

Featured Article

A univariate and multivariate Mendelian randomization study of the causal association of arterial stiffness with bone mineral density and osteoporosis

Bowen Hong^{1,2,†}, Shaoshuo Li^{1,2,†}, Yi Zhou^{1,2}, Jiapeng Ye³, Mao Wu^{1,2}, Yang Shao^{1,2}, Jianwei Wang^{1,2,*}

¹ Department of Traumatology and Orthopedics, Wuxi Affiliated Hospital of Nanjing University of Chinese Medicine, Wuxi 214000, China

² Nanjing University of Chinese Medicine, Nanjing 210000, China

³ Department of Traumatology and Orthopedics, Changzhou Affiliated Hospital of Nanjing University of Chinese Medicine, Changzhou 213000, China

* Corresponding author: Jianwei Wang, wxzy006@njucm.edu.cn

† These authors contributed equally to this work.

CITATION

Hong B, Li S, Zhou Y, et al. A univariate and multivariate Mendelian randomization study of the causal association of arterial stiffness with bone mineral density and osteoporosis. *Psycho-Oncologie*. 2025; *Psycho-Oncology Research in China*: 4561.

ARTICLE INFO

Received:

Accepted:

Available online:

COPYRIGHT



Copyright © 2025 by author(s).

Psycho-Oncologie is published by PiscoMed Publishing Pte. Ltd. This work is licensed under the Creative Commons Attribution (CC BY) license.

<https://creativecommons.org/licenses/by/4.0/>

Abstract: This investigation employed Mendelian randomization (MR) analysis to explore the causal associations of arterial stiffness with bone loss or osteoporosis. Genetic instruments for arterial stiffness index (ASI) were identified in previous genome-wide association studies, with single-nucleotide polymorphisms (SNPs) subjected to rigorous selection criteria. The causal links between ASI and osteoporosis and bone mineral density (BMD) (femoral neck, forearm, lumbar spine) were examined using the inverse variance weighted (IVW) method. Leave-one-out (for SNPs) and reverse MR analyses were also performed. An increased ASI was causally related to a decreased forearm BMD risk (IVW method; odds ratio [OR] = 0.593, 95% confidence interval [CI]: 0.408–0.862); no other causal links were identified. The multivariate MR analyses confirmed persistent links between ASI and forearm BMD after adjusting for body mass index (OR = 0.551, 95% CI: 0.309–0.983) or type 2 diabetes mellitus (OR = 0.690, 95% CI: 0.547–0.872). The reverse MR analysis identified no significant effects of BMD or osteoporosis on ASI. Overall, increased ASI was causally associated with reduced forearm BMD.

Keywords: causal association; arterial stiffness; bone mineral density; osteoporosis; Mendelian randomization

Introduction

The prevalence of osteoporosis and cardiovascular disease (CVD) is escalating, posing significant challenges to global public health [1]. As the population ages, the social burden of osteoporosis and CVD increases [1]. Osteoporosis and CVD share several common risk factors, potentially suggesting a causal link [1,2]. Arteriosclerosis manifests through functional and structural alterations in the vascular media, primarily driving arterial stiffening in large elastic arteries [3]. Arterial stiffness reflects the functional characteristics of the arteries and is a parameter used in estimating cardiovascular risk [4]. Arterial stiffness is considered an autonomous predictor of vascular aging and CVD, serving as a subclinical indicator for cardiovascular health [5].

The arterial stiffness index (ASI) represents a clinically practical and non-invasive assessment technique that rapidly measures arterial stiffness through infra-red finger sensors (photoplethysmography); higher ASIs indicate greater arterial stiffness and a higher atherosclerosis risk [6]. Previous cohort studies reported a positive link between ASI and the occurrence of CVD and its related risk factors [7,8]. Moreover, a causal association between ASI and ischemic stroke has been confirmed

[6]. However, whether a causal association exists between arterial stiffness and osteoporosis is not known. Additionally, multiple cross-sectional studies have consistently demonstrated an inverse correlation of arterial stiffness with bone mass [9,10]. A recent Chinese cohort study revealed a correlation between arterial stiffness and incident fragility fractures [11]. However, a European cohort study found no substantial correlation of arterial stiffness with bone mineral density (BMD) changes in individuals with hyperhomocysteinemia [12]. Therefore, the correlation of arterial stiffness with bone health remains controversial. Furthermore, conventional observational studies face inherent limitations in establishing causality due to residual confounding and potential reverse causation.

Mendelian randomization (MR) methodology overcomes these constraints by employing genetic variants as instrumental variables [13], and it reduces bias due to confounding factors relative to traditional observational epidemiological studies [14]. MR analyses are also less susceptible to bias caused by reverse causality, as the genetic code is not affected by preclinical diseases or environmental factors [15]. Therefore, this investigation conducted a two-sample MR analysis utilizing genome-wide association studies (GWAS) datasets to evaluate causal links between arterial stiffness and bone loss or osteoporosis.

Methods

Study design

Two-sample MR infers causal link of exposure phenotypes with clinical outcomes via instrumental variables of genetic variation. This study leveraged publicly available, large-scale GWAS datasets to evaluate the link between ASI (exposure) with osteoporosis or BMD (outcomes) via two-sample MR analysis, addressing limitations commonly associated with observational studies. The concept map of the study design is depicted in **Figure 1**.

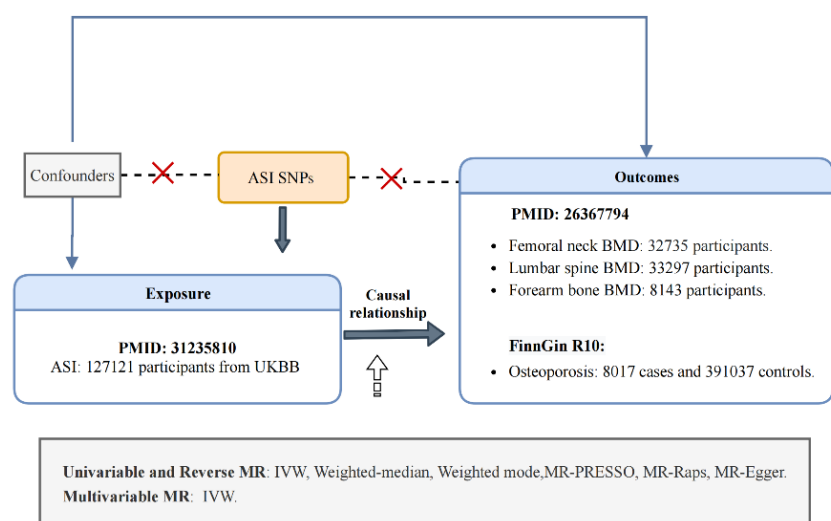


Figure 1. The concept map of the Mendelian randomization (MR) analysis of a causal link between arterial stiffness and bone loss or osteoporosis.

Data sources

The summary GWAS statistics of ASI were examined in an analysis of 127,121 European-ancestry subjects in the UK Biobank [16]. The summary GWAS statistics of BMD (forearm, femoral neck, lumbar spine) were primarily analyzed in 32,965 participants of European ancestry from nine cohorts using three genotyping methods: whole-exome sequencing, whole-genome sequencing, and genome-wide genotyping with imputation to the UK10K/1000Genomes Reference Panel [17]. The summary GWAS data of osteoporosis was extracted from the FinnGen. All dataset were sourced from publicly accessible repositories including the GWAS Catalog (ebi.ac.uk), IEU OpenGWAS project (mrcieu.ac.uk), and Access results in FinnGen websites (Supplementary Table S1).

MR Assumptions

As secondary analysis using previous databases, our study was conducted according to three MR assumptions: (1) genetic instruments are directly related to ASI (relevance); (2) genetic instruments are not correlated to confounders (independence); and (3) genetic instruments do not affect BMD or osteoporosis, except via ASI (exclusion restriction) [18].

Selection of single-nucleotide polymorphisms (SNPs) associated with ASI, osteoporosis or BMD

The GWAS database was queried to select SNPs based on the aforementioned assumptions. The threshold for SNPs was set at $P < 5 \times 10^{-8}$ to ensure relevance (assumption 1). SNPs were subjected to clumping to mitigate the effects of linkage disequilibrium using a stringent clump window ($r^2 = 0.001$ and $kb = 10,000$). Palindromic SNPs were also dropped. Then, eligible SNPs were included and analyzed. F-statistics were estimated to evaluate instrument strength and address sample overlap concerns. F -values of < 10 indicated potential bias.

Horizontal pleiotropy analysis

Horizontal pleiotropy was systematically assessed through MR-Egger regression analysis of SNP effects. The presence of correlated pleiotropy and uncorrelated pleiotropy would violate assumptions 2 and 3, respectively [19]. SNPs directly related to osteoporosis or BMD but not via ASI and SNPs related to confounders were excluded.

Statistical analysis

The present study employed an MR analysis to measure whether ASI was causally linked to osteoporosis or BMD, utilizing eligible SNPs. The primary analytical approach, the inverse variance weighted (IVW) method, provided unbiased estimates of exposures on outcomes through a multiplicative random-effects model utilizing Wald ratio calculations [20]. Complementary validation was achieved through Weighted median [21], MR-RAPS [22], weighted mode [23], and MR-PRESSO [24] methods. Sensitivity analysis using a leave-one-out analysis was conducted to measure individual SNPs associated with the ASI influencing the observed outcomes, and the symmetry results indicate an absence of pleiotropy.

Heterogeneity among SNPs was detected by Cochran's Q -test, and a P -value of ≥ 0.05 indicated no significant heterogeneity. Moreover, multivariable MR analyses were employed to evaluate body mass index (BMI) and type 2 diabetes mellitus confounders on BMD. Multivariable MR is a further extension of univariable MR to analyze causal effects under the influence of multiple risk factors. Results of causal links were reported as odds ratios (ORs) and 95% confidence intervals (95% CIs) using R version 4.2.3 (2023-03-15ucrt) with specialized packages: MRPRESSO (version 1.0), TwoSampleMR (version 0.5.7), MVMR (version 0.4), mr.raps (version 0.2), and MRInstruments (version 0.3.2).

Ethics statement

These analyses leveraged publicly accessible datasets that had received approval from the appropriate ethics committees, thus obviating the need for additional ethical approval and consent from participants.

Results

Selection of SNPs associated with ASI and results of pleiotropy analysis

In total, 92 SNPs linked to the ASI (with $P < 5 \times 10^{-8}$) were included. After removing SNPs with linkage disequilibrium and palindromic SNPs in intermediate allele frequencies, 4 SNPs were included as instrumental variables of the ASI for the MR analysis. The MR-Egger analysis revealed no pleiotropic bias in the retained SNPs ($P > 0.05$) (Table 1). The SNPs explained in the ASI variability was 0.1223% (Supplementary Table S2). The power of the 4 SNPs was exhibited in Supplementary Table S3, the power of SNPs related to ASI concerning BMD (femoral neck, forearm, lumbar spine) was 1.00, and concerning osteoporosis was 0.07.

Table 1. The horizontal pleiotropy analysis of SNPs associated with ASI. ASI, arterial stiffness index; BMD, bone mineral density; IVW, inverse variance weighted; MR, Mendelian randomization; SNP, single nucleotide polymorphism.

Variables	SNP after $P < 5 \times 10^{-8}$ (n)	After removing linkage disequilibrium (n)	After dropping palindromic SNP (n)	Horizontal pleiotropic test		Heterogeneity test				Strength	
				Egger intercept	P	MR Egger Q	P	IVW Q	P	F-value	R ² (%)
Femoral neck BMD	92	4	3	-0.01	0.790	0.003	0.958	0.12	0.942	37	0.09
Forearm BMD	92	4	4	-0.03	0.755	0.933	0.627	1.06	0.787	39	0.12
Lumbar spine BMD	92	4	3	-0.08	0.488	2.350	0.125	4.89	0.087	37	0.09
Osteoporosis	92	4	4	0.03	0.842	5.173	0.075	5.30	0.151	39	0.12

MR analysis for a causal link between ASI and BMD or osteoporosis

The IVW-based results revealed that increased ASI values were causally correlated with decreased forearm BMD risk (OR = 0.593, 95% CI: 0.408–0.862). Causal links between the ASI and femoral neck BMD, lumbar spine BMD, and osteoporosis were not identified (all $P > 0.05$) (Table 2). The weighted mode, weighted median, MR-RAPS, and MR-PRESSO analyses produced similar findings

to those of the IVW analysis. Supplementary **Table S4** and **Figure 2** present detailed estimates of the causal links between ASI and BMD or osteoporosis in these models. The multivariate MR analyses confirmed persistent links between ASI and forearm BMD after adjusting for body mass index (OR = 0.551, 95% CI: 0.309–0.983) or type 2 diabetes mellitus (OR = 0.690, 95% CI: 0.547–0.872) (**Table 3**).

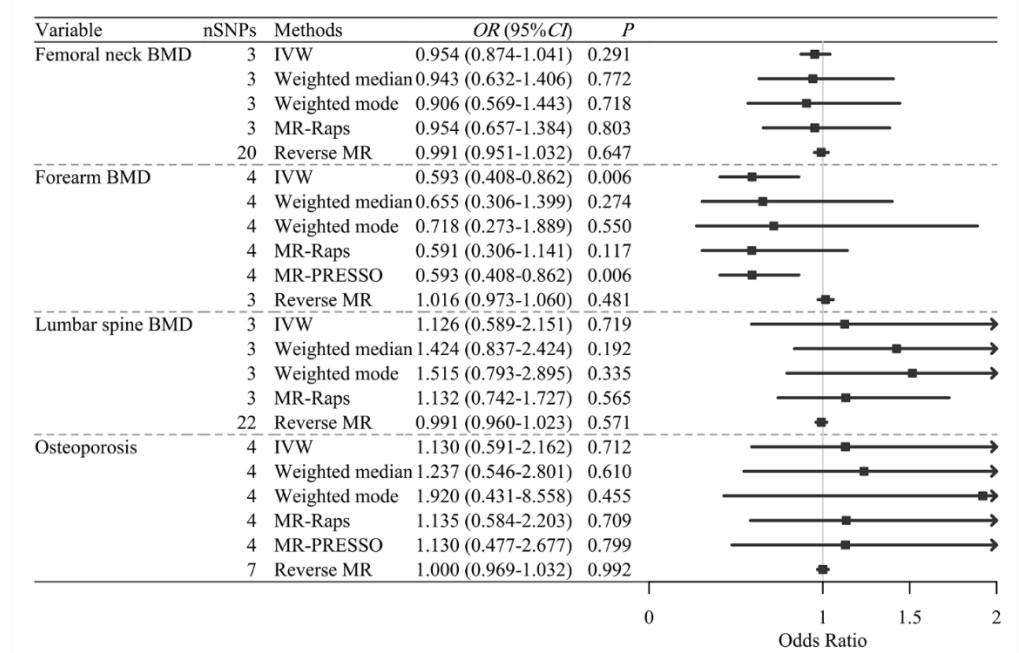


Figure 2. Mendelian randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO), weighted mode, weighted median, MR robust adjusted profile score (MR-RAPS), and reverse MR analysis results.

Table 1 further summarizes instrumental variables' strength/heterogeneity statistical evaluations. Pleiotropic bias in the SNPs was not identified based on the MR-Egger analysis. There were strong associations of ASI-associated SNPs with the femoral neck BMD ($F = 37$), forearm BMD ($F = 39$), lumbar spine BMD ($F = 37$), and osteoporosis ($F = 39$).

Table 2. The MR analysis results of the relationships between ASI and BMD and osteoporosis based on the IVW method. ASI, arterial stiffness index; BMD, bone mineral density; CI, confidence interval; IVW, inverse variance weighted; OR, odds ratio; SNP, single nucleotide polymorphism.

Outcome	nSNPs	IVW	
		OR (95%CI)	P
Femoral neck BMD	3	0.954 (0.874–1.041)	0.291
Forearm BMD	4	0.593 (0.408–0.862)	0.006
Lumbar spine BMD	3	1.126 (0.589–2.151)	0.719
Osteoporosis	4	1.130 (0.477–2.677)	0.781

Table 3. The multivariable MR analysis results of the relationships between ASI and BMD and osteoporosis. ASI, arterial stiffness index; BMD, bone mineral density;

BMI, body mass index; CI, confidence interval; IVW, inverse variance weighted; MVMR, multivariable Mendelian randomization; OR, odds ratio; SNP, single nucleotide polymorphism; T2DM, type 2 diabetes mellitus.

Variable	Outcome	MVMR	OR (95%CI)	P
Adjusted BMI	Forearm BMD	IVW	0.551 (0.309–0.983)	0.043
Adjusted T2DM	Forearm BMD	IVW	0.690 (0.547–0.872)	0.002

Sensitivity analysis

None of the SNPs significantly influenced the causal link between the ASI and forearm BMD based on the leave-one-out analysis results (**Figure 3**), suggesting that the results are reliable.

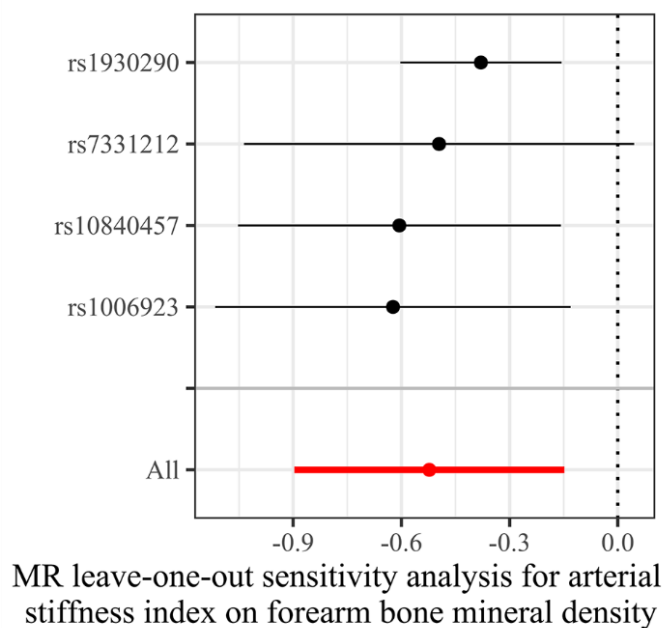


Figure 3. Sensitivity analysis using the leave-one-out method.

Reverse MR analysis

A reverse MR analysis was executed using the same procedure as the above MR analysis to assess the reverse causality. Significant results would indicate reverse causality from BMD or osteoporosis (as exposures) to ASI (as an outcome). However, causal associations of BMD or osteoporosis with ASI were not identified (Supplementary **Table S5**, **Figure 2**).

Discussion

The investigation examined the causal correlations of arterial stiffness with bone loss or osteoporosis through an MR analysis utilizing GWAS data, finding that an increased ASI had a causal link with decreased forearm BMD risk. A reverse causal association of BMD or osteoporosis with ASI was not found. The multivariate MR analysis illustrated that the causal link between ASI and forearm BMD remained statistically significant after adjusting for BMI or type 2 diabetes mellitus. These findings provide a new insight for managing bone health in the general population.

Arterial stiffness, a clinical marker reflecting diminished vascular compliance, represents pathological remodeling of medial arterial layers and biomechanical dysfunction [25]. High levels of arterial stiffness have been correlated to elevated atherosclerotic disease risk, which has been validated in various contexts [7]. The ASI measures large artery stiffness based on the pulse waveform contour, which propagates and reflects in the arterial tree. A higher ASI value indicates augmented arterial stiffness and is linked to unfavorable ischemic cardiovascular outcomes. Conversely, a lower ASI value suggests improved arterial compliance and vascular health [26]. CVD correlates with elevated vascular calcification and arterial stiffness risk, both of which exhibit an inverse correlation with BMD [27]. Evidence from a UK Biobank study reported a correlation between poor bone quality and greater arterial stiffness [9]. Kim et al. also reported a significant inverse link of pulse wave velocity with femur neck and lumbar BMDs, suggesting a relationship between total femur arterial stiffness and BMD in females [28]. This study confirmed that increased ASI values were causally related to decreased forearm BMD. Previously, a causal association between mechanistic target-of-rapamycin (mTOR)-dependent EIF-4E circulating protein and forearm BMD was identified [29], and the mTOR pathway was identified to be related to large elastic artery stiffening [30]. Notably, diagnostic challenges arise in the elderly population with cardiovascular comorbidities, as degenerative spinal changes may increase lumbar spine BMD measurements, potentially compromising the sensitivity of osteoporosis detection, thus forearm BMD might be a more reliable biomarker for the bone health in this population [31]. Also, forearm BMD assessment emerges as a more reliable diagnostic parameter due to its composite cortical-trabecular bone composition, which demonstrates superior responsiveness to anti-osteoporosis therapies compared to other skeletal sites [32]. These might help explain the observed positive correlation of ASI with forearm BMD. BMD of forearm measurements via peripheral dual-energy x-ray absorptiometry devices provides an inexpensive, time-saving method for osteoporosis evaluation [33,34].

Inflammation, impaired glucose metabolism, and hormonal dysregulation may contribute to the link of arterial stiffness with bone loss [35]. In addition, arterial stiffness can cause blood flow disorders and tissue hypoperfusion, which might accelerate bone loss [36]. Improving glucose and calcium phosphate metabolism and suppressing oxidative stress have shown promising results for decreasing vascular calcification and enhancing bone mineralization [37]. In atherosclerosis, Runx2 upregulation is induced by increased levels of oxidized lipids and high calcium and phosphate conditions, regulated by activating various signaling pathways, such as the BMP, MAPK, Msx2/Wnt, and AKT pathways. Notably, in bone cells, some of these pathways exhibit distinct functionalities due to inhibition induced by hyperglycemia, oxidative stress, and elevated phosphate levels in osteoblasts, reducing bone mineralization [37].

Study limitations include that the data were primarily from people of European descent; thus, they should be validated before they can be generalized to other ethnicities. Second, associations between the ASI and BMD at other sites were not analyzed because of the lack of data. Third, the small sample size of the analyzed instrumental variables necessitated further validation in future studies. Fourth, some

detailed information such as how often aortic calcification or arch calcification was presented in subjects whose SNPs affected arterial stiffness was unclear. Nonetheless, this investigation establishes a causal link of ASI with BMD and osteoporosis by bidirectional MR and multivariate MR, which provides evidence for the future exploring the etiology of bone disease including osteoporosis. Moreover, the MR analysis mitigated confounding bias and reverse causality, and the sensitivity analysis ensured robust results.

Conclusion

This investigation examined the causal links of arterial stiffness with bone loss or osteoporosis via two-sample MR analysis, finding that increased ASI values were causally associated with reduced forearm BMD, presenting a novel insight into bone health management.

Author contributions: Conceptualization and design, BH; download data, SL; analyze the data, BH; interpretation of the results, YZ and SL; visualization, YZ and JY; writing—original draft preparation, BH and SL; writing—review and editing, MW, YS and JW; project administration, JW; supervision, JW. All authors have read and agreed to the published version of the manuscript.

Acknowledgments: We sincerely thank the researchers who shared the GWAS data. In addition, we would like to thank Editage (www.editage.cn) for English language editing and Nanjing ShuChuang Information Consulting Co., LTD for the revisions.

Funding: This study was supported by the National Natural Science Foundation of China (82274546, 82405520), the Jiangsu Province Traditional Chinese Medicine Science and Technology Development Program (QN202322), the Top Talent Support Program for young and middle-aged people of Wuxi Health Committee (HB2023074), and the Jiangsu Provincial Graduate Research and Practice Innovation Program (SJCX24_1029).

Data availability: The datasets analyzed for this study can be found on the GWAS Catalog (ebi.ac.uk), IEU OpenGWAS project (mrcieu.ac.uk), and Access results in FinnGen websites.

Conflict of interest: The authors declare no conflict of interest.

Abbreviations

MR	Mendelian randomization
SNPs	Single-nucleotide polymorphisms
IVW	Inverse variance weighted
ASI	Arterial stiffness index
BMD	Bone mineral density
OR	Odds ratio
CI	Confidence interval
BMI	Body mass index
T2DM	Type 2 diabetes mellitus

References

1. Azeez TA. Osteoporosis and cardiovascular disease: a review. *Molecular Biology Reports*. 2022; 50(2): 1753-1763. doi: 10.1007/s11033-022-08088-4
2. Rodríguez-Gómez I, Gray SR, Ho FK, et al. Osteoporosis and Its Association with Cardiovascular Disease, Respiratory Disease, and Cancer: Findings From the UK Biobank Prospective Cohort Study. *Mayo Clinic Proceedings*. 2022; 97(1): 110-121. doi: 10.1016/j.mayocp.2021.07.019
3. Tousoulis D. Arterial stiffness: A clinical index or a research tool?. *Hellenic Journal of Cardiology*. 2019; 60(2): 69-71. doi: 10.1016/j.hjc.2019.03.010
4. Baykara M, Ozturk C, Elbuenken F. The assessment of relationship between bone mineral density and arterial stiffness in turkish women. *Diagnostic and Interventional Radiology*; 2011. doi: 10.4261/1305-3825.dir.5330-11.1
5. Berger M, Fesler P, Roubille C. Arterial stiffness, the hidden face of cardiovascular risk in autoimmune and chronic inflammatory rheumatic diseases. *Autoimmunity Reviews*. 2021; 20(9): 102891. doi: 10.1016/j.autrev.2021.102891
6. Liu W, Zhang L, Gao Y, et al. The association of arterial stiffness index with cerebrovascular and cardiometabolic disease: A Mendelian randomization study. *International Journal of Stroke*. 2022; 17(10): 1145-1150. doi: 10.1177/17474930211066432
7. Said MA, Eppinga RN, Lipsic E, et al. Relationship of Arterial Stiffness Index and Pulse Pressure with Cardiovascular Disease and Mortality. *Journal of the American Heart Association*. 2018. doi: 10.1161/jaha.117.007621
8. Wang M, Huang J, Wu T, et al. Arterial Stiffness, Genetic Risk, and Type 2 Diabetes: A Prospective Cohort Study. *Diabetes Care*. 2022; 45(4): 957-964. doi: 10.2337/dc21-1921
9. Raisi-Estabragh Z, Biasioli L, Cooper J, et al. Poor Bone Quality is Associated with Greater Arterial Stiffness: Insights from the UK Biobank. *Journal of Bone and Mineral Research*. 2020; 36(1): 90-99. doi: 10.1002/jbmr.4164
10. EL-Bikai R, Tahir MR, Tremblay J, et al. Association of age-dependent height and bone mineral density decline with increased arterial stiffness and rate of fractures in hypertensive individuals. *Journal of Hypertension*. 2015; 33(4): 727-735. doi: 10.1097/hjh.0000000000000475
11. Guo L, Zhang N, Zhang Y, et al. Arterial stiffness and risk of new-onset fragility fracture in Chinese men and women: The Kailuan cohort study. *Bone*. 2024; 180: 116991. doi: 10.1016/j.bone.2023.116991
12. van Dijk SC, de Jongh RT, Enneman AW, et al. Arterial stiffness is not associated with bone parameters in an elderly hyperhomocysteinemic population. *Journal of Bone and Mineral Metabolism*. 2015; 34(1): 99-108. doi: 10.1007/s00774-015-0650-x
13. Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. *Human Molecular Genetics*. 2014; 23(R1): R89-R98. doi: 10.1093/hmg/ddu328
14. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ*; 2018. doi: 10.1136/bmj.k601
15. Li P, Wang H, Guo L, et al. Association between gut microbiota and preeclampsia-eclampsia: a two-sample Mendelian randomization study. *BMC Medicine*; 2022. doi: 10.1186/s12916-022-02657-x
16. Fung K, Ramirez J, Warren HR, et al. Genome-wide association study identifies loci for arterial stiffness index in 127,121 UK Biobank participants. *Scientific Reports*; 2019. doi: 10.1038/s41598-019-45703-0
17. Zheng H, Forgetta V, Hsu Y, et al. Whole-genome sequencing identifies EN1 as a determinant of bone density and fracture. *Nature*. 2015; 526(7571): 112-117. doi: 10.1038/nature14878
18. Larsson SC, Butterworth AS, Burgess S. Mendelian randomization for cardiovascular diseases: principles and applications. *European Heart Journal*. 2023; 44(47): 4913-4924. doi: 10.1093/eurheartj/ehad736
19. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *International Journal of Epidemiology*. 2015; 44(2): 512-525. doi: 10.1093/ije/dyv080
20. Chen X, Hong X, Gao W, et al. Causal relationship between physical activity, leisure sedentary behaviors and COVID-19 risk: a Mendelian randomization study. *Journal of Translational Medicine*. 2022; 20(1). doi: 10.1186/s12967-022-03407-6
21. Bowden J, Davey Smith G, Haycock PC, et al. Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. *Genetic Epidemiology*. 2016; 40(4): 304-314. doi: 10.1002/gepi.21965
22. Zeng Y, Cao S, Yang H. The causal role of gastroesophageal reflux disease in anxiety disorders and depression: A bidirectional Mendelian randomization study. *Frontiers in Psychiatry*; 2023. doi: 10.3389/fpsyt.2023.1135923

23. Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. *International Journal of Epidemiology*. 2017; 46(6): 1985-1998. doi: 10.1093/ije/dyx102
24. Verbanck M, Chen CY, Neale B, et al. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nature Genetics*. 2018; 50(5): 693-698. doi: 10.1038/s41588-018-0099-7
25. Xuereb RA, Magri CJ, Xuereb RG. Arterial Stiffness and its Impact on Cardiovascular Health. *Current Cardiology Reports*. 2023; 25(10): 1337-1349. doi: 10.1007/s11886-023-01951-1
26. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *European Heart Journal*. 2006; 27(21): 2588-2605. doi: 10.1093/eurheartj/ehl254
27. Toussaint ND, Lau KK, Strauss BJ, et al. Relationship between vascular calcification, arterial stiffness and bone mineral density in a cross-sectional study of prevalent Australian haemodialysis patients. *Nephrology*. 2009; 14(1): 105-112. doi: 10.1111/j.1440-1797.2008.01056.x
28. Kim NL, Suh HS. Correlation of Arterial Stiffness and Bone Mineral Density by Measuring Brachial-Ankle Pulse Wave Velocity in Healthy Korean Women. *Korean Journal of Family Medicine*. 2015; 36(6): 323. doi: 10.4082/kjfm.2015.36.6.323
29. Cheng T, Zhang YC, Fan KY, et al. Genetic Evidence Supporting a Causal Association Between mTOR-Dependent EIF-4E Circulating Protein Level and Osteoporosis. *Advances in Therapy*. 2023; 40(11): 4987-4998. doi: 10.1007/s12325-023-02676-x
30. Donato AJ, Machin DR, Lesniewski LA. Mechanisms of Dysfunction in the Aging Vasculature and Role in Age-Related Disease. *Circulation Research*. 2018; 123(7): 825-848. doi: 10.1161/circresaha.118.312563
31. Frisoli Jr A, Paes AT, Kimura AD, et al. Measuring forearm bone density instead of lumbar spine bone density improves the sensitivity of diagnosing osteoporosis in older adults with cardiovascular diseases: Data from SARCOS study. *Bone Reports*. 2021; 15: 101134. doi: 10.1016/j.bonr.2021.101134
32. Biver E, Durosier-Izart C, Chevalley T, et al. Evaluation of Radius Microstructure and Areal Bone Mineral Density Improves Fracture Prediction in Postmenopausal Women. *Journal of Bone and Mineral Research*. 2017; 33(2): 328-337. doi: 10.1002/jbmr.3299
33. Jankowski LG, Warner S, Gaither K, et al. Cross-calibration, Least Significant Change and Quality Assurance in Multiple Dual-Energy X-ray Absorptiometry Scanner Environments: 2019 ISCD Official Position. *Journal of Clinical Densitometry*. 2019; 22(4): 472-483. doi: 10.1016/j.jocd.2019.09.001
34. Baim S, Binkley N, Bilezikian JP, et al. Official Positions of the International Society for Clinical Densitometry and Executive Summary of the 2007 ISCD Position Development Conference. *Journal of Clinical Densitometry*. 2008; 11(1): 75-91. doi: 10.1016/j.jocd.2007.12.007
35. Tap L, Kirkham FA, Mattace-Raso F, et al. Unraveling the Links Underlying Arterial Stiffness, Bone Demineralization, and Muscle Loss. *Hypertension*. 2020; 76(3): 629-639. doi: 10.1161/hypertensionaha.120.15184
36. Ramasamy SK, Kusumbe AP, Schiller M, et al. Blood flow controls bone vascular function and osteogenesis. *Nature Communications*. 2016; 7(1). doi: 10.1038/ncomms13601
37. Chen Y, Zhao X, Wu H. Arterial Stiffness. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2020; 40(5): 1078-1093. doi: 10.1161/atvbaha.120.313131