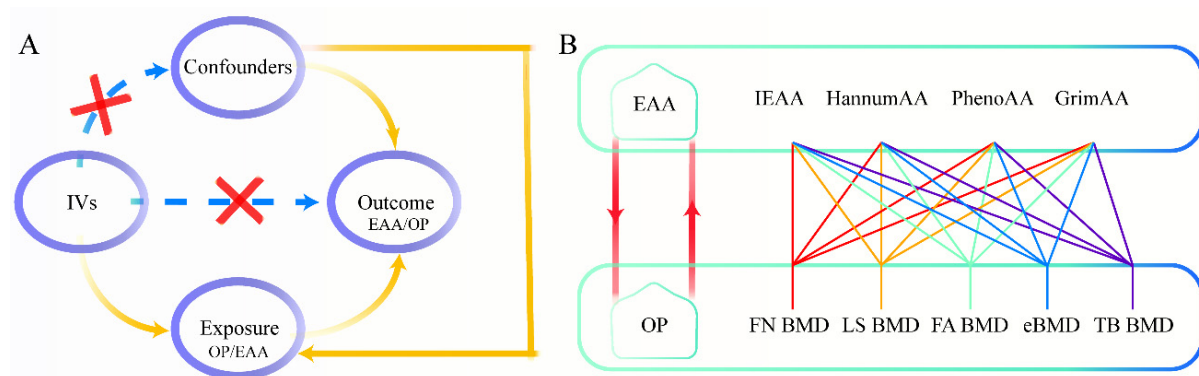


Figure 1. Study design flow chart of Mendelian randomization. IVs: Instrumental variable; OP: osteoporosis; EAA: epigenetic age acceleration; TB BMD: total body bone mineral density; FA BMD: forearm bone mineral density; LS BMD: lumbar spine bone mineral density; FN BMD: femoral neck bone mineral density; eBMD: heel bone mineral density; IEAA: intrinsic age acceleration; HannumAA: Hannum Age acceleration; PhenoAA: PhenoAge acceleration; GrimAA: GrimAge acceleration.

Phase I. Effects of EAA traits on BMD

The analysis results of the influence of EAA on BMD in different parts are shown in Figure 2. IVW results suggest that GrimAA accelerates bone loss in TB BMD [odds ratio (OR) = 1.035, 95% confidence interval (95% CI) = (1.003, 1.069), $P = 0.033$]. When the OR > 1, the exposure factor will increase the risk of the outcome; conversely, it will have an inhibitory effect. Statistical significance could not be obtained between other EAAs and BMDs in Supplementary Table 2. Scatterplots and leave-one-out sensitivity analysis are in the Supplementary Figure 1. MR-Egger was then subjected to intercept analysis and Cochran's Q test, and the results are shown in Table 2.

Phase 2. Effect of BMD traits on EAA

The analysis results of the influence of BMD on EAA in different parts are shown in Figure 3. The effect of BMD on EAA was studied, showing a causal relationship between FA BMD and Grim AA [OR = 0.682, (95%CI) = (0.508, 0.916), $P = 0.011$]. There was a causal relationship between FN BMD and Pheno AA [OR = 1.452, (95%CI) = (1.007, 2.096), $P = 0.046$]. Statistical significance could not be obtained between other BMDs and EAAs in Supplementary Table 2. Scatterplots and leave-one-out sensitivity analysis are in Supplementary Figures 2-3. The presence of horizontal pleiotropy between TB BMD and IEAA did not affect the final results, so the MR analysis group of TB BMD on IEAA was excluded and the results are

Table 2. Heterogeneity and pleiotropic analysis for epigenetic age acceleration

Exposure	Outcome	Cochran's Q		MR egger
		MR egger (p)	IVW (p)	Intercept (p)
IEAA	FN BMD	0.3167702	0.2920560	0.250202
IEAA	LS BMD	0.6661622	0.6583614	0.3164924
IEAA	FA BMD	0.0532878	0.0670260	0.694507
IEAA	eBMD	3e-07	5e-07	0.7034014
IEAA	TB BMD	0.0001437	0.0000094	0.0597628
HannumAA	FN BMD	0.1900621	0.2667009	0.9685754
HannumAA	LS BMD	0.0012420	0.0015689	0.5726428
HannumAA	FA BMD	0.4685172	0.5702795	0.8099111
HannumAA	eBMD	0.1292642	0.1252460	0.3797651
HannumAA	TB BMD	0.0743077	0.1163888	0.8684581
PhenoAA	FN BMD	0.3548912	0.4438756	0.7995509
PhenoAA	LS BMD	0.9226880	0.9292814	0.4855223
PhenoAA	FA BMD	0.8855043	0.7403278	0.1658422
PhenoAA	eBMD	0.2824209	0.3616090	0.8518695
PhenoAA	TB BMD	0.9406984	0.9490757	0.5178656
GrimAA	FN BMD	0.6110190	0.4103183	0.3024067
GrimAA	LS BMD	0.8281508	0.7467965	0.4541538
GrimAA	FA BMD	0.3734250	0.5165973	0.6343293
GrimAA	eBMD	0.0221043	0.0015830	0.2918637
GrimAA	TB BMD	0.7810016	0.5806332	0.3496158

IVW: Inverse-variance weighted; IEAA: intrinsic epigenetic age acceleration; HannumAA: Hannum Age acceleration; PhenoAA: PhenoAge acceleration; GrimAA: GrimAge acceleration; BMD: bone mineral density; FN BMD: femoral neck BMD; LS BMD: lumbar spine BMD; FA BMD: forearm BMD; eBMD: heel-BMD; TB BMD: total body BMD; MR: mendelian randomization.

shown in [Table 3](#).

DISCUSSION

The acceleration of global aging has led to a surge in the incidence and mortality of various age-related diseases, posing a serious challenge to social healthcare. Research on the physiopathological mechanisms of aging has been a hot topic. At the same time, determining an accurate measure of an individual's biological age is one of the major challenges in aging research^[30]. The ability of epigenetic clocks to accurately predict actual age has been validated, while the understanding of biological age has increased with the increase in diversity of epigenetic clocks, revolutionizing geriatric experimental science^[31]. For instance, the m⁶A modification of mRNA has a regulatory effect on atrial fibrillation, heart failure, and other aspects^[32].

Based on our findings, we found a significant and potentially causal effect of GrimAA on whole-body BMD. On the other hand, the reduction of forearm BMD and femoral neck BMD was found to accelerate Grim Age and PhenoAge, respectively. However, other EAAs were unable to establish a relevant causal relationship with BMD. A study of blood samples from 32 patients with osteoporosis and 16 controls showed no differences in DNAm patterns of blood samples and stated that OP was independent of peripheral blood epigenetic aging^[19]. However, Fuggle^[33] claimed that the conclusions of this study were obtained using only the first epigenetic clock and that the second epigenetic clock was not validated. Unlike first-generation clocks (e.g., Horvath, Hannum) or even PhenoAge, GrimAge integrates plasma proteins [e.g., growth differentiation factor 15 [GDF-15]]^[16,34] and smoking-related DNA methylation (DNAm)^[16] signatures-factors directly linked to inflammation, oxidative stress, and tissue degeneration, all of which

Table 3. Heterogeneity and pleiotropic analysis for osteoporosis

Exposure	Outcome	Cochran's Q		MR egger
		MR egger (p)	IVW (p)	Intercept (p)
FN BMD	IEAA	0.0956065	0.1242909	0.9901674
FN BMD	HannumAA	0.0793301	0.1032180	0.8565282
FN BMD	PhenoAA	0.0760703	0.0888360	0.5519918
FN BMD	GrimAA	0.0258980	0.0161663	0.1957208
LS BMD	IEAA	0.0753599	0.0912601	0.6252111
LS BMD	HannumAA	0.0008716	0.0011972	0.6584138
LS BMD	PhenoAA	0.1341368	0.1641073	0.7291078
LS BMD	GrimAA	0.0006546	0.0007867	0.5384433
FA BMD	IEAA	0.8040078	0.6999756	0.5675987
FA BMD	HannumAA	0.4818490	0.6782634	0.6893335
FA BMD	PhenoAA	0.4484625	0.6792502	0.7328757
FA BMD	GrimAA	0.8732347	0.9676701	0.8739192
eBMD	IEAA	0.0001428	0.0001642	0.9170362
eBMD	HannumAA	0.0002654	0.0003042	0.9927886
eBMD	PhenoAA	0.0008701	0.0009630	0.6784637
eBMD	GrimAA	0.0786103	0.0637420	0.0549965
TB BMD	IEAA	0.0004205	0.0001127	0.0360505
TB BMD	HannumAA	0.0712066	0.0623359	0.1959204
TB BMD	PhenoAA	0.0228811	0.0258643	0.603979
TB BMD	GrimAA	0.1821983	0.2034602	0.9275554

IVW: Inverse-variance weighted; IEAA: intrinsic epigenetic age acceleration; HannumAA: Hannum Age acceleration; PhenoAA: PhenoAge acceleration; GrimAA: GrimAge acceleration; BMD: bone mineral density; FN BMD: femoral neck BMD; LS BMD: lumbar spine BMD; FA BMD: forearm BMD; eBMD: heel-BMD; TB BMD: total body BMD; MR: mendelian randomization.

contribute to bone loss. This is further corroborated by the positive causal relationship between GrimAA and whole-body BMD shown in our MR analysis, and the use of GrimAA as a second-generation epigenetic age acceleration. In addition, GrimAA has a significant advantage over other epigenetic ages in the prediction of many functional health and cognitive performance metrics^[35]. Epigenomic-wide association studies (EWAS), although already underway, have been relatively understudied in relation to BMD. One study examined the association of osteoporosis with 100 CpG sites methylated in 2,529 genes that have been determined to be associated with BMD in postmenopausal women^[36]. Cheishvili^[37] identified 1,233 differentially methylated CpG sites to predict the development of early osteoporosis. A controlled study of osteoporotic versus non-osteoporotic women predicts early osteoporosis development. del Real^[38] noted that MSCs from OP patients exhibit RUNX2/OSX proliferation, which may accelerate DNAm age aging. We confirmed genetically that there is a positive correlation between OP and EAA, accelerating aging. Elderly patients with osteoporosis are prone to predispose to forearm distal radius fractures and hip fractures^[39,40]. Furthermore, their fracture incidence continues to increase with aging. Decreased FA BMD and FN BMD are important risk factors for inducing fractures in the elderly. We demonstrated that decreased FA BMD and FN BMD accelerated EAA in inverse MR analysis, and thus, decreased FA BMD and FN BMD are potential factors for accelerated aging in the elderly. In addition, whether fractures induced by decreased forearm BMD and femoral neck BMD can also accelerate EAA is a new question that needs to be further explored. These findings redefine osteoporosis as both a cause and consequence of accelerated epigenetic aging, urging integrated strategies to monitor and modulate biological aging in bone health management.

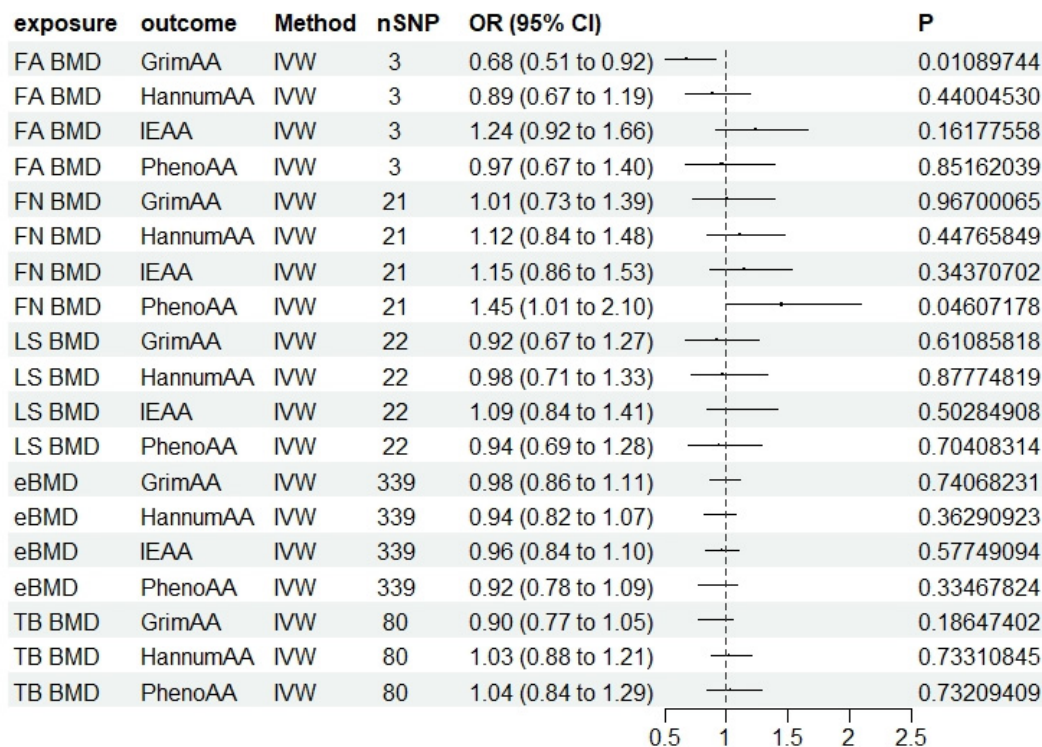


Figure 3. Mendelian randomization analysis for BMD on EAA. nSNP: the number of single-nucleotide polymorphisms; IVW: inverse-variance weighted; EAA: epigenetic age acceleration; IEAA: intrinsic epigenetic age acceleration; HannumAA: Hannum Age acceleration; PhenoAA: PhenoAge acceleration; GrimAA: GrimAge acceleration; BMD: bone mineral density; FN BMD: femoral neck BMD; LS BMD: lumbar spine BMD; FA BMD: forearm BMD; eBMD: heel-BMD; TB BMD: total body BMD; OR: odds ratio; 95%CI: 95% confidence interval; P: P-value.

However, the limitations of our study remain unavoidable. The data sources were mainly from European populations, and genetic studies on epigenetic age acceleration in osteoporosis among different races are lacking. This may lead to maladaptation of observations in other races. Secondly, in the existing GWAS data, there is heterogeneity in the measurement sites and populations (age, gender) of BMD, which may affect the specificity of the EAA association. The association between GrimAA and whole-body BMD may be partially driven by smoking behavior, but smoking data are difficult to completely correct in MR. Furthermore, it is currently unclear why GrimAA is selectively associated with systemic BMD, while PhenoAA is associated with FN BMD, and experimental studies are needed for verification. Future research should focus on the differences in responses of bones in different parts to apparent aging in order to optimize the risk prediction model of osteoporosis.

CONCLUSIONS

In conclusion, epigenetic age acceleration was bi-directionally causally associated with osteoporosis. GrimAge acceleration increased the risk of decreased generalized BMD. Forearm BMD accelerated GrimAge and femoral neck BMD accelerated PhenoAge. However, the relationship between aging and osteoporosis still needs to be further studied.

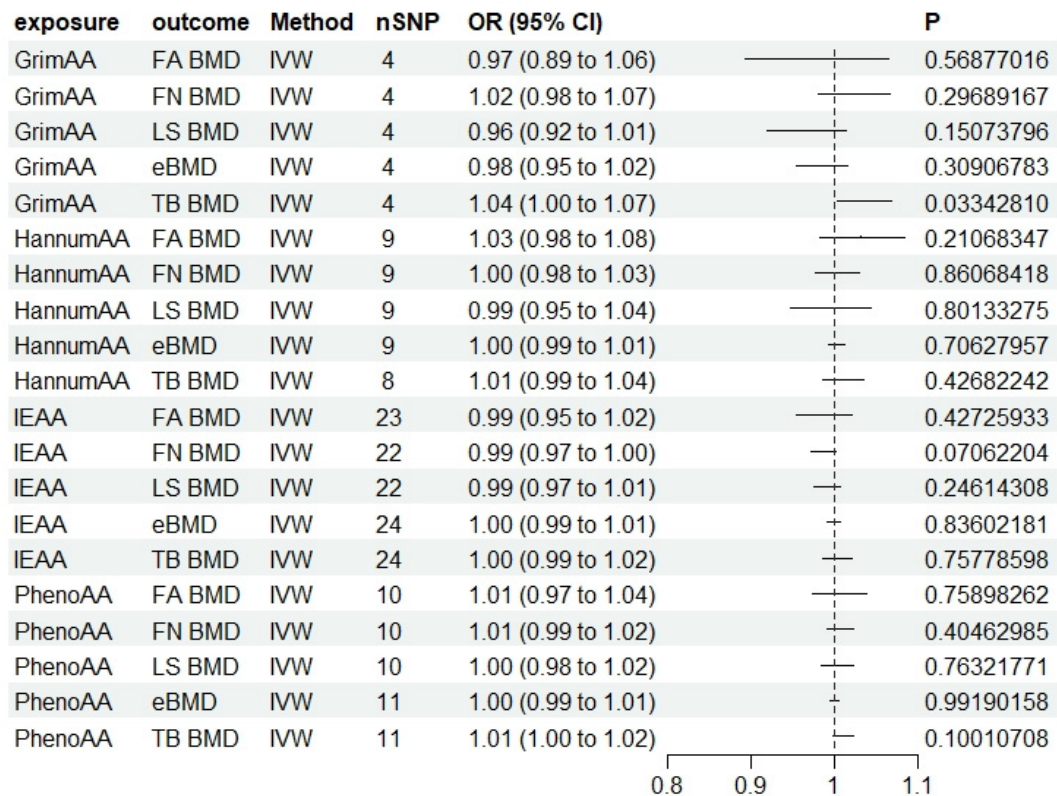


Figure 2. Mendelian randomization analysis for EAA on BMD. nSNP: the number of single-nucleotide polymorphisms; IVW: inverse-variance weighted; EAA: epigenetic age acceleration; IEAA: intrinsic epigenetic age acceleration; HannumAA: Hannum Age acceleration; PhenoAA: PhenoAge acceleration; GrimAA: GrimAge acceleration; BMD: bone mineral density; FN BMD: femoral neck BMD; LS BMD: lumbar spine BMD; FA BMD: forearm BMD; eBMD: heel-BMD; TB BMD: total body BMD; OR: odds ratio; 95%CI: 95% confidence interval; P: P-value.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Wang C, Wang W, Yan B, Wu W, Luo D, Guo Y, Yu H

Performed data acquisition, as well as providing administrative, technical, and material support: Ma L, Wang W

Availability of data and materials

The original data presented in the study are openly available in [IEU GWAS database] at [<https://gwas.mrcieu.ac.uk/>].

Conflicts of interest

Wang W is a Junior Editorial Board member of *Journal of Translational Genetics and Genomics*. Wang W was not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, or decision making. The other authors declared that there are no conflicts of interest.

Financial support and sponsorship

This study was supported by Key Technology Research and Development Program of Shandong Province, China (No. 2021CXGC010501), Taishan Scholar Project of Shandong Province (No. tsqn202211350), and Shandong Province Traditional Chinese Medicine Science and Technology Project of 2024 (MR20241850).

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Copyright

© The Author(s) 2025.

REFERENCES

1. Song S, Guo Y, Yang Y, Fu D. Advances in pathogenesis and therapeutic strategies for osteoporosis. *Pharmacol Ther.* 2022;237:108168. DOI
2. Black DM, Eastell R, Adams AL. Atypical femur fracture risk versus fragility fracture prevention with bisphosphonates.Reply. *N Engl J Med.* 2020;383:2188-90. DOI
3. Wang J, Xing F, Sheng N, Xiang Z. associations of the geriatric nutritional risk index with femur bone mineral density and osteoporosis in american postmenopausal women: data from the national health and nutrition examination survey. *Front Nutr.* 2022;9:860693. DOI PubMed PMC
4. Khosla S, Hofbauer LC. Osteoporosis treatment: recent developments and ongoing challenges. *Lancet Diabetes Endocrinol.* 2017;5:898-907. DOI PubMed PMC
5. Liu J, Curtis EM, Cooper C, Harvey NC. State of the art in osteoporosis risk assessment and treatment. *J Endocrinol Invest.* 2019;42:1149-64. DOI PubMed PMC
6. Ayers C, Kansagara D, Lazur B, Fu R, Kwon A, Harrod C. Effectiveness and safety of treatments to prevent fractures in people with low bone mass or primary osteoporosis: a living systematic review and network meta-analysis for the American college of physicians. *Ann Intern Med.* 2023;176:182-95. DOI PubMed
7. Wu YL, Lin ZJ, Li CC, et al. Epigenetic regulation in metabolic diseases: mechanisms and advances in clinical study. *Signal Transduct Target Ther.* 2023;8:98. DOI PubMed PMC
8. Chen YS, Lian WS, Kuo CW, et al. Epigenetic regulation of skeletal tissue integrity and osteoporosis development. *Int J Mol Sci.* 2020;21:4923. DOI PubMed PMC
9. Yu W, Wang HL, Zhang J, Yin C. The effects of epigenetic modifications on bone remodeling in age-related osteoporosis. *Connect Tissue Res.* 2023;64:105-16. DOI
10. Duan R, Fu Q, Sun Y, Li Q. Epigenetic clock: a promising biomarker and practical tool in aging. *Ageing Res Rev.* 2022;81:101743. DOI
11. Jylhävä J, Pedersen NL, Hägg S. Biological age predictors. *EBioMedicine.* 2017;21:29-36. DOI PubMed PMC
12. Marioni RE, Shah S, McRae AF, et al. DNA methylation age of blood predicts all-cause mortality in later life. *Genome Biol.* 2015;16:25. DOI PubMed PMC
13. Horvath S. DNA methylation age of human tissues and cell types. *Genome Biol.* 2013;14:R115. DOI
14. Hannum G, Guinney J, Zhao L, et al. Genome-wide methylation profiles reveal quantitative views of human aging rates. *Mol Cell.* 2013;49:359-67. DOI PubMed PMC
15. Levine ME, Lu AT, Quach A, et al. An epigenetic biomarker of aging for lifespan and healthspan. *Aging (Albany NY).* 2018;10:573-91. DOI PubMed PMC
16. Lu AT, Quach A, Wilson JG, et al. DNA methylation GrimAge strongly predicts lifespan and healthspan. *Aging (Albany NY).* 2019;11:303-27. DOI PubMed PMC
17. Hillary RF, Stevenson AJ, McCartney DL, et al. Epigenetic measures of ageing predict the prevalence and incidence of leading causes of death and disease burden. *Clin Epigenetics.* 2020;12:115. DOI PubMed PMC
18. Huang M, Xu S, Liu L, et al. m6A methylation regulates osteoblastic differentiation and bone remodeling. *Front Cell Dev Biol.* 2021;9:783322. DOI PubMed PMC
19. Fernandez-Rebollo E, Eipel M, Seefried L, et al. Primary osteoporosis is not reflected by disease-specific dna methylation or accelerated epigenetic age in blood. *J Bone Miner Res.* 2018;33:356-61. DOI PubMed
20. Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. *Hum Mol Genet.* 2014;23:R89-98. DOI PubMed PMC
21. Lawlor DA, Harbord RM, Sterne JA, Timpson N, Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med.* 2008;27:1133-63. DOI PubMed
22. Xu W, Zhang F, Shi Y, Chen Y, Shi B, Yu G. Causal association of epigenetic aging and COVID-19 severity and susceptibility: A bidirectional Mendelian randomization study. *Front Med (Lausanne).* 2022;9:989950. DOI PubMed PMC
23. Zhang F, Deng S, Zhang J, et al. Causality between heart failure and epigenetic age: a bidirectional Mendelian randomization study. *ESC Heart Fail.* 2023;10:pp.2903-13. DOI PubMed PMC
24. Pan Y, Sun X, Huang Z, et al. Effects of epigenetic age acceleration on kidney function: a Mendelian randomization study. *Clin*

- Epigenetics.* 2023;15:61. DOI PubMed PMC
25. Liu C, Liu N, Xia Y, Zhao Z, Xiao T, Li H. osteoporosis and sarcopenia-related traits: a bi-directional Mendelian randomization study. *Front Endocrinol (Lausanne).* 2022;13:975647. DOI PubMed PMC
 26. Tang F, Wang S, Zhao H, Xia D, Dong X. Mendelian randomization analysis does not reveal a causal influence of mental diseases on osteoporosis. *Front Endocrinol (Lausanne).* 2023;14:1125427. DOI PubMed PMC
 27. Lin L, Luo P, Yang M, Wang J, Hou W, Xu P. Causal relationship between osteoporosis and osteoarthritis: a two-sample Mendelian randomized study. *Front Endocrinol (Lausanne).* 2022;13:1011246. DOI PubMed PMC
 28. Hartwig FP, Davies NM, Hemani G, Davey Smith G. Two-sample Mendelian randomization: avoiding the downsides of a powerful, widely applicable but potentially fallible technique. *Int J Epidemiol.* 2016;45:1717-26. DOI PubMed PMC
 29. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol.* 2016;40:304-14. DOI PubMed PMC
 30. Yu M, Hazelton WD, Luebeck GE, Grady WM. Epigenetic aging: more than just a clock when it comes to cancer. *Cancer Res.* 2020;80:367-74. DOI PubMed PMC
 31. Simpson DJ, Chandra T. Epigenetic age prediction. *Aging Cell.* 2021;20:e13452. DOI PubMed PMC
 32. Jiang Z, Liu X, Hu J, Zheng Y, Shen Y. Integration analysis of epigenetic-related m⁶A-SNPs associated with atrial fibrillation. *CVIA.* 2023;8. DOI
 33. Fuggle NR, Laskou F, Harvey NC, Dennison EM. A review of epigenetics and its association with ageing of muscle and bone. *Maturitas.* 2022;165:12-7. DOI PubMed
 34. Conte M, Giuliani C, Chiariello A, Iannuzzi V, Franceschi C, Salvioli S. GDF15, an emerging key player in human aging. *Ageing Res Rev.* 2022;75:101569. DOI
 35. McCrory C, Fiorito G, Hernandez B, et al. GrimAge outperforms other epigenetic clocks in the prediction of age-related clinical phenotypes and all-cause mortality. *J Gerontol A Biol Sci Med Sci.* 2021;76:741-9. DOI PubMed PMC
 36. Reppe S, Refvem H, Gautvik VT, et al. Eight genes are highly associated with BMD variation in postmenopausal Caucasian women. *Bone.* 2010;46:604-12. DOI
 37. Cheishvili D, Parashar S, Mahmood N, et al. Identification of an epigenetic signature of osteoporosis in blood DNA of postmenopausal women. *J Bone Miner Res.* 2018;33:1980-9. DOI
 38. Del Real A, Pérez-Campo FM, Fernández AF, et al. Differential analysis of genome-wide methylation and gene expression in mesenchymal stem cells of patients with fractures and osteoarthritis. *Epigenetics.* 2017;12:113-22. DOI PubMed PMC
 39. Ethans KD, MacKnight C. Hip fracture in the elderly. An interdisciplinary team approach to rehabilitation. *Postgrad Med.* 1998;103:167-70. DOI PubMed
 40. Lawson A, Naylor JM, Buchbinder R, et al; Combined Randomised and Observational Study of Surgery for Fractures in the Distal Radius in the Elderly (CROSSFIRE) Study Group. Surgical plating vs closed reduction for fractures in the distal radius in older patients: a randomized clinical trial. *JAMA Surg.* 2021;156:229-37. DOI PubMed PMC