Check for updates

OPEN ACCESS

EDITED BY Afshin Ostovar, Tehran University of Medical Sciences, Iran

REVIEWED BY Abbas Dehghan, Imperial College London, United Kingdom Hengyi Xu, The University of Texas at Austin, United States

*CORRESPONDENCE Chan Kang Saschan@daum.net

[†]These authors have contributed equally to this work

RECEIVED 28 December 2023 ACCEPTED 06 May 2024 PUBLISHED 22 May 2024

CITATION

Zhang J, Xu P, Liu R, Gyu JM, Cao P and Kang C (2024) Osteoporosis and coronary heart disease: a bi-directional Mendelian randomization study. *Front. Endocrinol.* 15:1362428. doi: 10.3389/fendo.2024.1362428

COPYRIGHT

© 2024 Zhang, Xu, Liu, Gyu, Cao and Kang. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Osteoporosis and coronary heart disease: a bi-directional Mendelian randomization study

Junsheng Zhang^{1†}, Pai Xu^{1†}, Rongcan Liu^{1†}, Jin Min Gyu^{1†}, Peng Cao^{2†} and Chan Kang^{1*}

¹Department of Orthopedic Surgery, Chungnam National University School of Medicine, Daejeon, Republic of Korea, ²Burn & Trauma Treatment Center, Affiliated Hospital of Jiangnan University, Wuxi, China

Background: Osteoporosis (OP) and cardiovascular disease (CVD) are major global public health issues, especially exacerbated by the challenges of an aging population. As these problems intensify, the associated burden on global health is expected to increase significantly. Despite extensive epidemiological investigations into the potential association between OP and CVD, establishing a clear causal relationship remains elusive.

Methods: Instrumental variables were selected from summary statistics of the IEU GWAS database. Five different components of BMD (heel BMD, LS BMD, FA BMD, FN BMD, and TB BMD) were used as OP phenotypes. CHD, MI, and stroke were selected to represent CVD. Multiple analysis methods were used to evaluate the causal relationship between CVD and OP comprehensively. In addition, sensitivity analyses(Cochran's Q test, MR-Egger intercept test, and "leave one out" analysis) were performed to verify the reliability of the results.

Results: The MR showed a significant causal relationship between CHD on heel BMD and TB BMD; in the reverse analysis, there was no evidence that OP has a significant causal effect on CVD. The reliability of the results was confirmed through sensitivity analysis.

Conclusion: The study results revealed that CHD was causally associated with Heel BMD and TB BMD, while in the reverse MR analysis, the causal relationship between OP and CVD was not supported. This result posits CHD as a potential etiological factor for OP and prompts that routine bone density assessment at traditional sites (forearm, femoral neck, lumbar spine) using DAX may inadequately discern underlying osteoporosis issues in CHD patients. The recommendation is to synergistically incorporate heel ultrasound or DAX for total body bone density examinations, ensuring clinical diagnostics are both precise and reliable. Moreover, these findings provide valuable insights for public health, contributing to the development of pertinent prevention and treatment strategies.

KEYWORDS

osteoporosis, cardiovascular disease, bidirectional, two-sample Mendelian randomization study, causality

Cardiovascular disease (CVD) stands as a predominant contributor to global morbidity and mortality. The prevalence of CVD nearly doubled from 1990 to 2019, rising from 271 million to 523 million. Concurrently, deaths from CVD surged from 12.1 million to 18.6 million (1). Notably, in 2019, CVD emerged as the primary cause of death in Asia, claiming 10.8 million lives and representing approximately 35% of total fatalities in the region (2). According to the most recent published reports by the American College of Cardiology, the global incidence of cardiovascular diseases witnessed a 29.01% increase over the past decade, culminating in 607.64 million cases in 2020. Correspondingly, the death toll rose to 19.05 million, marking an 18.71% surge over the same period (3). While the current trajectory of CVD prevention appears promising, there remains a compelling imperative to formulate and implement effective monitoring and prevention strategies aimed at alleviating the burden of CVD, particularly in underserved global populations (4). Additionally, with a trend toward younger onset of CVD, a pressing need exists to comprehensively comprehend the pathogenesis of CVD to confront this inevitable challenge (5).

Osteoporosis (OP), a metabolic bone disorder stemming from a convergence of multifactorial elements, may result in a reduction of bone density in mild cases, while in severe instances, it can culminate in fractures. The fundamental etiology of the condition lies in the dysregulation between bone formation and resorption processes (6, 7). Epidemiological data underscores a staggering global prevalence of osteoporosis is 19.7%, and osteopenia is as high as 40.4% (8). Projections based solely on population aging portend a substantial escalation in the majority of osteoporosis and fragility fractures in the coming decade (9). Regrettably, a worldwide survey targeting older demographics reveals an osteoporosis prevalence of 21.7%, with the highest rates observed in Asian countries at 24.3%, succeeded by Europe (16.7%) and the United States (11.5%) (10). In light of these findings, some scholars boldly advocate for universal osteoporosis assessment and intervention, positing it as a requisite measure to mitigate the direct and indirect global burden imposed by osteoporosis (11). Evidently, osteoporosis's disconcerting status necessitates urgently exploring its causative factors to curtail its global impact.

OP and CVD commonly coexist in clinical settings. Despite numerous observational studies attempting to ascertain the precise relationship between them, a definitive consensus remains elusive. Given this context, the imperative to clarify the causal link between OP and CVD becomes even more pronounced. Not only does this hold clinical significance, but it also fortifies our preparedness to confront ensuing challenges. Observational studies, susceptible to confounding factors, need to ascertain the causal relationship between OP and CVD more adequately. To circumvent these limitations, Mendelian randomization (MR) emerges as a potent method for causal inference, utilizing genetic variation as an instrumental variable (IV). This approach effectively mitigates confounding biases inherent in traditional epidemiological research (12). Consequently, to establish the causal relationship between OP and CVD definitively, we conducted a bi-directional MR study.

2 Materials and methods

2.1 Research design

This study adheres to the methodological tenets outlined in the Guideline (13). Employing bi-directional Mendelian randomization (MR) analysis involving two datasets, we sought to delineate the directional causality between CVD and OP, encompassing diverse analytical facets. Initially, we scrutinized potential causal associations between CVD (coronary heart disease [CHD], myocardial infarction [MI], Stroke) and OP indicators (total body BMD [TB BMD], lumbar spine BMD [LS BMD], forearm BMD [FA BMD], femoral neck BMD [FN BMD], Heel BMD). Subsequently, we conducted a reciprocal analysis in the opposite direction. The bi-directional MR analysis involving two datasets is depicted in Figure 1 below. All data used in this study were obtained from free and open databases or existing publications and did not require ethical approval to be conducted.

2.2 Data sources

OP and cardiovascular disease CVD exhibit a substantial hereditary component, with evidence suggesting heritability rates of up to 40% to 60% for coronary artery disease and 60% to 80% for BMD (14, 15). This hereditary influence poses significant challenges to our endeavors to alleviate the burdens imposed by these conditions. The most recent Global Burden of Disease (GBD) statistics underscore the pivotal role of ischemic heart disease (IHD) and stroke in contributing to the overall burden of CVD (1). IHD, predominantly manifesting as coronary artery disease, serves as the primary pathological process underlying IHD, with the terms often employed interchangeably (16). Acute cardiovascular events, including common strokes and myocardial infarctions, constitute emergencies within the spectrum of CVD (5). Consequently, representative CVDs such as CHD, stroke, and MI were selected for investigation. Osteoporosis diagnosis, as per the World Health Organization (WHO), is established when BMD measured at the spine, hip, or wrist falls more than 2.5 standard deviations below the average BMD reference value for young adults (17). Currently, dual-energy X-ray absorptiometry (DXA) serves as the standard clinical method for detecting osteoporosis. Despite its widespread use, DXA measurements may yield errors for individuals with immature bones, necessitating the adoption of whole-body measurements, particularly in pediatric populations (18). Given the limitations of DXA for large-scale osteoporosis screening, quantitative ultrasound (QUS) emerges as a viable alternative characterized by simplicity, portability, costeffectiveness, and the absence of ionizing radiation; it is suitable for bone health assessments in diverse populations, including young children. Furthermore, when juxtaposed with DXA for fracture prediction, the overall advantages of QUS are relatively apparent (19). Additionally, heel bone density estimation using ultrasound has high heritability and a strong correlation with DXA-based bone density (20). Consequently, our selection of LS BMD, FA BMD, and



FN BMD measured by DXA, along with TB BMD and Heel BMD, as representative components for OP aimed to guarantee the reliability and persuasiveness of the chosen BMD parameters. In assembling the largest GWAS database to date, encompassing three separate GWAS summary statistics for LS BMD (n = 28,498), FN BMD (n = 32,735), and FA BMD (n = 8143), our study stands at the forefront of DXA-measured BMD research. While age is a recognized common risk factor for both OP and CVD, the majority of prior investigations have concentrated on adults, particularly older women. However, compelling evidence indicates that children with congenital heart disease are also susceptible to severe metabolic bone disease and fragility-related fractures (21). Motivated by this insight, our study explored the potential age-specific relationship between CVD and TB BMD across five distinct age groups (0-15, 15-30, 30-45, 45-60, and over 60 years old) as detected by DXA. This targeted approach aims to facilitate early and precise intervention in corresponding age cohorts While fortifying the reliability of our research outcomes. To the best of our knowledge, this study represents the first relatively comprehensive evaluation of Mendelian randomization between CVD and OP. Detailed information on the data employed is available in (Table 1).

2.3 Genetic instrumental variable selection criteria

To identify Proper single nucleotide polymorphisms(SNPs) of CVD and BMD, our approach in the OPEN GWAS databases involved a meticulous series of steps. Firstly, SNPs demonstrating robust association (p < 5E-8), independent inheritance (r2 < 0.001,

kb = 10,000), and lack of linkage disequilibrium (LD) were meticulously selected from the GWAS data of CVD or BMD. This curation process was executed through the clump data function within the Two-Sample Mendelian Randomization (MR) package in R software (version 4.3.1). Subsequently, outcomeassociated SNPs were systematically eliminated by querying each one individually using the PhenoScanner database (http:// www.phenoscanner.medschl.cam.ac.uk). Following this, SNPs featuring palindromic alleles and incompatible variations were systematically excluded to preclude chain ambiguity issues. The remaining SNPs underwent F-statistics calculation to assess the correlation between exposure and SNPs, with the value less than 10 indicating weakness and necessitating elimination (22). The resultant SNPs, which were deemed robust, were employed for the subsequent MR analysis. To evaluate the efficacy of instrumental variables (IVs), F statistics for each SNP were computed using the formula F = R2(N-2)/(1-R2). The calculation formula for R2 is articulated as R2 = $(2 \times EAF \times (1 - EAF) \times beta^2)/[(2 \times (1 - EAF)/[(2 \times (1 - EAF)/[(2 \times (1 - EAF)/[(2 \times (1 -$ EAF) x beta 2 + (2 x EAF x (1 - EAF) x N x (SE(beta) 2))], where EAF represents the effect allele frequency, N is the sample size, beta signifies the estimated impact of the genetic effect on the outcome, and SE denotes the standard error of the genetic effect (23).

2.4 MR analysis

To fortify the robustness of our study findings, we employed a comprehensive approach encompassing four distinct methods within the MR analysis framework. These methodologies included inverse variance weighting (IVW), MR-Egger regression, weighted mode, and weighted median. The selection of IVW as the primary analytical method stems from its superior statistical power in scenarios where instrumental variables (IVs) exhibit no pleiotropic effects (24). The utilization of either fixed effects IVW or random effects IVW models depends on the presence or absence of heterogeneity within the dataset (25). In cases over 50% of data is obtained from null instrumental variables, the weighted median approach provides an impartial causal estimate (26). The MR-Egger method, capable of accommodating horizontal pleiotropic effects in all SNPs, serves as a valuable tool for estimating the causal possibility of exposure on the outcome (27). The Bonferroni method was applied to mitigate the risk of false positives resulting from multiple comparisons. Consequently, associations with a P value <0.003 (0.05 divided by 3*5) were deemed significant evidence of a causal link, while the P value less than 0.05 but greater than 0.003 were considered suggestive evidence.

2.5 Sensitivity analysis

In order to fortify the reliability of the outcomes derived from MR analysis, a thorough assessment of both heterogeneity and horizontal pleiotropy was meticulously conducted (28). Cochran's Q test estimates, derived from IVW estimates, were used to rule out heterogeneity among IVs (29). A P value < 0.05 denoted the presence of substantial heterogeneity. The assessment of horizontal pleiotropy and the correction of potential outliers were performed using MR Pleiotropy Residual Sum and Outliers (MR-Presso) (30). A P value < 0.05 in this context was considered indicative of significant horizontal pleiotropy. Additionally, the leave-one-out sensitivity analysis was employed to discern the potential influence of individual SNPs (31).

3 Results

3.1 Effects of CVD characteristics on BMD in different parts or at different ages

3.1.1 Set the following conditions

The Instrumental Variable Selection (IVS) exhibited no linkage disequilibrium (LD) (r2 < 0.001), adhered to the physical distance threshold (10,000 kb), and possessed genome-wide dominance (p< 5E-8). The data extracted from the Genome-Wide Association Study (GWAS) database underwent meticulous screening for Coronary Heart Disease (CHD) (15 SNPs), Myocardial Infarction (MI) (80 SNPs), and Stroke (17 SNPs) within IVS, as outlined in Supplementary Table 2; Supplementary Figure S1. Subsequently, SNPs associated with Bone Mineral Density (BMD) risk factors were systematically eliminated one by one, aided by the website (http://www.phenoscanner.medschl.cam.ac.uk), with detailed information presented in Supplementary Table 2; Supplementary Figure S2. Following this, the Minor Allele Frequency (MAF) threshold (>0.01) was applied via the two-sample Mendelian Randomization (MR) function of the R package to exclude palindromic or incompatible SNPs, as elucidated in Supplementary Table 2; Supplementary Figure S3. F statistics computed for the ultimately obtained SNPs revealed values exceeding 10, affirming the absence of weak instruments. Comprehensive details are available in (Supplementary Table 2; Supplementary Figure S1).

3.1.2 The causal impact of CVD on BMD in different parts

The outcomes of the IVW method analysis are depicted in Figure 2. During the MR-Presso global test evaluating CVD impact on BMD across diverse regions, outliers were identified between CHD and BMD (LS BMD, Heel BMD), between MI and Heel BMD, and between stroke and BMD (LS BMD, Heel BMD) (Supplementary Table 2; Supplementary Figure S4). Following their removal and subsequent reanalysis, no outliers were observed (Table 1). Notably, a substantial causal association emerged between genetically predicted CHD and Heel BMD, as well as Total Body BMD (Heel BMD: Odds Ratio [OR]: 0.949, 95% Confidence Interval [CI]: 0.928-0.970, p< 0.001; TB BMD: OR: 0.940, 95% CI: 0.903–0.976, *p*= 0.002), as depicted in Figure 2. The beta values direction acquired through IVW analysis aligned consistently with those analyses with the MR-Egger regression, weighted mode, and weighted median. Cochran's Q test revealed no evidence of heterogeneity in the effects of CHD on Heel BMD and TB BMD (p > 0.05) (Table 2). Furthermore, MR-Egger intercept tests indicated no horizontal pleiotropy (Table 2). Leave-one-out analysis results demonstrated that the IVW outcomes were not forced by potential single SNPs (Supplementary Table 1; Supplementary Figure S8, S10), affirming the significant causal relationship. Similarly, the IVW results indicated suggestive causal associations between Stroke and LS BMD and Heel BMD (LS BMD: OR = 1.113, 95% CI: 1.000-1.237, *p* = 0.049; Heel BMD: OR = 0.962, 95% CI: 0.933–0.992, *p* = 0.013), with related Cochran's Q test and MR-Egger intercept test P values exceeding 0.05 (Table 2). MR-Presso global tests identified no outliers, signifying the absence of heterogeneity and horizontal pleiotropy. However, inconsistencies were noted in the direction of IVW and MR-Egger results for Stroke on Lumbar Spine BMD and Heel BMD (Supplementary Table 2; Supplementary Figure S5), urging caution regarding the robustness of the suggestive causal relationship.

The IVW method proves that no discernible causal relationship was identified between other CVDs and BMD at different sites (p >0.05). Due to heterogeneity between MI and TB BMD and Heel BMD (p < 0.05) (Table 2), the random-effects IVW method was employed for analysis. Rigorous sensitivity analyses confirmed the steadfastness of these Mendelian Randomization effect estimates (Table 2). Detailed scatter plots, leave-one-out analyses, forest plots, and funnel plots elucidating the causal relationship between the remaining CVD and BMD at various sites are available in Supplementary Table 1; Supplementary Figures S1-S20.

3.1.3 The causal impact of CVD on BMD at different ages

The results of the IVW test suggest a potential causal association between CHD and TB BMD in the age group of 0–15

Exposure	Outcome	nsnp o	MR.method		OR(95%CI)	P.value
CHD	FA DIVID	9	IVW	H	0.99(0.90 to 1.10)	0.916
			MB-Enger		1 17(0 84 to 1 63)	0.377
			Meighted median	1	0.07(0.84 to 1.12)	0.729
			Weighted mode		1 17(0.02 to 1.48)	0.243
	EN BMD	Q	weighted mode		1.17(0.52 (0 1.40)	0.240
	T IN DIVID	9	BAA/	1	1.01(0.96 to 1.06)	0.694
			MR-Engor		0.02(0.77 to 1.11)	0.462
			MR=Egger		0.93(0.77 to 1.11)	0.455
			Weighted median		0.99(0.92 to 1.00)	0.703
	LODMO	7	weighted mode		0.96(0.91 to 1.07)	0.720
	LO DIVID	1	B.04/		1 02/0 07 to 1 10)	0.005
			MD Free	. T.	1.03(0.97 to 1.10)	0.295
			MR-Egger		1.00(0.83 to 1.21)	0.989
			vveighted median	HEH	1.05(0.96 to 1.14)	0.328
			vveighted mode		1.06(0.94 to 1.20)	0.309
	Heel DIVID	0	0.004		0.05/0.00 +- 0.070	10.004
			IVVV		0.95(0.93 to 0.97)	<0.001
			MR-Egger	HIN	0.96(0.86 to 1.08)	0.5/4
			Weighted median		0.94(0.92 to 0.97)	< 0.001
			Weighted mode	-	0.93(0.88 to 0.98)	0.05
	TB BMD	9				
			IVW		0.94(0.90 to 0.98)	0.002
			MR-Egger	Here	0.94(0.83 to 1.06)	0.37
			Weighted median		0.96(0.91 to 1.01)	0.122
			Weighted mode	H	0.98(0.90 to 1.06)	0.563
MI	FA BMD	49				
			IVW	refe	0.97(0.91 to 1.04)	0.451
			MR-Egger	HeH	0.96(0.83 to 1.11)	0.55
			Weighted median	H	0.96(0.86 to 1.07)	0.437
			Weighted mode	Here is a second se	0.90(0.76 to 1.06)	0.23
	FN BMD	45				
			IVW		1.01(0.97 to 1.04)	0.781
			MR-Egger	Hei	0.95(0.88 to 1.02)	0.19
			Weighted median	-	0.98(0.93 to 1.04)	0.539
			Weighted mode	NBN .	0.98(0.93 to 1.04)	0.557
	LS BMD	45				
			IVW		1.04(1.00 to 1.08)	0.063
			MR-Egger	HH I	1.01(0.91 to 1.12)	0.875
			Weighted median	iles .	1.03(0.97 to 1.10)	0.332
			Weighted mode	HEH	1.03(0.96 to 1.11)	0.403
	Heel BMD	48				
			IVW	+	1.01(0.99 to 1.03)	0.271
			MR-Egger		1.01(0.97 to 1.04)	0.763
			Weighted median		1.00(0.98 to 1.02)	0.751
			Weighted mode	+	1.00(0.99 to 1.02)	0.704
	TB BMD	52				
			IVW		0.98(0.95 to 1.01)	0.206
			MR-Egger	101	0.98(0.92 to 1.04)	0.547
			Weighted median	+	1.01(0.97 to 1.05)	0.793
			Weighted mode		1.00(0.95 to 1.05)	0.95
					,	
Stroke	FA BMD	12				
			IVW		1.04(0.87 to 1.24)	0.702
			MR-Egger	·	1.09(0.22 to 5.30)	0.918
			Weighted median		0.99(0.76 to 1.30)	0.94
			Weighted mode	—	0.94(0.61 to 1.43)	0.768
	EN BMD	12				
			IVW	April 1	1.06(0.97 to 1.16)	0.195
			MR-Eager		0.82(0.47 to 1.42)	0 494
			Weighted median		1.06(0.94 to 1.10)	0.358
			Weighted mode		1.07(0.89 to 1.19)	0.485
	LS BMD	11	o.gnieu moue			0.400
	LO DMD		NAW		1 11(1 00 to 1 24)	0.049
			MR-Egger		0.63(0.30 to 1.24)	0.252
			Moightod modia		1 14(0 08 to 1.32)	0.202
			Weighted median		1.14(0.96 to 1.33)	0.099
	Heel PMP	11	veignieu mode		1.24(0.90 t0 1.60)	0.134
	neer BMD		NAM		0.96(0.92 to 0.00)	0.012
			MD-Egger		1.06(0.95 to 1.99)	0.013
			Moighted modi		0.05(0.02 to 1.33)	0.011
			vveignted median		0.95(0.92 to 1.00)	0.03
	TD DHO	12	vveighted mode	101	0.94(0.88 to 1.00)	0.086
	I B BMD	12	D.04/	1	1.05(0.08 to 1.10)	0.474
			MD-Ease-	EN .	1.05(0.98 to 1.12)	0.1/4
			MK-Egger		1.20(0.79 to 2.03)	0.354
			vveignted median	HPH	1.02(0.93 to 1.11)	0.722
			vveighted mode	H0-1	1.03(0.90 to 1.17)	0.708
-	a second state and		the setting a factor of the second	· · · · · · · · · · · · · · · · · · ·		

FIGURE 2

CHD, coronary heart disease; MI, myocardial infarction; FA BMD, Forearm bone mineral density; FN BMD, Femoral neck bone mineral density; LS BMD, Lumbar spine bone mineral density; TB BMD, Total body bone mineral density; IVW, inverse variance weighted.

years (OR: 0.876, 95% CI: 0.800–0.959, p= 0.004> 0.003) (Figure 3). Cochran's Q test revealed no marked heterogeneity (p > 0.05) (Table 3). Both MR-Egger regression and the assessment of horizontal pleiotropy through the MR-Presso global test for CHD and TB BMD (0–15 years old) indicated no compelling evidence of horizontal pleiotropic effects (Table 3). Leave-one-out test confirmed the result's robustness against the influence of any single SNP driver (Supplementary Table 1; Supplementary Figure

S26). Detailed scatter plots, forest maps, and funnel plots illustrating the relationship between CHD and TB BMB(0-15 years old) are provided in Supplementary Table 1; Supplementary Figure S21, S31, S36. Similarly, it can be seen that there is a potential causal relationship between MI and TB BMD in the age group of 0-15 years (OR: 0.917, 95% CI: 0.849-0.990, p= 0.027 > 0.003) (Figure 3).

Other IVW results indicated no evidence of a significant causal relationship between various CVD and TB BMD across different age groups (Figure 3). While outliers were initially identified in the MR-Presso global test for MI on TB BMD in the age group of 15–30 years, subsequent removal of outliers (Supplementary Table 2; Supplementary Figure S4) did not alter the findings. Sensitivity analysis further supported the stability of these results (Table 3). Additional visualization results are presented in Supplementary Table 1. In summary, there is no discernible proof supporting a causal rapport between CVD and TB BMD across different age groups.

3.2 Impact of OP characteristics on CVD

3.2.1 Set the following conditions

The Instrumental Variable Selection (IVS) exhibits no linkage disequilibrium (r2 < 0.001), adheres to the physical distance threshold (10,000 kb), and possesses significant genome-wide prominence (p < p5E-8). Our comprehensive screening of IVS for TB BMD (85 SNPs), FA BMD (3 SNPs), FN BMD (21 SNPs), LS BMD (24 SNPs), and Heel BMD (359 SNPs) is outlined in Supplementary Table 2; Supplementary Figure S1. Subsequently, aided by professional tools (http://www.phenoscanner.medschl.cam.ac.uk), we manually removed SNPs connection with risk factors for different BMDs, detailed in Supplementary Table 2; Supplementary Figure S2. The Minor Allele Frequency (MAF) threshold (> 0.01) was applied using the two-sample Mendelian Randomization (MR) function settings of the R package to eliminate outliers (Supplementary Table 2; Supplementary Figure S3). F statistics calculated for the ultimately obtained SNPs revealed values all exceeding 10, affirming the absence of weak instruments. Detailed information is provided in Supplementary Table 2; Supplementary Figure S1.

3.2.2 Causal impact of OP on CVD

The Reverse Mendelian Randomization (MR) analysis is depicted in Figure 4. Overall, no evidence of a reverse causal relationship between OP indicators (Heel BMD, TB BMD, LS BMD, FA BMD, FN BMD) and CVD (CHD, MI, Stroke) was observed. Only a suggestive causal association emerged between Heel BMD and CHD (OR= 1.083, 95% CI: 1.000–1.172, p =0.049), as well as LS BMD and MI (OR= 1.090, 95% CI: 1.029– 1.155, p = 0.004). In the sensitivity analysis, only an abnormal SNP association between Heel BMD and TB BMD on MI was identified (Supplementary Table 2; Supplementary Figure S4). Upon removal and re-analysis, no evidence of horizontal pleiotropy persisted (Table 4). Cochran's Q test discovered heterogeneity in the causal impact of Femoral Neck BMD on

	Traits	Year	Sample	Population	PMID/Dataset
BMD	FA BMD	2015	8,143	European	26367794
	FN BMD	2015	32,735	European	26367794
	LS BMD	2015	28,498	European	26367794
	Heel BMD	2018	265627	European	ukb-b-8875
	TB BMD	2018	56284	European	29304378
	TB BMD (age 0–15)	2018	11807	Mixed	29304378
	TB BMD (age 15-30)	2018	4180	Mixed	29304378
	TB BMD (age 30-45)	2018	10062	Mixed	29304378
	TB BMD (age 45-60)	2018	18805	European	29304378
	TB BMD (age over 60)	2018	22504	Mixed	29304378
CVD	CHD	2011	86995	European	21378990
	Stroke	2018	446696	Mixed	29531354
	MI	2021	395,795	European	33532862

TABLE 1 The GWAS datasets used for MR analysis.

CHD, coronary heart disease; MI, myocardial infarction; FA BMD, Forearm bone mineral density; FN BMD, Femoral neck bone mineral density; LS BMD, Lumbar spine bone mineral density; TB BMD, Total body bone density.

CHD (p = 0.041) and Heel BMD on MI (p < 0.001). To address this heterogeneity, a random-effects IVW analysis was employed, ensuring the robustness and reliability of the IVW results. Additionally, leave-one-out analysis yielded no evidence of potential SNP-driven influences (Supplementary Table 1; Supplementary Figures S44-S46). Detailed scatter plots, forest maps, and funnel plots related to these findings can be found in Supplementary Table 1.

TABLE 2 Heterogeneity, pleiotropy test and MR-PRESSO Global test of exposure (Cardiovascular diseases) on bone density in different parts of the body.

Exposure	Outcome	Cochran Q statistic	Heterogeneity P-value	MR- Egger Intercept	Intercept p-value	MR-PRESSO Global test P-value
CHD	FA BMD	9.981257188	0.266343882	-0.021708211	0.333103117	0.239
CHD	FN BMD	12.08571868	0.14742011	0.011001709	0.368521369	0.181
CHD	LS BMD	6.002037674	0.422961858	0.004317761	0.731418586	0.438
CHD	Heel BMD	6.223863792	0.285041471	-0.001767004	0.79939395	0.342
CHD	TB BMD	7.502252345	0.483534629	-0.000336768	0.965948036	0.528
MI	FA BMD	39.44951252	0.805513645	0.001558789	0.789557916	0.769
MI	FN BMD	40.67336071	0.615000025	0.00496603	0.102940633	0.642
MI	LS BMD	58.76266838	0.067447088	0.00275713	0.497732763	0.076
MI	Heel BMD	109.195188	7.37644E-07	0.000432389	0.757968854	NA
MI	TB BMD	78.76635325	0.007556748	-4.81662E-05	0.98528366	NA
Stroke	FA BMD	19.49416314	0.052779715	-0.002917025	0.046735383	0.053
Stroke	FN BMD	9.855103431	0.543465987	0.015080821	0.375462836	0.557
Stroke	LS BMD	13.84694923	0.180087894	0.032675732	0.160174796	0.188
Stroke	Heel BMD	14.43156378	0.154200894	-0.005762571	0.405716145	0.186
Stroke	TB BMD	13.81145052	0.243602861	-0.011021547	0.445767771	0.264

CHD, coronary heart disease; MI, myocardial infarction; FA BMD, Forearm bone mineral density; FN BMD, Femoral neck bone mineral density; LS BMD, Lumbar spine bone mineral density; TB BMD, Total body bone mineral density.

Exposure	Outcome	Cochran Q statistic	Heterogeneity P-value	MR- Egger Intercept	Intercept p-value	MR-PRESSO Global test P-value
CHD	TB BMD(0-15)	15.24543109	0.054545261	-3.68793E-05	0.998895535	0.069
CHD	TB BMD(15-30)	1.62705036	0.99039186	-0.002622299	0.933568547	0.989
CHD	TB BMD(30-45)	11.50377187	0.17475509	-0.030391399	0.201769059	0.189
CHD	TB BMD(45-60)	5.791901082	0.670529056	0.01298506	0.362509046	0.666
CHD	TB BMD (over 60)	6.310036709	0.612546448	0.009398325	0.486422765	0.607
MI	TB BMD(0-15)	91.04625989	0.000481157	-0.005731015	0.370706372	NA
MI	TB BMD(15-30)	61.42786061	0.128963805	-0.005689807	0.536746683	0.146
MI	TB BMD(30-45)	46.17481527	0.66535308	-0.002433807	0.646606169	0.644
MI	TB BMD(45-60)	55.30637531	0.315410365	0.00525933	0.194744373	0.354
MI	TB BMD (over 60)	46.29174082	0.660843888	0.002462153	0.496651743	0.63
Stroke	TB BMD(0-15)	5.662353483	0.894916813	0.030383226	0.297748447	0.901
Stroke	TB BMD(15-30)	6.960129909	0.802303007	-0.028194446	0.577522332	0.794
Stroke	TB BMD(30-45)	12.46657314	0.329612743	-0.024649746	0.493198086	0.338
Stroke	TB BMD(45-60)	13.1239661	0.285300354	-0.03850296	0.130545905	0.288
Stroke	TB BMD (over 60)	11.49791518	0.40253988	0.016636366	0.459810141	0.408

TABLE 3 Heterogeneity, pleiotropy test and MR-PRESSO Global test of exposure (Cardiovascular diseases) on bone density in different ages of the body.

CHD, coronary heart disease; MI, myocardial infarction; FA BMD, Forearm bone mineral density; FN BMD, Femoral neck bone mineral density; LS BMD, Lumbar spine bone mineral density; TB BMD, Total body bone density.

Due to insufficient variables for FA BMD, MR-Presso analysis could not be conducted. Nevertheless, the MR multi-effect residual P-value exceeded 0.05, and the identified Instrumental Variables (IVs) have been previously applied in related MR studies (32, 33). Furthermore, screening conditions from the same database with p < 5E-6, r2 < 0.001, and kb = 10000 were employed to obtain additional FA BMD IVs (16 SNPs). No evidence of causal association was observed (Figure 4), and sensitivity analysis confirmed the stability of the results (Table 4). In summary, we assert that there is no compelling evidence supporting a causal relationship between OP and CVD, affirming the reliability of our findings.

4 Discussion

In this bidirectional MR study, we assessed the causal association between CVD and OP. The results indicate a causal relationship between genetically predicted CHD and Heel BMD, as well as TB BMD. Reverse MR analysis found no evidence linking genetic predispositions for BMD in different anatomical sites to these CVDs. Although we did not observe a significant causal relationship between the genetic predisposition to BMD at different sites and these CVD diseases, we did observe a significant causal association between CHD with Heel BMD and TB BMD. Initially, we conducted thorough sensitivity analyses to validate adherence to the three fundamental assumptions inherent in MR. The outcomes of the MR study, employing diverse methodologies, consistently exhibited coherence. Subsequently, we systematically examined each instrumental variable independently to alleviate the impact of confounding factors. This meticulous scrutiny involved a step-by-step screening of instrumental variables to minimize the potential interference of confounding factors. Given that FA BMD presented fewer instrumental variables and the possibility of outliers could not be ruled out, we undertook rigorous efforts to substantiate this aspect. Ultimately, we applied the rigorous Bonferroni method to address multiple comparisons, eliminating the risk of false positive results. Consequently, our MR findings stand as robust and reliable, ensuring the validity of the study outcomes.

As prevalent public health issues with widespread impact and significant consequences, OP and CVD have consistently garnered considerable attention. While numerous prior epidemiological studies have reported the connection between these conditions, the precise association remains elusive (34–43). Several factors may contribute to this ambiguity. Firstly, common risk factors such as age, vitamin D deficiency, inactivity, smoking, and diabetes are shared between osteoporosis and CVD (44). Early investigations highlighted a potential "bone-vascular axis," and subsequent research recognized shared pathogenic processes involving oxidative stress, inflammation, and lipid metabolism, mediated by common regulatory factors like bone morphogenetic protein (BMP), osteopontin (OPN), matrix GLA protein (MGP),

Mix Weighted median Weighted median We	Exposure CHD	TB BMD(0-15)	nsnp 9	MR.method		UR(95%CI)	P.value
MR-Egger 0.800 55 10 1.30 0.556 MR-Egger 0.901 07 10 10.30 0.110 MR-Egger 0.901 07 10 10.30 0.110 MR-Egger 0.901 07 10 10.00 0.110 Weighted median 0.901 07 10 10.00 0.910 MR-Egger 0.910 07 10 10.00 0.910 Weighted median 0.910 07 10 10.00 0.980 MR-Egger 0.910 07 10 10.00 0.980 Weighted median 0.910 07 10 10.00 0.980 Weighted median 0.910 07 10 10.00 0.980 MR-Egger 0.910 07 10 10.00 0.400 Weighted median 0.910 07 10 10.00 0.270 MR-Egger 0.930 082 10 10.00 0.270 Weighted median 0.900 081 0.00 0.270 MR-Egger 0.930 081 0.100 0.270 MR-Egger 0.930 081 0	0110	10 0110(0 10)		IVW	101	0.88(0.80 to 0.96)	0.004
TB BMD(15-50) 9 NV 930(0.75 to 1.03) 0.118 TB BMD(15-50) 9 NV 930(0.75 to 1.13) 0.409 TB BMD(20-55) 9 NV 930(0.75 to 1.13) 0.409 TB BMD(20-55) 9 NV 0.30(0.75 to 1.10) 0.220 TB BMD(20-56) 9 NV 0.30(0.75 to 1.10) 0.220 TB BMD(20-56) 9 NV 0.30(0.75 to 1.10) 0.220 Weighted mode 0.30(0.75 to 1.10) 0.220 NV 0.30(0.75 to 1.10) 0.220 Weighted mode 0.30(0.75 to 1.10) 0.220 NV 0.30(0.75 to 1.10) 0.220 TB BMD(20-50) 9 NV 0.30(0.75 to 1.10) 0.210 NV 0.30(0.75 to 1.10) 0.210 TB BMD(20-51) 52 NV 0.30(0.75 to 1.10) 0.210 NV 0.30(0.75 to 1.10) 0.210 TB BMD(20-51) 52 NV 0.30(0.35 to 1.10) 0.313 NV 0.30(0.35 to 1.10) 0.313 Weighted median 0.40(0.85 to 1.32) 0.313				MR-Enger		0.88(0.58 to 1.33)	0.556
TB BMD(15-30) 9 NW 98(0.75 to 1.13) 0.400 TB BMD(15-30) 9 NW 98(0.75 to 1.13) 0.400 TB BMD(35-46) 9 NW 98(0.75 to 1.13) 0.400 TB BMD(35-46) 9 NW 98(0.75 to 1.13) 0.400 TB BMD(45-60) 9 NW 97(0.85 to 1.12) 0.880 Weighted median 97(0.85 to 1.12) 0.880 710 100 0.410 Weighted median 97(0.85 to 1.12) 0.880 710 100 0.43 MR-Egger 97(0.85 to 1.12) 0.880 710 100 0.43 MR-Egger 0.89(0.71 to 1.09) 0.43 0.89(0.71 to 1.09) 0.43 MR-Egger 0.89(0.81 to 1.01) 0.710 0.800 710 100 0.42 Weighted median 99(0.80 to 1.01) 0.72 0.88(0.71 to 1.09) 0.43 MR-Egger 1000 980 to 1.010 0.77 0.800 410 100 0.77 MWeighted median 99(0.90 to 1.10) 0.77 0.800 410 100 0.77 MM				Weighted median	Here's	0.90(0.79 to 1.03)	0.118
TB BMD(15-30) P NW P Description Description <thdescription< th=""> <thdescription< th=""></thdescription<></thdescription<>				Weighted mode	يلغب	0.91(0.73 to 1.13)	0.409
ICLUMIC 6:00 0 IVV 0 000000000000000000000000000000000000		TB BMD(15-30)	9	weighted mode		0.91(0.73101.13)	0.405
MR-Egger 990(0.55 to 1.49) 0.395 TE BMD(20-45) 9 0 0.395 MR-Egger 0.390(0.55 to 1.49) 0.284 TE BMD(20-45) 9 0 0.290(0.55 to 1.49) 0.284 TE BMD(45-60) 9 0 0.270(0.51 to 1.10) 0.225 Weighted mode 0.970(0.55 to 1.49) 0.890(0.55 to 1.49) 0.890(0.55 to 1.49) 0.890(0.55 to 1.49) 0.890(0.55 to 1.49) 0.281 MR-Egger 0.970(0.50 to 1.10) 0.270(0.50 to 1.10) 0.270(0.50 to 1.10) 0.231 MR-Egger 0.930(0.55 to 1.49) 0.430 MR-Egger 0.930(0.55 to 1.10) 0.431 MR-Egger 0.930(0.55 to 1.10) 0.241 Weighted median 0.940(0.85 to 1.10) 0.241 MI TE BMD(45-00) 51 NW 0.930(0.85 to 1.91) 0.179 Weighted median 0.920(0.85 to 1.92) 0.920(0.85 to 1.92) 0.921 0.921 0.921 0.921 0.921 0.921 0.921 0.921 0.921 0.921 0.921 0.921 0.921 0.921<		10 0100(10 00)		NAW/	Hand I	0.88(0.75 to 1.04)	0 127
TB BMD(0-45) 9 0.330 0.310 0.330				MB-Eggor		0.00(0.F6 to 1.49)	0.605
TB BMD(30-45) 9 0.700 11 0 1.050 0.18 0.240 21 0 1.00 0.220 TB BMD(30-45) 9 0.700 10 1.00 0.220 0.240 0.250 1.10 0 0.220 MR-Egger 0.070 0.051 0 1.10 0 0.220 0.250 0.751 0 1.19 0 0.250 0.220 MR-Egger 0.070 0.051 0 1.00 0 0.051 0 1.00 0 0.051 0.220 0.270 0.190 0 0.027 0.050 0.271 0 1.09 0 0.270 MR-Egger 0.070 0.051 0 1.00 0 0.051 0 0.041 0.070 0.051 0 1.00 0 0.270 0.030 0.221 0 1.05 0 0.027 MR-Egger 0.030 0.221 0 1.05 0 0.027 0.030 0.221 0 1.05 0 0.027 0.030 0.221 0 1.05 0 0.027 MR-Egger 0.030 0.221 0 1.05 0 0.027 0.030 0.221 0 1.05 0 0.027 0.030 0.221 0 1.05 0 0.027 MR-Egger 0.030 0.21 0 1.00 0.027 0.030 0.21 0 1.00 0.027 0.030 0.21 0 0.027 MR-Egger 0.030 0.021 0 0.027 0.030 0.027 0.01 0.00 0.010 0 0.027 0.030 0.010 0 0.027 MR-Egger 0.030 0.010 0 0.027 0.030 0.010 0 0.027 0.030 0.010 0 0.027 MR-Egger 0.030 0.010 0 0.027 0.030 0.010 0 0.027 0.030 0.010 0 0.027 MR-Egger 0.030 0.010 0 0.027 0.030 0.010 0 0.027 0.030 0.010 0 0.027 MR-Egger 0.030 0.010 0				Mix-Lgger		0.50(0.55 (0 1.46)	0.055
TB BMD(30-45) 9 NW 100(0.90 to 1.1) 0.242 NW 100(0.90 to 1.1) 0.242 100(0.90 to 1.1) 0.242 Weighted median 0.97(0.80 to 1.1) 0.245 0.250 Weighted median 0.97(0.80 to 1.10) 0.851 Weighted median 0.97(0.80 to 1.10) 0.43 MM = Egger 0.97(0.80 to 1.10) 0.43 MM = Egger 0.93(0.82 to 1.00) 0.43 MM = Egger 0.93(0.82 to 1.00) 0.43 MM = Egger 0.93(0.82 to 1.00) 0.41 Weighted median 0.93(0.82 to 1.00) 0.47 Weighted median 0.93(0.82 to 1.00) 0.47 Weighted median 0.93(0.82 to 1.10) 0.47 Weighted median 0.93(0.84 to 1.01) 0.93 TB BMD(45-60) 51 NW <td< td=""><td></td><td></td><td></td><td>vveignted median</td><td></td><td>0.87(0.71 to 1.06)</td><td>0.16</td></td<>				vveignted median		0.87(0.71 to 1.06)	0.16
Ite BMD(30-45) 9 IVW 100(0.05 to 1:10) 0.988 Weighted median 0.97(0.26 to 1:10) 0.651 0.95 TB BMD(45-60) 9 IVW 0.97(0.26 to 1:10) 0.261 TB BMD(60 over) 9 IVW 0.97(0.26 to 1:10) 0.276 MR-Egge 0.98(0.27 to 1:06) 0.413 0.98(0.27 to 1:06) 0.413 Weighted median 0.98(0.27 to 1:06) 0.276 0.98(0.27 to 1:06) 0.249 MM-Egger 0.98(0.27 to 1:06) 0.249 0.98(0.27 to 1:06) 0.249 Weighted median 0.94(0.86 to 1:01) 0.249 0.98(0.27 to 1:06) 0.249 Weighted median 0.94(0.86 to 1:01) 0.779 0.98(0.26 to 1:02) 0.779 Weighted median 0.94(0.86 to 1:01) 0.984 0.110 0.763 MR-Egger 0.99(0.90 to 1:10) 0.950 0.277 0.99(0.90 to 1:10) 0.950 TB BMD(15-30) 52 IVW 0.99(0.90 to 1:10) 0.950 0.327 TB BMD(26-450) 52 IVW 0.99(0.90 to 1:10		70 010 00 10	0	vveighted mode		0.84(0.63 to 1.11)	0.252
NV 1000000161100 0.00000010100 0.020 MR-Egger 1000000161100 0.020 Weighted median 0.97(0.081616.00 0.020 MW 0.97(0.08161.00 0.43 MR-Egger 0.97(0.08161.00 0.43 MR-Egger 0.98(0.27161.01 0.43 MR-Egger 0.98(0.27161.01 0.43 MR-Egger 0.98(0.2716.01.00 0.43 MR-Egger 0.98(0.2716.01.00 0.43 MR-Egger 0.98(0.2716.01.00 0.44 MR-Egger 0.98(0.2716.01.00 0.478 MI TB BMD(15-30) 52 IVV 0.92(0.8510.0.09) 0.277 MR-Egger 0.98(0.2810.1.01) 0.478 MR-Egger 0.98(0.2810.1.01) 0.478 MR-Egger 0.98(0.2810.1.01) 0.970 0.970 0.970 0.970 MR-Egger 0.98(0.810.1.01) 0.980 MR-Egger 0.98(0.810.1.01) 0.781 Weighted median 0.99(0.9310.1.01) 0.990 0.971 0.990 0.990 0.971		TB BMD(30-45)	9			4 00/0 00 1 4 40	0.000
Mixelegger 12/03/03/10 100 0.20 TB BMD(45-60) 9 NW 0.970/03/01 10 100 0.413 MR-Egger 0.890/07 10 100 0.413 Weighted median 0.990/07 10 100 0.249 Weighted median 0.940/08 10 100 0.249 Weighted median 0.940/08 10 100 0.249 Weighted median 0.940/08 10 100 0.249 Weighted median 0.990/08 10 1100 0.779 Weighted median 0.990/08 10 1100 0.78 MI TB BMD(15-50) 51 1000/08 10 110 0.960 TB BMD(26-50) 52 1000/08 10 110 0.960 0.977 TB BMD(45-60) 52 1000/08 10 100 0.977 0.990/08 10 100 0.977 TB BMD(45-60) 52 1000/08 510 100 0.977				IVW	HTT I	1.00(0.90 to 1.10)	0.988
Weighted median 0.97(0.85 to 1.12) 0.88 TB BMD(45-60) 9 NW 0.97(0.85 to 1.12) 0.88 TB BMD(45-60) 9 NW 0.97(0.85 to 1.12) 0.88 TB BMD(45-60) 9 NW 0.97(0.85 to 1.12) 0.88 TB BMD(60 over) 9 NW 0.97(0.85 to 1.12) 0.88 MI TB BMD(60 over) 9 NW 0.98(0.81 to 1.10) 0.42 MI TB BMD(60 over) 52 NW 0.98(0.81 to 1.10) 0.478 MI TB BMD(15-50) 52 NW 0.98(0.81 to 1.10) 0.478 MI TB BMD(15-30) 51 NW 0.98(0.81 to 1.10) 0.990 TB BMD(15-30) 51 NW 0.99(0.93 to 1.12) 0.957 TB BMD(45-60) 52 NW 0.99(0.93 to 1.10) 0.990 Weighted median 0.99(0.93 to 1.10) 0.990 0.91 0.91 Weighted median 0.99(0.93 to 1.05) 0.91 0.91 0.91 0.91 TB BMD(45-60) <td></td> <td></td> <td></td> <td>MR-Egger</td> <td></td> <td>1.27(0.89 to 1.80)</td> <td>0.226</td>				MR-Egger		1.27(0.89 to 1.80)	0.226
Weighted mode 0.95(0.75 to 1.19) 0.651 IDE BMD(45-60) 9 0.97(0.80 to 1.09) 0.43 MR-Egger 0.86(0.87 to 1.06) 0.413 0.95(0.87 to 1.06) 0.413 Weighted median 0.95(0.87 to 1.06) 0.413 0.95(0.87 to 1.06) 0.413 Weighted median 0.95(0.87 to 1.06) 0.413 0.95(0.87 to 1.06) 0.249 Weighted median 0.94(0.88 to 1.00) 0.249 0.95(0.87 to 1.16) 0.249 Weighted median 0.94(0.88 to 1.00) 0.249 0.95(0.87 to 1.16) 0.249 Weighted median 0.95(0.87 to 1.10) 0.478 0.95(0.87 to 1.10) 0.478 MI TB BMD(15-50) 51 FW 0.95(0.84 to 1.12) 0.832 Weighted median 0.95(0.85 to 1.12) 0.832 0.833 0.833 0.833 TB BMD(15-50) 51 FW 0.90(0.80 to 1.10) 0.905 0.903 0.903 0.903 0.903 0.903 0.903 0.903 0.903 0.903 0.903 0.903 0.903 0.903				Weighted median	HH	0.97(0.85 to 1.12)	0.688
TB BMD(45-60) 9 NW 9 0.77(0.30 to 1.0.0) 0.43 MR-Egger 0.86(0.71 to 1.06) 0.43 Weighted mode 0.96(0.87 to 1.06) 0.43 Vieghted mode 0.96(0.87 to 1.06) 0.43 MI TB BMD(60 over) 9 IVV 0.96(0.88 to 1.01) 0.94(0.88 to 1.01) 0.94(0.88 to 1.01) 0.94(0.88 to 1.01) 0.43 MI TB BMD(60-15) 52 IVV 0.92(0.85 to 0.99) 0.270 MI TB BMD(15-30) 51 IVV 0.92(0.85 to 1.01) 0.788 MR-Egger 0.99(0.93 to 1.10) 0.788 0.99(0.93 to 1.10) 0.788 Weighted median 0.99(0.93 to 1.10) 0.908 0.712 0.951 MR-Egger 0.99(0.93 to 1.10) 0.908 0.810 0.331 Vieghted median 0.99(0.93 to 1.10) 0.908 0.810 0.910 MR-Egger 1.00(0.95 to 1.02) 0.978 0.930 0.930 TB BMD(45-60) 52 IVV 0.99(0.83 to 1.05) 0.940				Weighted mode		0.95(0.75 to 1.19)	0.651
IVW im 0.37(0.30 to 1:40, 0.37) MR-Egger 0.38(0.71 to 1:00, 0.37) Weighted median 0.38(0.71 to 1:00, 0.33) TB BMD(60 over) 9 IVW im 0.94(0.81 to 1:00, 0.33) MR-Egger 0.94(0.81 to 1:10, 0.478) Weighted median 0.94(0.81 to 1:10, 0.478) Weighted median 0.94(0.81 to 1:10, 0.478) Weighted median 0.94(0.85 to 1:32, 0.432) Weighted median 1.00(0.90 to 1:12, 0.478) Weighted median 1.06(0.85 to 1:32, 0.432) Weighted median 0.96(0.81 to 1:10, 0.478) Weighted median 0.96(0.81 to 1:10, 0.478) Weighted median 0.96(0.81 to 1:0, 0.478) Weighted median 0.96(0.81 to 1:0, 0.48) Weighted median 0.96(0.81 to 1:0, 0.48) Weighted median 0.96(0.81 to 1:0, 0.48) W		TB BMD(45-60)	9				
MR—Egger 0.88(0.71 to 1.10) 0.273 TB BMD(60 over) 9 0.93(0.82 to 1.06) 0.331 VW MR—Egger 0.94(0.88 to 1.01) 0.084 MI TB BMD(60 over) 52 VV 0.94(0.88 to 1.01) 0.478 MI TB BMD(6-15) 52 VV 0.94(0.88 to 1.01) 0.478 MI TB BMD(6-5) 52 VV 0.92(0.85 to 0.99) 0.027 MR—Egger 0.93(0.84 to 1.12) 0.378 Weighted median 0.93(0.84 to 1.12) 0.378 Weighted median 0.93(0.84 to 1.12) 0.353 0.990 0.027 MR—Egger 0.99(0.90 to 1.12) 0.353 Weighted median 0.93(0.84 to 1.12) 0.532 0.532 0.532 0.532 0.532 0.532 0.532 0.532 0.532 0.532 0.532 0.532 0.532 0.533 0.532 0.532 0.532 0.532 0.532 0.532 0.532 0.532 0.532 0.532 0.532 0.532 0.533 0.5333 0.533 </td <td></td> <td></td> <td></td> <td>IVW</td> <td>H</td> <td>0.97(0.90 to 1.04)</td> <td>0.43</td>				IVW	H	0.97(0.90 to 1.04)	0.43
Weighted median 0.90(0.87 to 1.06) 0.331 TB BMD(60 over) 9 0.93(0.82 to 1.09) 0.331 TB BMD(60 over) 9 0.94(0.88 to 1.01) 0.0249 Weighted median 0.94(0.88 to 1.01) 0.94(0.88 to 1.01) 0.778 MI TB BMD(6-15) 52 V 0.95(0.81 to 1.10) 0.778 MI TB BMD(15-30) 51 VW 0.92(0.85 to 0.99) 0.027 ME Mergger 0.93(0.84 to 1.14) 0.758 0.93(0.84 to 1.14) 0.758 Weighted median 0.93(0.84 to 1.14) 0.758 0.93(0.84 to 1.14) 0.758 Mergger 1.00(0.90 to 1.12) 0.956 0.957				MR-Egger		0.88(0.71 to 1.09)	0.276
TB BMD(60 over) 9 IVW 0.94(0.88 to 1.01) 0.084 MA 0.94(0.88 to 1.01) 0.040 MI TB BMD(60 over) 52 VVV MI TB BMD(5-50) 52 VVV TB BMD(5-50) 52 VVV 0.94(0.88 to 1.01) 0.9478 MI TB BMD(15-30) 52 VVV 0.99(0.90 to 1.12) 0.950 TB BMD(15-30) 51 VVV 0.99(0.90 to 1.12) 0.950 MR<=Egger				Weighted median	H	0.96(0.87 to 1.06)	0.413
TB BMD(80 over) 9 NW 0.40.0.81 to 1.01 0.684 MR-Egger 0.84(0.81 to 1.01 0.749 Weighted median 0.94(0.85 to 1.03 0.778 MI TB BMD(0-15) 52 VW 0.92(0.85 to 0.99) 0.027 MR-Egger 0.98(0.81 to 1.10) 0.784 0.98(0.81 to 1.10) 0.784 Weighted median 0.93(0.84 to 1.14) 0.783 0.93(0.84 to 1.14) 0.783 Weighted median 0.93(0.84 to 1.14) 0.784 0.99(0.90 to 1.10) 0.905 TB BMD(15-30) 51 VW 0.99(0.90 to 1.10) 0.906 MR-Egger 1.00(0.83 to 1.22) 0.784 0.99(0.93 to 1.10) 0.906 MR-Egger 1.00(0.83 to 1.22) 0.784 0.99(0.93 to 1.10) 0.906 MR-Egger 1.00(0.83 to 1.02) 0.784 0.99(0.93 to 1.10) 0.905 TB BMD(45-60) 52 VW 0.99(0.93 to 1.10) 0.905 TB BMD(45-60) 52 VW 1.00(0.95 to 1.03) 0.784 Weighted median 0.94(0.85 to 1.04) 0.251 0.900 TB BMD(45-60)				Weighted mode	Hele Contraction	0.93(0.82 to 1.06)	0.331
IVW 0.04(0.88 to 1.01) 0.040 MI TB BMD(0-15) 52 0.88(0.71 to 1.08) 0.249 MI TB BMD(15-00) 52 0.88(0.71 to 1.08) 0.978 MI TB BMD(15-00) 52 0.98(0.81 to 1.10) 0.778 MI TB BMD(15-00) 51 0.98(0.81 to 1.10) 0.978 Weighted median 0.93(0.84 to 1.12) 0.353 0.999 0.905 0.997 MR-Egger 0.99(0.90 to 1.10) 0.908 0.990 0.901 0.908 0.903 0.904 0.903 0.904 0.904 0.903 0.903 0.904 0.904 0.903 0.904 0.903 0.903 0.904 0.904 0.904 0.904 0.904 0.904 0.904 0.904 0.904 0.904 0.905 0.904 0.904 0.904 0.904 0.904 0.904 0.904 </td <td></td> <td>TB BMD(60 over)</td> <td>9</td> <td></td> <td></td> <td></td> <td></td>		TB BMD(60 over)	9				
MR-Egger 0.88(0.71 to 1.08) 0.249 Wieighted median 0.94(0.85 to 1.33) 0.779 MI TB BMD(0-15) 52 VW 0.92(0.85 to 1.99) 0.227 MI TB BMD(15-30) 51 VW 0.92(0.85 to 0.99) 0.227 MR-Egger 0.96(0.84 to 1.14) 0.780 VW 0.96(0.84 to 1.14) 0.780 Weighted median 0.96(0.84 to 1.14) 0.780 VW 0.96(0.84 to 1.14) 0.780 Weighted median VW 0.96(0.84 to 1.14) 0.780 0.632 0.632 Weighted median VW 0.96(0.84 to 1.32) 0.632 0.632 0.632 Weighted median VW 0.96(0.83 to 1.02) 0.832 0.632 0.632 TB BMD(40-45) 52 VW 0.96(0.83 to 1.05) 0.338 VW 0.96(0.83 to 1.05) 0.338 Weighted median VW 0.96(0.85 to 1.05) 0.338 VW 0.96(0.85 to 1.05) 0.338 TB BMD(45-60) 52 VW 1.00(0.96 to 1.04) 0.977 <t< td=""><td></td><td>. ,</td><td></td><td>IVW</td><td>101</td><td>0.94(0.88 to 1.01)</td><td>0.084</td></t<>		. ,		IVW	101	0.94(0.88 to 1.01)	0.084
Mil TB BMD(0-15) 52 0.00000 0.40000 0.00000 MI TB BMD(0-15) 52 1 0.96(0.81 to 1.10) 0.478 MI TB BMD(15-30) 51 1 0.92(0.85 to 0.112) 0.93 TB BMD(15-30) 51 1 0.99(0.90 to 1.10) 0.96 MR-Egger 0.99(0.90 to 1.10) 0.96 0.973 Weighted median 1.00(0.81 to 1.20) 0.33 MR-Egger 0.99(0.90 to 1.10) 0.960 MR-Egger 0.99(0.90 to 1.10) 0.960 MR-Egger 0.99(0.90 to 1.10) 0.973 Weighted median 1.00(0.81 to 1.20) 0.333 Weighted median 0.99(0.90 to 1.10) 0.960 MR-Egger 0.99(0.91 to 1.10) 0.784 Weighted median 0.960,03 to 1.60) 0.325 TB BMD(45-60) 52 10/V 1.00(0.95 to 1.03) 0.371 MR-Egger 0.960,03 to 1.06) 0.271 0.977 0.977 0.970,08 to 1.03) 0.471 MR-Egger 0.970,08				MR-Egger		0.88(0.71 to 1.08)	0.249
MI TB BMD(0-15) 52 Vieigned media Correction (1000) 0.179 MI TB BMD(15-30) 51 Vieigned media 0.39(0.81 to 1.14) 0.768 MI TB BMD(15-30) 51 Vieigned media 0.39(0.81 to 1.14) 0.768 TB BMD(15-30) 51 Vieigned media 0.39(0.81 to 1.14) 0.560 TB BMD(30-45) 52 Vieigned media 0.39(0.81 to 1.14) 0.560 TB BMD(30-45) 52 Vieigned media 0.39(0.81 to 1.12) 0.578 TB BMD(45-60) 52 Vieigned media 0.39(0.81 to 1.15) 0.338 TB BMD(45-60) 52 Vieigned media 0.39(0.81 to 1.15) 0.338 TB BMD(45-60) 52 Vieigned media 0.39(0.81 to 1.15) 0.338 TB BMD(60 over) 52 Vieigned media 0.39(0.81 to 1.15) 0.338 TB BMD(60 over) 52 Vieigned media 0.39(0.81 to 1.10) 0.391 TB BMD(60 over) 52 Vieigned media 0.39(0.81 to 1.00) 0.474 MR-Egger 0				Weighted median	يلهر	0.94(0.86 to 1.02)	0.179
MI TB BMD(0-15) 52 MI TB BMD(15-15) 52 TB BMD(15-30) 51 TB BMD(15-30) 52 TB BMD(15-30) 12 TB BMD(15-30)				Weighted median		0.05(0.91 to 1.03)	0.479
MI TB BMD(0-15) 52 IVW 0.92(0.85 to 0.99) 0.027 MR-Egger 0.93(0.84 to 1.02) 0.135 Weighted median 0.93(0.84 to 1.02) 0.135 VWW 0.99(0.90 to 1.12) 0.95 TB BMD(15-30) 51 0.99(0.90 to 1.12) 0.95 TB BMD(30-45) 52 0.99(0.90 to 1.12) 0.97 TB BMD(30-45) 52 0.99(0.90 to 1.12) 0.97 TB BMD(45-60) 52 0.99(0.90 to 1.10) 0.90(0.90 to 1.12) 0.97 TB BMD(45-60) 52 0.99(0.90 to 1.10) 0.90(0.90 to 1.12) 0.97 TB BMD(45-60) 52 0.99(0.91 to 1.00) 0.91 0.99(0.91 to 1.00) 0.93 TB BMD(60 over) 52 1.90(0.95 to 1.05) 0.99(0.91 to 1.00) 0.91 TB BMD(60 over) 52 1.90(0.95 to 1.03) 0.192 TB BMD(60 over) 52 1.90(0.95 to 1.03) 0.192 TB BMD(60 over) 12 1.90(0.95 to 1.03) 0.410 Weighted median 1.90(0.95 to 1.29)				++Gignieu moue		0.00(0.0110 1.10)	0.470
Init ID BMD(0-15) 52 IVW IVM IVM 0.32(0.85 to 0.99) 0.027 MR—Egger 0.38(0.84 to 1.14) 0.758 Weighted mode 0.30(0.95 to 1.02) 0.355 TB BMD(15-30) 51 IVW 0.99(0.90 to 1.10) 0.990 0.990 0.607 Weighted mode 1.06(0.85 to 1.32) 0.632 0.607 0.607 0.607 TB BMD(30-45) 52 IVW 0.99(0.93 to 1.01) 0.990 0.930 0.810 0.607 Weighted mode 1.05(0.85 to 1.32) 0.632 0.637 0.607 0.607 0.607 0.607 0.607 0.607 0.607 0.607 0.608 0.607 0.607 0.607 0.607 0.607 0.607 0.607 0.607 0.607 0.607 0.607 0.325 TB BMD(45-60) 52 IVW 1<000.056 to 1.05		TO DMD/2 12	50				
TB BMD(15-30) 51 TB BMD(15-30) 52 TB BMD(15-30) 12	IVI	IB BMD(0-15)	92			0.00/0.051 0.05	0.007
MR-Egger 0.98(0.84 to 1:14, 0.758) Weighted median 0.93(0.84 to 1:12, 0.95) TB BMD(15-30) 51 VW 0.99(0.90 to 1:12, 0.95) VW 0.99(0.90 to 1:12, 0.95) TB BMD(30-45) 52 VW 0.99(0.90 to 1:10, 0.906, 0.900 Weighted median 0.99(0.90 to 1:10, 0.906, 0.900 Weighted median 0.99(0.93 to 1:05, 0.936, 0.900 Weighted median 0.99(0.93 to 1:06, 0.850, 0.336, 0.940, 0.830, 1.06, 0.325 TB BMD(45-60) 52 TB BMD(60 over) 52 VW 1.000,0.95 to 1:05, 0.964, 0.936, 0				IVW	Her	0.92(0.85 to 0.99)	0.027
Weighted median 0-39(0.8 ko 1.12) 0.39 TB BMD(15-30) 51 0-99(0.90 to 1.10) 0.990 MR-Egger 0-99(0.90 to 1.10) 0.900 0.900 MR-Egger 0-99(0.90 to 1.10) 0.900 0.900 Weighted median 1.00(0.8 to 1.22) 0.632 Weighted median 1.00(0.8 to 1.20) 0.900 MR-Egger 0.99(0.91 to 1.00) 0.807 MR-Egger 0.99(0.91 to 1.00) 0.320 MR-Egger 0.99(0.91 to 1.00) 0.325 MR-Egger 0.94(0.81 to 1.00) 0.351 MR-Egger 0.94(0.81 to 1.00) 0.351 MR-Egger 0.94(0.81 to 1.00) 0.352 MR-Egger 0.94(0.81 to 1.00) 0.853 MR-Egger 0.94(0.81 to 1.00) 0.853 MR-Egger 0.94(0.81 to 1.00) 0.853 MR-Egger 0.94(0.81 to 1.00) 0				MR-Egger	H	0.98(0.84 to 1.14)	0.758
TB BMD(16-30) 51 TB BMD(16-30) 51 MR-Egger 0.99(0.910.11.2) 0.95 Weighted median 0.99(0.910.11.2) 0.632 Weighted median 0.99(0.910.11.2) 0.670 Weighted median 0.99(0.910.11.2) 0.670 TB BMD(30-45) 52 700 99(0.910.11.2) 0.784 Weighted median 0.99(0.910.11.2) 0.784 0.99(0.910.11.2) 0.784 Weighted median 0.99(0.910.11.2) 0.784 0.99(0.910.11.2) 0.784 Weighted median 0.99(0.910.11.2) 0.784 0.99(0.910.11.2) 0.784 Weighted median 0.99(0.910.11.2) 0.784 0.99(0.910.10.2) 0.335 Weighted median 0.99(0.910.10.2) 0.910.23 0.910.23 0.912 TB BMD(60 over) 52 700 1.90(0.9510.10.2) 0.912 TB BMD(60 over) 52 700 1.90(0.9510.10.2) 0.912 TB BMD(60 over) 12 700 1.90(0.9510.10.2) 0.912 Weighted median <t< td=""><td></td><td></td><td></td><td>Weighted median</td><td>Her</td><td>0.93(0.84 to 1.02)</td><td>0.135</td></t<>				Weighted median	Her	0.93(0.84 to 1.02)	0.135
TB BMD(15-30) 51 IVW 0.99(0.90 to 1.10) 0.996 MR-Egger 1.06(0.85 to 1.32) 0.632 Weighted median 1.06(0.85 to 1.32) 0.632 TB BMD(30-45) 52 IVW 0.996(0.81 to 1.16) 0.897 TB BMD(45-60) 52 IVW 0.996(0.81 to 1.06) 0.897 TB BMD(45-60) 52 IVW 0.996(0.81 to 1.06) 0.392 TB BMD(45-60) 52 IVW 0.996(0.81 to 1.06) 0.392 TB BMD(65-60) 52 IVW 0.996(0.81 to 1.06) 0.392 TB BMD(60 over) 52 IVW 0.996(0.81 to 1.06) 0.392 TB BMD(60 over) 52 IVW 0.996(0.81 to 1.06) 0.392 Vieighted median 0.996(0.81 to 1.06) 0.994 0.996(0.81 to 1.06) 0.391 Vieighted median 0.997(0.81 to 1.06) 0.392 0.997 0.996(0.81 to 1.06) 0.994 Vieighted median 0.970(0.81 to 1.06) 0.434 Vieighted median 0.907(0.81 to 1.06) 0.544 Vi				Weighted mode	H++	1.00(0.90 to 1.12)	0.95
NW 0.99(0.90 to 1:10.00.900 0.99(0.90 to 1:10.00.900 0.99(0.90 to 1:10.00 0.99(0.80 to 1:10.0		TB BMD(15-30)	51				
ME-Egger 1.06(0.85 to 1.32) 0.632 TB BMD(30-45) 52 0.607 Weighted median 1.000.83 to 1.21) 0.607 Weighted median 1.000.83 to 1.21) 0.607 Weighted median 0.960.93 to 1.05) 0.368 Weighted median 0.960.93 to 1.05) 0.368 Weighted median 0.960.85 to 1.05) 0.968 Weighted median 0.960.85 to 1.05) 0.978 Weighted median 0.960.85 to 1.05) 0.978 Weighted median 0.960.85 to 1.05) 0.978 Weighted median 0.960.85 to 1.05) 0.544 Weighted median 1.000.96 to 1.04) 0.543 Weighted median 1.000.96 to 1.09) 0.543 Weighted median 1.000.96 to 1.09) 0.543 Weighted median 1.000.96 to 1.09) 0.543 Weighted median 1.000.96 to 1.09) <t< td=""><td></td><td></td><td></td><td>IVW</td><td>HH</td><td>0.99(0.90 to 1.10)</td><td>0.906</td></t<>				IVW	HH	0.99(0.90 to 1.10)	0.906
BMD(30-45) 52 TB BMD(30-45) 52 TB BMD(45-60) 52 TB BMD(60 over) 52				MR-Egger		1.06(0.85 to 1.32)	0.632
Weighted mode 1.00(0.83 to 1.21) 0.978 TB BMD(30-45) 52 0.990 0.978 0.990 0.978 0.990 0.978 TB BMD(45-60) 52 0.990 0.950 0.950 0.950 0.950 0.935 TB BMD(45-60) 52 0.990 0.940 0.940 0.940 0.950 <t< td=""><td></td><td></td><td></td><td>Weighted median</td><td></td><td>1.05(0.88 to 1.24)</td><td>0.607</td></t<>				Weighted median		1.05(0.88 to 1.24)	0.607
TB BMD(30-45) 52 IVW 0.99(0.33 to 1.06) 0.807 MRT-Egger 0.94(0.33 to 1.06) 0.784 Weighted median 0.94(0.33 to 1.06) 0.325 TB BMD(45-60) 52 IVW 1.00(0.95 to 1.05) 0.336 MRT-Egger 0.94(0.83 to 1.06) 0.926 0.94(0.81 to 1.06) 0.325 TB BMD(60 over) 52 IVW 1.00(0.95 to 1.05) 0.336 Vielighted median 0.94(0.81 to 1.04) 0.251 Weighted median 0.96(0.81 to 1.03) 0.192 TB BMD(60 over) 52 IVW 1.00(0.96 to 1.04) 0.977 0.977(0.89 to 1.06) 0.544 Weighted median 1.00(0.96 to 1.04) 0.950 0.877(0.89 to 1.06) 0.544 Weighted median 1.01(0.96 to 1.29) 0.174 MRT-Egger 0.66(0.26 to 1.69) 0.404 Weighted median 1.01(0.96 to 1.29) 0.174 MRT-Egger 0.66(0.26 to 1.69) 0.404 Weighted median 1.01(0.96 to 1.29) 0.174 MRT-Egger 0.66(0.26 to 1.69) 0.404 0.837				Weighted mode		1.00(0.83 to 1.21)	0.978
IVW 0.99(0.33 ho 1.06) 0.807 MR-Egger 1.02(0.30 ho 1.16) 0.784 Weighted mode 0.94(0.83 ho 1.06) 0.837 TB BMD(45-60) 52 IVW 0.94(0.83 ho 1.06) 0.235 TB BMD(45-60) 52 IVW 0.94(0.85 ho 1.05) 0.944 MWEighted mode 0.94(0.85 ho 1.05) 0.940 0.950 0.251 Weighted mode 0.94(0.85 ho 1.05) 0.940 0.950 0.251 Weighted mode 0.94(0.85 ho 1.05) 0.940 0.950 0.950 TB BMD(60 over) 52 IVW 1.00(0.94 ho 1.04) 0.977 Weighted mode 0.970.98 ho 1.06) 0.544 0.970.98 ho 1.06) 0.544 Weighted mode 1.10(0.92 ho 1.54) 0.404 0.977 0.970.98 ho 1.00) 0.543 Weighted mode 1.100.94 ho 1.070 0.935 0.940 0.940(0.945 ho 1.04) 0.977 TB BMD(15-30) 12 IVW 1.110.945 ho 1.290 0.174 0.940(0.945 ho 1.24) 0.940 Weighted modian 0		TB BMD(30-45)	52				
MR-Egger 102(0.90 to 11:6) 0.784 Weighted median 0.96(0.85 to 10.5) 0.325 TB BMD(45-60) 52 1000 0.95 to 10.50 0.325 MR-Egger 0.94(0.83 to 10.5) 0.940 <td></td> <td></td> <td></td> <td>IVW</td> <td>100</td> <td>0.99(0.93 to 1.06)</td> <td>0.807</td>				IVW	100	0.99(0.93 to 1.06)	0.807
TB BMD(45-60) 52 TB BMD(45-60) 52 TB BMD(60 over) 12 TW 1.00(0.96 to 1.04) 0.977 MR-Egger 0.660 co 26 to 1.60) 0.440 Weighted median 0.610 co 20 0.514 Weighted median 0.610 co 20 0.714 MR-Egger 0.610 co 20 0.610 co 20 WW 1.11(0.98 to 1.29 0.610 co 20 WW 1.11(0.98 to 1.20 0.610 co 20 WW 1.11(0.98 to 1.20 0.610 co 20				MR-Enger	Here a	1.02(0.90 to 1.16)	0 784
TB BMD(45-60) 52 IVW 1.00(0.95 to 1.05) 0.328 TB BMD(60 over) 52 IVW 1.00(0.95 to 1.05) 0.328 TB BMD(60 over) 52 IVW 1.00(0.95 to 1.05) 0.668 Weighted median ever 0.98(0.91 to 1.06) 0.658 0.668 Weighted median ever 0.98(0.91 to 1.06) 0.544 Weighted median ever 0.97(0.98 to 1.04) 0.574 MR~Egger 0.97(0.98 to 1.04) 0.535 Vieighted median ever 0.97(0.89 to 1.04) 0.544 Weighted median ever 0.66(0.25 to 1.69) 0.454 Weighted median ever 0.66(0.25 to 1.69) 0.474 MR~Egger 1.01(0.92 to 1.54) 0.174 0.66(0.25 to 1.69) 0.414 Weighted median ever 1.06(0.84 to 1.20) 0.637 TB BMD(15-30) 12 IVW 1.11(0.96 to 1.29) 0.174 MR~Egger issue 1.118(0.68 to 2.02) 0.547 0.56(0.85 to 1.68) 0.308 Weighted median				Weighted median	and a	0.95(0.86 to 1.05)	0.336
TB BMD(45-60) 52 TB BMD(45-60) 52 TB BMD(60 over) 12 TW 1.01(0.95 to 1.29) 0.774 MR=Egger 0.86(0.26 to 1.69) 0.404 Weighted mode 1.11(0.96 to 1.29) 0.61 Weighted mode 1.11(0.95 to 1.29) 0.74 MR=Egger 1.11(0.95 to 1.29) 0.74 MR=Egger 1.11(0.95 to 1.29) 0.61 Weighted mode 1.11(1.96.95 to 2.20) 0.54 Weighted mode 1.11(1.96.95 to 2.20) 0.54 Weighted mode 1.11(1.10.95 to 1.29) 0.74				Weighted media		0.04(0.93 to 1.06)	0.000
INDERCIPATION 22 IVW 1.00(0.95 to 1.05) 0.964 MR—Egger 0.94(0.86 to 1.04) 0.251 Weighted median 0.95(0.87 to 1.03) 0.152 TB BMD(60 over) 52 1.00(0.95 to 1.05) 0.964 Weighted median 0.97(0.88 to 1.04) 0.977 0.977 MR—Egger 0.97(0.88 to 1.06) 0.44 0.955 VWW 1.00(0.96 to 1.04) 0.977 0.985 Stroke TB BMD(6-15) 12 12 1.01(0.92 to 1.100) 0.853 Stroke TB BMD(15-30) 12 1.01(0.92 to 1.54) 0.194 TB BMD(16-30) 12 VW 1.01(0.92 to 1.54) 0.194 TB BMD(15-30) 12 VW 1.11(0.05 to 1.29) 0.174 TB BMD(16-30) 12 VW 1.01(0.82 to 1.54) 0.194 MR—Egger VW 1.91(0.92 to 1.54) 0.194 MR-Egger 0.80(0.85 to 1.02) 0.547 TB BMD(30-45) 12 VW 0.91(0.77 to 1.08) 0.278 MR-Egger			50	weighted mode		0.94(0.03 t0 1.00)	0.325
TB BMD(60 over) 12 TB BMD(5-30) 12 VW 1.11(0.96 to 1.29) VW 1.11(0.96 to 1.20)		TB BMD(45-00)	52	0.04/	1	4 00/0 05 1- 4 05)	0.004
MR-Egger 0.94(0.88 to 1.04) 0.251 TB BMD(60 over) 52 0.95(0.87 to 1.03) 0.192 IVW 1.00(0.96 to 1.04) 0.977 MR-Egger 0.97(0.87 to 1.03) 0.453 Vieighted median 0.977 0.970.098 to 1.04) 0.977 MR-Egger 0.970.098 to 1.04) 0.977 Vieighted median 1.01(0.92 to 1.10) 0.853 Stroke TB BMD(6-15) 12 1.11(0.96 to 1.29) 0.714 MR-Egger 0.967(0.87 to 1.03) 0.457 0.967(0.87 to 1.03) 0.457 TB BMD(15-30) 12 1.11(0.96 to 1.29) 0.714 MR-Egger 0.967(0.87 to 1.03) 0.457 TB BMD(15-30) 12 1.92(0.37 to 1.03) 0.457 TB BMD(15-30) 12 1.92(0.37 to 1.03) 0.457 TB BMD(30-45) 12 1.92(0.37 to 1.03) 0.457 TB BMD(30-45) 12 1.92(0.37 to 1.03) 0.92 TB BMD(45-60) 12 1.92(0.37 to 1.03) 0.92 TB BMD(45-60) 12 1.92(0.37 to 1.03) 0.92 TB BMD(45-60) 12 1.92(0.37 to 1.20) 0.92 TB BMD(45-60) 12 1.92(0.37 to 1.20) 0.92 Weighted median <				1000	T	1.00(0.95 to 1.05)	0.964
TB BMD(60 over) 12 TB BMD(50 over) 12 IVW 100(0.95 to 1.03) Vieighted median 0.97(0.89 to 1.06) MR-Egger 0.97(0.89 to 1.06) Vieighted median 1.00(0.95 to 1.03) Vieighted median 1.00(0.95 to 1.03) Vieighted median 1.01(0.92 to 1.10) Vieighted median 1.01(0.92 to 1.10) Vieighted median 1.01(0.92 to 1.10) Vieighted median 1.05(0.85 to 1.29) TB BMD(15-30) 12 TB BMD(30-45) 12 Vieighted median 1.11(0.93 to 1.20) Vieighted median 1.03(0.76 to 1.40) Vieighted median 1.11(0.93 to 1.20) Vieighted median 1.03(0.76 to 1.40) Vieighted median 1.11(0.08 to 1.20) Vieighted median 1.11(0.08 to 1.20) Vieighted median 0.96(0.25 to 1.56) Vieighted median 0.96(0.25 to 1.56) Vieighted median 0.96(0.85 to 1.20) Vieighted median 0.96(0.85 to 1.20) Vieighted median 0.97(0.47 to 1.80)				MK-Egger	1	0.94(0.86 to 1.04)	0.251
TB BMD(60 over) 52 IVW 1.00(0.96 to 1.04) 0.977 MR-Egger 0.96(0.87 to 1.03) 0.543 Weighted mode 1.00(0.96 to 1.04) 0.977 Stroke TB BMD(6-15) 12 1.11(0.96 to 1.29) 0.174 MR-Egger 0.660 28 to 1.63) 0.404 0.977 0.96 to 1.29) 0.174 MR-Egger 0.660 28 to 1.63) 0.404 0.962 28 to 1.63) 0.404 Weighted mode 1.11(0.96 to 1.29) 0.174 0.802 28 to 1.64) 0.404 Weighted mode 1.11(0.92 to 1.54) 0.404 0.837 28 to 1.03) 0.457 TB BMD(15-30) 12 IVW 1.11(0.92 to 1.54) 0.194 MR-Egger 1.11(0.28 to 1.63) 0.367 0.360 20 20 2.0547 0.360 20 20 2.0547 TB BMD(30-45) 12 IVW 1.11(0.08 to 1.20) 0.547 MR-Egger 1.11(0.08 to 1.03) 0.457 0.806.68 to 1.08) 0.20 TB BMD(45-60) 12 IVW 1.90(0.82 to 1.54) 0.990 MR-Egger <td< td=""><td></td><td></td><td></td><td>vveighted median</td><td>HH</td><td>0.98(0.91 to 1.06)</td><td>0.636</td></td<>				vveighted median	HH	0.98(0.91 to 1.06)	0.636
TB BMD(60 over) 52 IVW 1.00(0.96 to 1.04) 0.977 MR-Egger 0.97(0.89 to 1.06) 0.544 Weighted median 1.00(0.96 to 1.04) 0.573 Weighted median 1.00(0.96 to 1.07) 0.935 Stroke TB BMD(0-15) 12 IVW 1.11(0.96 to 1.29) 0.714 MR-Egger 0.66(0.26 to 1.59) 0.404 Weighted median 0.66(0.26 to 1.59) 0.404 Weighted median 0.66(0.26 to 1.69) 0.404 Weighted median 1.03(0.76 to 1.40) 0.837 TB BMD(15-30) 12 IVW 1.11(0.96 to 1.29) 0.114 MR-Egger 1.39(0.75 to 1.30) 0.457 0.404 0.86(0.26 to 1.59) 0.404 Weighted median IVW 1.11(0.96 to 1.29) 0.14 MR-Egger 1.39(0.75 to 1.30) 0.457 TB BMD(30-45) 12 IVW 0.96(0.68 to 1.08) 0.290 0.547 TB BMD(45-60) 12 IVW 0.96(0.68 to 1.12) 0.906 0.910 0.912 0.910 0.710 to 1.80 <t< td=""><td></td><td></td><td></td><td>Weighted mode</td><td>Her</td><td>0.95(0.87 to 1.03)</td><td>0.192</td></t<>				Weighted mode	Her	0.95(0.87 to 1.03)	0.192
IVW 1.00(0.96 to 1.04, 0.077) MR-Egger 0.70(0.89 to 1.06, 0.544 Weighted median 1.00(0.94 to 1.07) 0.853 Stroke TB BMD(0-15) 12 1.11(0.95 to 1.29) 0.853 Stroke TB BMD(1-53) 12 1.11(0.95 to 1.29) 0.66(0.26 to 1.69) 0.404 Weighted median 1.05(0.86 to 1.29) 0.67(0.86 to 1.69) 0.404 0.86(0.26 to 1.69) 0.404 Weighted median 1.05(0.86 to 1.29) 0.61 0.86(0.26 to 1.69) 0.404 Weighted median 1.16(0.82 to 1.29) 0.61 0.837 0.803(0.76 to 1.40) 0.837 TB BMD(15-30) 12 1.14 1.16(0.82 to 1.59) 0.194 MR-Egger 1.18(0.82 to 2.02) 0.547 1.18(0.82 to 2.02) 0.547 MR-Egger 1.18(0.82 to 2.02) 0.547 0.86(0.88 to 1.69) 0.278 MR-Egger 1.90(0.81 to 1.12) 0.900 0.740 0.910.77 to 1.08) 0.278 MR-Egger 1.90(0.81 to 1.12) 0.910 0.710 to 1.08) 0.278 0.860.68 to 1.60 0.02		TB BMD(60 over)	52				
MR-Egger 0.97(0.810 1.06) 0.954 Weighted median 0.000.94 to 107) 0.935 Stroke TB BMD(0-15) 12 1.01(0.92 to 1.10) 0.853 Stroke TB BMD(1-15) 12 1.01(0.92 to 1.10) 0.853 TB BMD(1-15) 12 1.01(0.92 to 1.10) 0.610 0.936 TB BMD(15-30) 12 1.01(0.92 to 1.10) 0.837 TB BMD(15-30) 12 1.03(0.76 to 1.40) 0.337 TB BMD(15-30) 12 1.92(0.37 to 10.03) 0.457 Weighted median 1.92(0.37 to 10.03) 0.457 0.946 Weighted median 1.92(0.37 to 10.03) 0.457 0.946 TB BMD(30-45) 12 1.100.08 to 1.20 0.578 TB BMD(45-60) 12 1.040 0.902 0.597 TB BMD(45-60) 12 1.040 0.902 0.902 0.902 TB BMD(60 over) 12 1.020 0.740 4.98 to 1.130 0.902 TB BMD(60 over) 12 1.020 1.900.08 to 1.120 0.908 Weighted median 1.92(0.377 to 1.34) 0.902				IVW		1.00(0.96 to 1.04)	0.977
Weighted median 1.00(0.94 to 1.07) 0.833 Stroke TB BMD(0-15) 12 IV III (10.96 to 1.29) 0.174 MR-Egger 0.66(0.26 to 1.69) 0.040 0.633 0.66(0.26 to 1.69) 0.401 TB BMD(15-30) 12 IV III (10.96 to 1.29) 0.174 MR-Egger 0.66(0.26 to 1.69) 0.401 0.66(0.26 to 1.69) 0.401 TB BMD(15-30) 12 IV III (10.96 to 1.29) 0.61 Weighted median III (10.96 to 1.29) 0.61 0.837 Weighted median III (10.96 to 1.20) 0.61 0.837 Weighted median III (10.96 to 1.20) 0.61 0.837 Weighted median III (10.96 to 1.20) 0.61 0.36 Weighted median III (10.96 to 1.20) 0.547 0.547 TB BMD(45-60) 12 IV IIII (10.96 to 1.10) 0.518 Weighted median IIII (10.96 to 1.10) 0.152 0.547 MR-Egger IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII				MR-Egger	Here	0.97(0.89 to 1.06)	0.544
Stroke TB BMD(0-15) 12 1 1.01(0.92 to 1.10) 0.853 Stroke TB BMD(0-15) 12 1 1.11(0.96 to 1.12) 0.174 MR=Egger 0.66(0.26 to 1.60) 0.404 0.66(0.26 to 1.60) 0.404 Weighted median 0.96(0.26 to 1.61) 0.404 0.837 TB BMD(15-30) 12 12 1.19(0.92 to 1.54) 0.944 MR=Egger 1.92(0.37 to 10.03) 0.457 0.86(0.26 to 1.62) 0.61 MR=Egger 1.92(0.37 to 10.03) 0.457 0.940 0.853 0.306 TB BMD(30-45) 12 IVW 1.16(0.82 to 1.63) 0.396 0.957 TB BMD(45-60) 12 IVW 0.91(0.77 to 1.08) 0.781 0.912 0.597 TB BMD(45-60) 12 IVW 0.90(0.88 to 1.12) 0.910 0.912 TB BMD(60 over) 12 IVW 0.90(0.88 to 1.12) 0.902 0.910 TB BMD(60 over) 12 IVW 0.90(0.88 to 1.12) 0.902 0.910 0.910 0.				Weighted median	101	1.00(0.94 to 1.07)	0.935
Stroke TB BMD(0-15) 12 IVW MR-Egger 0.66(0.28 to 169) 0.414 Weighted median Weighted median 0.66(0.28 to 169) 0.404 Weighted median Weighted median 1.03(0.76 to 1.40) 0.837 TB BMD(15-30) 12 IVW 1.19(0.92 to 1.54) 0.194 MR-Egger 1.92(0.37 to 10.03) 0.457 0.66(0.28 to 169) 0.304 Weighted median Weighted median 1.92(0.37 to 10.03) 0.457 0.567 TB BMD(30-45) 12 IVW 0.91(0.77 to 10.80) 0.278 MR-Egger Weighted median 0.96(0.28 to 1.12) 0.547 VW MR-Egger 1.39(0.43 to 4.52) 0.597 Weighted median Weighted median 0.74(0.49 to 1.13) 0.192 Weighted median Weighted median 0.90(0.88 to 1.12) 0.906 TB BMD(60 over) 12 VW 0.90(0.88 to 1.12) 0.902 TB BMD(60 over) 12 VW 0.90(0.88 to 1.12) 0.902 TB BMD(60 over) 12<				Weighted mode	144	1.01(0.92 to 1.10)	0.853
Stroke TB BMD(0-15) 12 IVW IIII (0.96 to 1.29) 0.174 MR~Egger 0.66(0.26 to 1.69) 0.404 Weighted median IIII (0.96 to 1.29) 0.61 Weighted median IIIII (0.96 to 1.29) 0.61 Weighted median IIIII (0.92 to 1.54) 0.687 TB BMD(15-30) 12 IVW IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII					1		
IVW 1.11(0.08 lo 12.2) 0.174 MR=Egger 0.66(0.26 lo 169) 0.404 Weighted median Weighted median 0.66(0.26 lo 169) 0.404 Weighted median Weighted median 1.30(0.76 lo 140) 0.837 TB BMD(15-30) 12 IVW 1.92(0.37 lo 10.30) 0.457 Weighted median Weighted median 1.92(0.37 lo 10.30) 0.457 Weighted median Weighted median 1.92(0.37 lo 10.30) 0.457 Weighted median Weighted median 0.96(0.68 lo 160) 0.268 Weighted median Weighted median 0.96(0.68 lo 160) 0.278 MR=Egger 1.38(0.43 lo 4.52) 0.592 0.547 Weighted median Weighted median 0.96(0.68 lo 10.8) 0.278 MR=Egger 1.39(0.43 lo 4.52) 0.592 0.592 Weighted median 0.96(0.68 lo 11.3) 0.192 0.192 TB BMD(60 over) 12 IVW 0.99(0.88 lo 1.12) 0.902 TB BMD(60 over) 12 IVW 0.90(0.88 lo 1.22) 0.118	Stroke	TB BMD(0-15)	12				
MR-Egger 0.66(0.26 lo 169) 0.61 Weighted median 1.05(0.86 lo 129) 0.61 Weighted median 1.05(0.86 lo 129) 0.61 Weighted median 1.05(0.86 lo 129) 0.61 Weighted median 1.16(0.82 lo 129) 0.81 Weighted median 1.19(0.92 lo 154) 0.194 MR-Egger 1.18(0.82 lo 163) 0.367 Weighted median 1.18(0.82 lo 129) 0.547 TB BMD(30-45) 12 1.18(0.83 lo 122) 0.547 TB BMD(45-60) 12 1.944 0.96(0.88 lo 1.08) 0.278 MR-Egger 1.39(0.43 lo 452) 0.990 N/04/04 lo 1.13) 0.192 TB BMD(45-60) 12 12 1.044 0.990(0.88 lo 1.12) 0.900 TB BMD(60 over) 12 1.044 0.990(0.88 lo 1.12) 0.902 0.990 TB BMD(60 over) 12 1.044 0.902 No 10.122 0.118 MR-Egger 1.02(0.71 lo 1.34) 0.992 1.02(0.71 lo 1.34) 0.992 TB BMD(60 over) 12 1.0				IVW		1.11(0.96 to 1.29)	0.174
Weighted median Weighted mode 1.05(0.86 to 1.29) 0.61 TB BMD(15-30) 12 10 1.03(0.76 to 1.40) 0.337 TB BMD(15-30) 12 IVW 1.19(0.92 to 1.54) 0.194 MR-Egger 1.92(0.37 to 1.00.3) 0.457 0.457 0.457 VWeighted median Weighted median 1.92(0.37 to 1.00.3) 0.457 0.94 TB BMD(30-45) 12 IVW 1.18(0.69 to 1.63) 0.597 Weighted median Weighted median 0.94(0.77 to 1.08) 0.278 0.597 TB BMD(45-60) 12 IVW 0.99(0.88 to 1.12) 0.902 TB BMD(60 over) 12 IVW 0.99(0.88 to 1.12) 0.902 TB BMD(60 over) 12 IVW 0.99(0.98 to 1.22) 0.118 Weighted median Weighted median 0.902 1.02(0.77 to 1.34) 0.902 TB BMD(60 over) 12 IVW 0.91(0.77 to 1.34) 0.902 TB BMD(60 over) 12 IVW 0.91(0.37 to 1.22) 0.118 MR-Egger 1.02(0.77 to 1.34) 0.902 IVW				MR-Egger		0.66(0.26 to 1.69)	0.404
Weighted mode 1.33(0.78 to 1.49) 0.337 TB BMD(15-30) 12 1/W 1.19(0.92 to 1.54) 0.194 ME-Egger 1.19(0.92 to 1.54) 0.194 1.19(0.82 to 1.56) 0.367 Weighted mode 1.18(0.82 to 1.56) 0.367 0.367 0.367 0.367 TB BMD(30-45) 12 1.18(0.82 to 1.56) 0.367 0.368 0.368 Weighted mode 1.18(0.82 to 1.56) 0.367 0.377 0.108 0.278 ME-Egger 1.39(0.43 to 4.52) 0.597 0.860(0.88 to 108) 0.290 0.74(0.49 to 1.13) 0.192 TB BMD(45-60) 12 1.000(0.84 to 1.12) 0.906 0.194 0.99(0.88 to 1.12) 0.906 ME-Egger 1.02(0.77 to 1.34) 0.992 1.02(0.77 to 1.34) 0.992 1.030(0.89 to 1.22) 0.118 ME-Egger 0.82(0.39 to 1.72) 0.613 0.303 (0.89 to 1.22) 0.118 ME-Egger 0.82(0.39 to 1.72) 0.613 0.902 1.03(0.89 to 1.22) 0.118 ME-Egger 0.90(0.88 to 1.22)				Weighted median		1.05(0.86 to 1.29)	0.61
TB BMD(15-30) 12 IVW Internet of radio constraints 0.194 MR-Egger Internet of radio constraints 119(0.92 to 1.54) 0.194 MR-Egger Internet of radio constraints 119(0.92 to 1.54) 0.194 TB BMD(30-45) 12 IVW Internet of radio constraints 0.396 MR-Egger Internet of radio constraints 0.91(0.77 to 1.08) 0.278 MR-Egger Internet of radio constraints 0.91(0.77 to 1.08) 0.278 MR-Egger Internet of radio constraints 0.91(0.77 to 1.08) 0.278 MR-Egger Internet of radio constraints 0.91(0.77 to 1.08) 0.278 MR-Egger Internet of radio constraints 0.91(0.77 to 1.08) 0.278 Velighted mode Internet of radio constraints 0.910 0.910 VB Internet of radio constraints 0.910 0.910 0.910 TB BMD(45-60) 12 IVW Internet of radio constraints 0.900 TB BMD(60 over) 12 IVW Internet of radio constraints 0.900 TB BMD(60 over) 12 IVW Interegger 0.82(0.391 to 1.72)				Weighted mode		1.03(0.76 to 1.40)	0.837
IVW 1.19(0.92 to 154) 0.194 MR-Egger 1.92(0.37 to 10.03) 0.457 VWeighted median 1.16(0.82 to 154) 0.194 Weighted median 1.16(0.82 to 154) 0.396 Weighted median 0.914 1.18(0.69 to 2.02) 0.547 TB BMD(30-45) 12 1.18(0.69 to 2.02) 0.547 Weighted median 0.91(0.77 to 10.8) 0.278 MR-Egger 1.39(0.43 to 4.52) 0.990 Weighted median 0.96(0.88 to 10.8) 0.292 Weighted median 0.90(0.88 to 11.2) 0.902 TB BMD(45-60) 12 IVW 0.99(0.88 to 11.2) 0.902 Weighted median 1.92(0.37 to 1.34) 0.902 INO(0.84 to 11.34) 0.902 TB BMD(60 over) 12 IVW 0.90(0.98 to 12.2) 0.118 MR-Egger 1.02(0.77 to 1.34) 0.902 IVW 0.90(0.98 to 12.2) 0.118 Weighted median 0.90(0.98 to 12.2) 0.118 INO(0.84 to 11.30) 0.818 Weighted median 0.90(0.98 to 12.2) 0.11		TB BMD(15-30)	12				
MR-Egger 1.80.93 20 1349 0.198 Weighted median 1.920.37 to 10.08 0.457 Weighted median 1.16(0.82 to 16.3) 0.396 Weighted median 0.91(0.77 to 10.8) 0.787 MR-Egger 0.91(0.77 to 1.8) 0.797 Weighted median 0.86(0.88 to 1.08) 0.2 Weighted median 0.74(0.49 to 1.13) 0.192 TB BMD(45-60) 12 IW 0.99(0.88 to 1.12) TB BMD(45-60) 12 IW 0.99(0.88 to 1.12) Weighted median 0.99(0.88 to 1.12) 0.990 MR-Egger 1.92(0.87 to 1.80) 0.990 TB BMD(60 over) 12 IW 0.99(0.88 to 1.12) Weighted median 0.99(0.98 to 1.22) 0.139 Weighted median 0.00(0.84 to 1.18) 0.990 TB BMD(60 over) 12 IW 0.90(0.98 to 1.22) Weighted median 0.92(0.37 to 1.39) 0.902 TB BMD(60 over) 12 IW 0.90(0.98 to 1.22) Weighted median 0.90(0.98 to 1.22) 0.118 Weighted median 0.92(0.39 to 1.22) 0.118 Weighted median 0.92(0.39 to 1.22) 0.118 Weighted median 0.92(0.39 to 1.22) 0.118 W		55(10 30)		IV/W	سمطر	1 19(0.92 to 1.54)	0 194
TB BMD(30-45) 12 VWeighted median VWeighted median WWeighted median VWeighted median WWeighted median VWeighted median TB BMD(30-45) 12 IVW 0.91(0.77 to 1.08) 0.278 MR-Egger 0.960(0.81 to 1.52) 0.547 VWeighted median 0.961(0.81 to 1.52) 0.960 Weighted median 0.961(0.81 to 1.52) 0.990 Weighted median 0.960(0.81 to 1.12) 0.902 VWeighted median 0.902(0.81 to 1.12) 0.902 TB BMD(60 over) 12 VW 0.90(0.88 to 1.12) 0.902 TB BMD(60 over) 12 VW 0.90(0.98 to 1.22) 0.118 MR-Egger 1.02(0.77 to 1.34) 0.902 118 MR-Egger 0.82(0.39 to 1.72) 0.613 VWeighted median 0.902,08 to 1.22) 0.118 MR-Egger 0.82(0.39 to 1.72) 0.613 Weighted median 0.902,08 to 1.22) 0.118 MR-Egger 0.82(0.39 to 1.72) 0.613 Weighted median 0.902,09 to 1.22) <				MR-Enger		1 92(0 37 to 10 02)	0.457
Weighted median Image: Sector Se				Weighted modion		1 16(0.82 to 1.62)	0.306
TB BMD(30-45) 12 I/W 0.91(0.77 to 1.08) 0.278 MR-Egger 139(0.43 to 4.52) 0.597 0.66(0.08 to 1.08) 0.2 Vieighted median 0.94(0.77 to 1.08) 0.78 0.96(0.08 to 1.08) 0.2 TB BMD(45-60) 12 I/W 0.90(0.88 to 1.12) 0.902 Weighted median 0.90(0.88 to 1.12) 0.902 0.902 TB BMD(60 over) 12 I/W 0.90(0.88 to 1.12) 0.902 TB BMD(60 over) 12 I/W 0.90(0.88 to 1.12) 0.902 TB BMD(60 over) 12 I/W 0.902 0.30(0.88 to 1.22) 0.118 Weighted median 0.90(0.98 to 1.22) 0.118 0.30(0.89 to 1.22) 0.118 Weighted median 0.90(0.98 to 1.22) 0.118 0.30(0.89 to 1.22) 0.118 Weighted median 0.90(0.98 to 1.22) 0.118 0.30(0.89 to 1.22) 0.118 Weighted median 0.90(0.98 to 1.22) 0.118 0.30(0.89 to 1.22) 0.118 Weighted median 0.90(0.98 to 1.22) 0.818 0.910(0.98				Weighted median		1.10(0.02 t0 1.03)	0.590
I/W 0.91(0.77 to 1.08) 0.278 MR-Egger 1.39(0.43 to 4.52) 0.597 Weighted median 0.86(0.68 to 106) 0.2 Weighted median 0.74(0.49 to 1.13) 0.192 TB BMD(45-60) 12 1.20(0.77 to 1.08) 0.278 Weighted median 0.94(0.88 to 1.12) 0.906 MR-Egger 1.39(0.43 to 4.52) 0.192 Weighted median 0.96(0.88 to 1.12) 0.906 Weighted median 1.92(0.87 to 4.26) 0.139 Weighted median 1.02(0.77 to 1.34) 0.992 TB BMD(60 over) 12 I/W 0.90(0.98 to 1.22) 0.118 MR-Egger 0.82(0.39 to 1.72) 0.613 0.30(0.89 to 1.22) 0.118 MR-Egger 0.82(0.39 to 1.72) 0.613 0.968 Weighted median 0.82(0.39 to 1.72) 0.613 Weighted median 0.964 1.03(0.89 to 1.22) 0.618 0.818		TR RMD/20 4C	12	vvelgnieu mode		- 1.10(0.09 to 2.02)	0.047
IVW 0.91(0.77 to 168) 0.278 MR-Egger →→→→ 0.86(0.68 to 1.08) 0.2 Weighted median →→→→ 0.86(0.68 to 1.08) 0.2 Weighted mode →→→→ 0.86(0.68 to 1.08) 0.2 TB BMD(45-60) 12 IVW 0.99(0.88 to 112) 0.992 Weighted median →→→→ 0.99(0.88 to 112) 0.902 Weighted median →→→→ 0.90(0.88 to 112) 0.902 TB BMD(60 over) 12 IVW →→→→ 1.02(0.77 to 1.34) 0.902 TB BMD(60 over) 12 IVW →→→→→ 1.02(0.77 to 1.34) 0.902 Weighted median →→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→		10 DMU(30-45)	12			0.04/0.7745.4.55	0.070
MK-t-gger 1.39(0.4310.452) 0.597 Weighted median 0.69(0.88 to 10.60) 0.2 Weighted mode 0.74(0.49 to 1.13) 0.192 TB BMD(45-60) 12 VW 0.99(0.88 to 1.12) 0.906 Weighted median 0.99(0.88 to 1.12) 0.906 0.900 0.900 0.900 TB BMD(60 over) 12 VW 1.92(0.37 to 4.26) 0.390 Weighted median 1.02(0.77 to 1.34) 0.902 1.090(0.88 to 1.22) 0.118 MR-E-gger 0.82(0.39 to 1.72) 0.613 0.902 1.03(0.89 to 1.22) 0.118 Weighted median 0.902 1.03(0.89 to 1.22) 0.118 0.902 0.903 to 1.72) 0.613 Weighted median 0.92(0.39 to 1.72) 0.613 0.908 to 1.22) 0.118 Weighted median 0.902 to 1.03(0.89 to 1.22) 0.618 0.908 to 1.22) 0.618 Weighted median 0.910 to 1.03(0.89 to 1.20) 0.818 0.818 0.818				IVVV	Here	0.91(0.77 to 1.08)	0.278
Weighted median +++ 0.86(0.68 to 1.08) 0.2 TB BMD(45-60) 12 0.74(0.49 to 1.13) 0.192 MR-Egger +++ 0.99(0.88 to 1.12) 0.906 MR-Egger +++ 0.99(0.88 to 1.12) 0.906 TB BMD(60 over) 12 1.02(0.77 to 1.34) 0.902 TB BMD(60 over) 12 +++ 1.02(0.77 to 1.34) 0.902 Weighted median +++ 1.02(0.77 to 1.34) 0.902 TB BMD(60 over) 12 +++ 1.02(0.77 to 1.34) 0.902 Weighted median +++ 1.02(0.77 to 1.34) 0.902 0.118 MR-Egger +++ 1.03(0.89 to 1.22) 0.118 Weighted median ++++ 1.03(0.89 to 1.22) 0.618 Weighted median +++++ 1.03(0.89 to 1.22) 0.618 Weighted median ++++++ 1.03(0.81 to 1.30) 0.818				MR-Egger		 1.39(0.43 to 4.52) 	0.597
Weighted mode 0.74(0.49 to 1.13) 0.192 TB BMD(45-60) 12 IVW 0.99(0.88 to 1.12) 0.906 MR-Egger 1.20(0.84 to 1.03) 0.902 0.130 0.902 TB BMD(60 over) 12 IVW 0.90(0.88 to 1.12) 0.906 TB BMD(60 over) 12 IVW 0.902 0.139 TB BMD(60 over) 12 IVW 0.902 0.902 VBIghted median IVW 0.82(0.39 to 1.22) 0.118 MR-Egger 0.82(0.39 to 1.22) 0.118 Weighted median IVW 0.82(0.39 to 1.22) 0.618 Weighted median IVW 1.03(0.89 to 1.22) 0.618 Weighted median IVW IVW 0.82(0.39 to 1.72) 0.613 Weighted median IVW IVW IVW 0.818 0.818				vveighted median		0.86(0.68 to 1.08)	0.2
TB BMD(45-60) 12 IVW 0.99(0.88 to 1.12) 0.906 MR-Egger 1.92(0.87 to 4.26) 0.139 Weighted median 1.00(0.84 to 1.18) 0.956 Weighted mode 1.02(0.77 to 1.34) 0.902 TB BMD(60 over) 12 IVW 1.09(0.98 to 1.22) 0.118 MR-Egger 0.82(0.39 to 1.22) 0.613 Weighted median 0.82(0.39 to 1.22) 0.618 Weighted median 1.03(0.81 to 1.20) 0.688 Weighted median 1.03(0.81 to 1.20) 0.688				Weighted mode		0.74(0.49 to 1.13)	0.192
I/W Image: 1 model 0.99(0.88 to 112) 0.99(0.98 to 122) 0.99(0.98		TB BMD(45-60)	12				
MR—Egger 1 32(0.87 to 4.26) 0.139 Vieighted median 100(0.84 to 118) 0.956 Weighted mode 1.02(0.77 to 1.34) 0.902 TB BMD(60 over) 12 1.02 0.118 MR—Egger 0.82(0.39 to 1.22) 0.118 MR—Egger 0.82(0.39 to 1.72) 0.613 Weighted median +				IVW	HH	0.99(0.88 to 1.12)	0.906
Weighted median Image: Constraint of the state of the st				MR-Egger	H	 1.92(0.87 to 4.26) 	0.139
Weighted mode 1.02(0.77 to 1.34) 0.902 TB BMD(60 over) 12 1.09(0.98 to 122) 0.118 MR-Egger 0.82(0.39 to 1.72) 0.613 Weighted median Image: Median to 1.03(0.89 to 1.22) 0.618 Weighted median Image: Median to 1.03(0.81 to 1.30) 0.818				Weighted median		1.00(0.84 to 1.18)	0.956
TB BMD(60 over) 12 VW INFEgger INFEGGE				Weighted mode		1.02(0.77 to 1.34)	0.902
IVW Image: Weighted median 1.09(0.98 to 1.22) 0.118 MR<= Egger		TB BMD(60 over)	12				
MR-Egger 0.82(0.39 to 172) 0.613 Weighted median 1.03(0.89 to 120) 0.688 Weighted mode 1.03(0.81 to 1.30) 0.818		, ,		IVW	40-1	1.09(0.98 to 1.22)	0.118
Weighted mode 1.03(0.81 to 1.20) 0.818				MR-Egger		0.82(0.39 to 1.72)	0.613
Weighted mode 1.03(0.81 to 1.30) 0.818				Weighted median	ينفير ا	1.03(0.89 to 1.20)	0.688
Vergined mode 1.03(0.81 to 1.30) 0.818				Weighted median	<u> </u>	1.03(0.03 t0 1.20)	0.000
the second				vveignieu mode			0.018

CHD, coronary heart disease; MI, myocardial infarction; FA BMD, Forearm bone mineral density; FN BMD, Femoral neck bone mineral density: LS BMD, Lumbar spine bone mineral density: TB BMD, Total body bone mineral density; IVW, inverse variance weighted.

proinflammatory cytokines (IL-6 and tumor necrosis factor-a (TNFa)), sclerostin, gamma-carboxy glutamic acid-rich matrix (GLA) protein (MGP), and fibroblast growth factor (FGF)-23 (45-49). Additionally, pathways such as the RANKL/RANK/OPG (osteoprotegerin) and Wnt signaling are implicated in the pathogenesis of vascular calcification and cardiovascular disease (50). Hyperhomocysteinemia has also been identified as a contributor to both vascular and bone diseases (51), emphasizing a shared pathological basis between OP and CVD. Furthermore, observations of patients' drug use and diet have reinforced the link between the two conditions. For instance, anticoagulants like warfarin and unfractionated heparin, commonly used in stroke and myocardial infarction patients, may increase the risk of OP (52). Conversely, excessive calcium supplements, particularly in a calcium-sufficient diet, have been associated with elevated cardiovascular risk, especially myocardial infarction risk (53). Statins, commonly used lipid-lowering drugs in CVD treatment, have been linked to bone changes (54). Various medications, including sclerostin-targeted drugs, SERMs, hypoglycemic drugs, antihypertensive drugs, selective estrogen receptor modulators, and anti-bone resorption drugs, have demonstrated effects on both OP and CVD. Even specific treatments like vitamin D have shown potential in reducing CVD risk (55, 56). Finally, the reliability of results from prior studies is constrained by divergent methodologies and populations (57). Notably, a substantial portion of past observational inquiries has disproportionately focused on the elderly, particularly postmenopausal women, introducing inherent crowd bias that undermines result generalizability. Moreover, inadequacies in sample sizes, potential bias in article selection, and methodological disparities can induce instability in research outcomes. For the first time, we posit CHD as a potential cause of OP from a genetic perspective. Acknowledging that MR studies may not represent the pinnacle of evidence-based medicine, we anticipate that future investigations with higher evidential levels will corroborate our findings. Nevertheless, in juxtaposition with observational research, the clinical significance of our MR results remains considerable. Simultaneously, in auxiliary examinations, conventional anatomical sites (forearm, femoral neck, lumbar spine) can be utilized for Dual-Energy DAX examination. Vice versa, for instance, Romosozumab, approved by the FDA, is accompanied by a black box warning indicating a potential increase in the risk of cardiovascular disease (58). If an osteoporotic patient requires the use of this medication for treatment, clinicians are encouraged to make a decision regarding the drug based on the individual patient's specific condition, even if cardiovascular disease is present. Conversely, disapprove that the use of the drug's potential risks is overly interpreted as an absolute contraindication, instigating apprehension and reluctance towards adoption. It is noteworthy that, following the prevailing gold standards in osteoporosis (OP) diagnosis-utilizing FN BMD, FA BMD, and LS BMD-our results are similar to the MR results of HE B, Gua C, and Bhatta L and others (32, 59). This not only bolsters the robustness of our research findings but also underscores pertinent clinical considerations. Grounded in the established diagnostic approach of DAX presently in common use, it may not sufficiently discern potential skeletal issues in patients with CHD. Particularly within adult cohorts enduring congenital heart disease over an extended duration, susceptibility to bone diseases is heightened (60, 61). Consequently, we advocate that, under the precondition of examining bone density in conventional anatomical regions (forearms, femoral neck, lumbar spine) through DAX for CHD patients, if circumstances allow, simultaneous consideration should be given to bone density assessments via heel ultrasound or DAX throughout the body. This holistic approach is good for

A BMD	CHD	asnp 3	mr.metnoa		07(35%01)	P.valu
			IVW		1.07(0.93 to 1.23)	0.324
			MK-Egger		0.99(0.66 to 1.48)	0.969
			Weighted mode		1.05(0.90 to 1.24)	0.59
	MI	3			,	
			IVW	-	1.02(0.95 to 1.10)	0.515
			MR-Egger		1.13(0.91 to 1.39)	0.475
			Weighted median	HEH	1.02(0.94 to 1.10)	0.616
	Stroko	2	Weighted mode	Here .	1.05(0.96 to 1.15)	0.382
	Stroke	3	IVW/		1.00(0.92 to 1.08)	0.932
			MR-Egger		1.03(0.81 to 1.30)	0.869
			Weighted median	-	1.00(0.92 to 1.09)	0.974
			Weighted mode	HH I	1.01(0.91 to 1.11)	0.924
				1		
A BMD*	CHD	10				
			MR=Enger		1.06(0.95 to 1.18) 1.09(0.81 to 1.45)	0.239
			Weighted median	allera in the	1.06(0.93 to 1.20)	0.405
			Weighted mode	Herei	1.05(0.91 to 1.22)	0.516
	MI	14				
			IVW	÷	1.03(0.98 to 1.07)	0.227
			MR-Egger	HH	1.02(0.91 to 1.14)	0.72
			Weighted median	apr .	1.02(0.95 to 1.09)	0.452
	Stroke	14	v eignieu mode	T	1.00(0.00 to 1.11)	0.49
	SHONG		IVW	4	1.00(0.96 to 1.05)	0.886
			MR-Egger	HH	1.00(0.89 to 1.11)	0.944
			Weighted median	+	1.00(0.94 to 1.07)	0.885
			Weighted mode	HH .	1.01(0.93 to 1.10)	0.844
N BMD	CHD	7			4 40/0 04	
			IVW MR-Enger		1.16(0.91 to 1.48)	0.242
			Weighted median		1.11(0.89 to 1.38)	0.366
			Weighted mode		1.09(0.77 to 1.53)	0.642
	MI	12				
			IVW	101	0.99(0.92 to 1.07)	0.826
			MR-Egger		0.98(0.65 to 1.48)	0.922
			Weighted median	Here and a second s	0.97(0.88 to 1.07)	0.516
	Stroke	12	weighted mode		0.99(0.85 to 1.16)	0.911
	Ollowe	14	IVW	-	1.01(0.93 to 1.09)	0.869
			MR-Egger	HH	0.98(0.88 to 1.09)	0.695
			Weighted median	Here and a second s	0.98(0.88 to 1.09)	0.695
			Weighted mode		0.98(0.84 to 1.15)	0.849
S BMD	CHD	11				
			IVW		1.14(0.99 to 1.31)	0.076
			MR-Egger		1.57(0.72 to 3.42)	0.287
			Weighted mode		1.08(0.80 to 1.45)	0.619
	MI	17	,		,	
			IVW	101	1.09(1.03 to 1.15)	0.004
			MR-Egger		1.10(0.88 to 1.36)	0.421
			Weighted median	101	1.10(1.02 to 1.19)	0.017
	Cheelee	47	Weighted mode		1.12(0.98 to 1.28)	0.115
	Stroke	17	10.00/		0.95/0.90 to 1.02)	0.14
			MR-Enger		1.00(0.78 to 1.27)	0.985
			Weighted median	10	0.93(0.86 to 1.01)	0.104
			Weighted mode		0.92(0.81 to 1.05)	0.215
leel BMD	CHD	168				
			IVW	-0-1	1.08(1.00 to 1.17)	0.049
			MR-Egger		1.09(0.93 to 1.28)	0.288
			Weighted median		1.03(0.93 to 1.19) 1.02(0.88 to 1.19)	0.434
	MI	240	argrade mode			0.70
			IVW	-	1.03(0.99 to 1.07)	0.177
			MR-Egger	HH	0.99(0.93 to 1.06)	0.817
			Weighted median	Here a	0.97(0.92 to 1.03)	0.363
			Weighted mode	-	0.98(0.91 to 1.05)	0.59
	Stroke	239		1		0.00
			IVW MR=Engor	1	1.00(0.95 to 1.04)	0.984
			Weighted median	1	0.98(0.91 to 1.04)	0.443
			Weighted mode	10H	0.97(0.92 to 1.04)	0.419
IB BMD	CHD	39		1.1		
			IVW	H	0.99(0.90 to 1.09)	0.807
			MR-Egger		1.17(0.91 to 1.50)	0.217
			Weighted median	Here a	1.01(0.87 to 1.16)	0.945
	MI	67	weighted mode		U.97(0.82 to 1.15)	0.724
	MI	5/	0.00/		1.04/0.00 to 1.00	0.000
			MR-Enger		1.04(0.99 to 1.08)	0.099
			Weighted median	101	1.05(0.98 to 1.12)	0,18
			Weighted mode	elee .	1.03(0.94 to 1.13)	0.485
	Stroke	58				2.100
			IVW	+	1.00(0.95 to 1.04)	0.944
			MR-Egger		1.04(0.93 to 1.17)	0.5
			Weighted median	Here and the second sec	1.00(0.93 to 1.07)	0.937

FIGURE 4

CHD, coronary heart disease; MI, myocardial infarction; FA BMD, Forearm bone mineral density(p < 5E-8); FA BMD*, Forearm bone mineral density(p < 5E-6); FN BMD, Femoral neck bone mineral density; LS BMD, Lumbar spine bone mineral density; TB BMD, Total body bone mineral density; IVW, inverse variance weighted.

preventing and treating skeletal diseases with them. As highlighted earlier, the advantages of bone ultrasound render it a preferred choice. Furthermore, our MR results offer valuable insights for public health in crafting comprehensive prevention and treatment strategies. These strategies stand to exert positive effects on a wide population, ultimately contributing to the effective management of the substantial burden imposed by both osteoporosis and cardiovascular diseases.

Our study has several limitations. First, this study is primarily from a European population, and our findings cannot be generalized to other populations. Second, due to the limited exposure variance explained by the SNP instrument or the limited

Exposure	Outcome	Cochran Q statistic	Heterogeneity P-value	MR- Egger Intercept	Intercept p-value	MR-PRESSO Global test P-value
FA BMD	CHD	0.17724079	0.915192919	0.010774879	0.755795167	
FA BMD	MI	0.842662038	0.65617286	-0.012808958	0.52730918	
FA BMD	Stroke	0.3326947	0.846752064	-0.003861565	0.843207372	
FA BMD*	CHD	5.469318279	0.791629648	-0.002911733	0.869737391	0.843
FA BMD*	MI	9.538775337	0.731144943	0.000877126	0.89910032	0.755
FA BMD*	Stroke	11.60054438	0.560639223	0.001009422	0.887301414	0.535
FN BMD	CHD	13.13664354	0.040916632	-0.032766747	0.624154903	0.059
FN BMD	MI	11.22098217	0.424940202	0.000872913	0.950565157	0.429
FN BMD	Stroke	12.46940067	0.329412951	-0.013581485	0.375703225	0.358
LS BMD	CHD	11.67929149	0.307093553	-0.022747696	0.430148672	0.357
LS BMD	MI	12.75957677	0.690248768	-0.000394365	0.961316768	0.687
LS BMD	Stroke	11.80310411	0.757418946	-0.003313896	0.717270374	0.765
Heel BMD	CHD	197.3724078	0.054068931	-0.000298103	0.910782468	0.058
Heel BMD	MI	315.2117255	0.000683149	0.0014408	0.234462054	NA
Heel BMD	Stroke	235.0078903	0.542655969	0.001035209	0.361120025	0.513
TB BMD	CHD	41.39537014	0.324748774	-0.009833151	0.149198444	0.332
TB BMD	MI	66.23340869	0.164585572	-0.003632699	0.274125272	0.641
TB BMD	Stroke	53.59576291	0.603573546	-0.002499529	0.448277601	0.61

TABLE 4	Heterogeneity,	pleiotropy	test, and	MR-PRESSO	Global te	est of e	exposure	(Bone	density) on card	iovascular	diseases
---------	----------------	------------	-----------	-----------	-----------	----------	----------	-------	---------	-----------	------------	----------

CHD, coronary heart disease; MI, myocardial infarction; FA BMD*, Forearm bone mineral density (p<5E-6); FN BMD, Femoral neck bone mineral density; LS BMD, Lumbar spine bone mineral density; TB BMD, Total bone mineral density.

sample size of the resulting GWAS (for example, there are only 3 SNPs with strong FA BMD correlations we extracted), it may lead to weak instrumental variable bias, so we relax the settings Conditional extraction of more FA BMD SNPs replicated the reliability of the results. However, larger-scale GWAS are still needed to enhance the ability of correlational MR studies to detect associations. Third, due to the limitations of GWAS summary statistics, MR analysis cannot be stratified according to gender, race, underlying diseases, etc. We studied the causal association between CVD and TB BMD in different age groups; the results showed a strong relationship between CHD and TB BMD. But, we only observed suggestive evidence of a causal association between CHD and MI and the 0-15 population. This may be due to the small number of TB BMD samples in each age group and the fact that they come from a mixed population. In the future, more data from the same population sample size will be needed to evaluate the relationship between CVD and TB BMD in different age groups further. Fourth, OP and CVD data sources employed in Mendelian Randomization analyses of two samples should refrain from including overlapping participants. Accurate estimation poses a significant challenge. Nonetheless, the utilization of robust instrumentation has the potential to effectively mitigate sample overlap, exemplified by F statistics that markedly exceed 10.

5 Conclusion

The study results revealed that CHD was causally associated with Heel BMD and TB BMD, while in the reverse MR analysis, the causal relationship between OP and CVD was not supported. This result posits CHD as a potential etiological factor for OP and prompts that routine bone density assessment at traditional sites (forearm, femoral neck, lumbar spine) using DAX may inadequately discern underlying osteoporosis issues in CHD patients. The recommendation is to synergistically incorporate heel ultrasound or DAX for total body bone density examinations, ensuring clinical diagnostics are both precise and reliable. Moreover, these findings provide valuable insights for public health, contributing to the development of pertinent prevention and treatment strategies.

Data availability statement

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

Author contributions

JZ: Writing – original draft, Writing – review & editing. PX: Writing – original draft, Writing – review & editing. RL: Writing – original draft, Writing – review & editing. JG: Writing – original draft, Writing – review & editing. PC: Writing – original draft, Writing – review & editing. CK: Supervision, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

All data used in this study were obtained from openly available databases and consortiums. We express our sincere appreciation to them.

References

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. *J Am Coll Cardiol.* (2020) 76:2982–3021. doi: 10.1016/j.jacc.2020.11.010

2. Zhao D. Epidemiological features of cardiovascular disease in Asia. JACC Asia. (2021) 1:1-13. doi: 10.1016/j.jacasi.2021.04.007

3. Tsao CW, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, et al. Heart disease and stroke statistics-2023 update: A report from the American heart association. *Circulation*. (2023) 147:e93–e621. doi: 10.1161/CIR.000000000001123

4. Shamia D, Abramowitz Y, Tsaban G. Global and regional cardiovascular risk and mortality: a right, but a long way to go. *Eur J Prev Cardiol.* (2023) 30:274–5. doi: 10.1093/eurjpc/zwac313

5. Liu X, Wang Y, Wang Z, Li L, Yang H, Liu J, et al. Association between sarcopenia-related traits and cardiovascular diseases: a bi-directional Mendelian randomization study. *Front Endocrinol (Lausanne)*. (2023) 14:1237971. doi: 10.3389/ fendo.2023.1237971

 Compston JE, McClung MR, Leslie WD. Osteoporosis. Lancet. (2019) 393:364– 76. doi: 10.1016/S0140-6736(18)32112-3

7. Hendrickx G, Boudin E, Van Hul W. A look behind the scenes: the risk and pathogenesis of primary osteoporosis. *Nat Rev Rheumatol.* (2015) 11:462–74. doi: 10.1038/nrrheum.2015.48

8. Xiao P-L, Cui A-Y, Hsu C-J, Peng R, Jiang N, Xu X-H, et al. Global, regional prevalence, and risk factors of osteoporosis according to the World Health Organization diagnostic criteria: a systematic review and meta-analysis. *Osteoporos Int.* (2022) 33:2137–53. doi: 10.1007/s00198–022-06454–3

9. Adami G, Fassio A, Gatti D, Viapiana O, Benini C, Danila MI, et al. Osteoporosis in 10 years time: a glimpse into the future of osteoporosis. *Ther Adv Musculoskelet Dis.* (2022) 14:1759720X221083541. doi: 10.1177/1759720X221083541

10. Salari N, Darvishi N, Bartina Y, Larti M, Kiaei A, Hemmati M, et al. Global prevalence of osteoporosis among the world older adults: a comprehensive systematic review and metaanalysis. J Orthop Surg Res. (2021) 16:669. doi: 10.1186/s13018-021-02821-8

11. Cianferotti L, Cipriani C, Corbetta S, Corona G, Defeudis G, Lania AG, et al. Bone quality in endocrine diseases: determinants and clinical relevance. *J Endocrinol Invest.* (2023) 46:1283–304. doi: 10.1007/s40618-023-02056-w

12. Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. *Hum Mol Genet.* (2014) 23:R89-98. doi: 10.1093/hmg/ddu328

13. Skrivankova VW, Richmond RC, Woolf BAR, Davies NM, Swanson SA, VanderWeele TJ, et al. Strengthening the reporting of observational studies in epidemiology using mendelian randomisation (STROBE-MR): explanation and elaboration. *BMJ*. (2021), n2233. doi: 10.1136/bmj.n2233

Conflict of interest

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

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1362428/ full#supplementary-material

14. Peacock M, Turner CH, Econs MJ, Foroud T. Genetics of osteoporosis. *Endocr Rev.* (2002) 23:303–26. doi: 10.1210/edrv.23.3.0464

15. Vinkhuyzen AAE, Wray NR, Yang J, Goddard ME, Visscher PM. Estimation and partition of heritability in human populations using whole-genome analysis methods. *Annu Rev Genet.* (2013) 47:75–95. doi: 10.1146/annurev-genet-111212–133258

16. Jensen RV, Hjortbak MV, Bøtker HE. Ischemic heart disease: an update. Semin Nucl Med. (2020) 50:195–207. doi: 10.1053/j.semnuclmed.2020.02.007

17. Sözen T, Özışık L, Başaran NÇ. An overview and management of osteoporosis. *Eur J Rheumatol.* (2017) 4:46–56. doi: 10.5152/eurjrheum.2016.048

18. Medina-Gomez C, Kemp JP, Trajanoska K, Luan J, Chesi A, Ahluwalia TS, et al. Life-course genome-wide association study meta-analysis of total body BMD and assessment of age-specific effects. *Am J Hum Genet.* (2018) 102:88–102. doi: 10.1016/j.ajhg.2017.12.005

19. Chin K-Y, Ima-Nirwana S. Calcaneal quantitative ultrasound as a determinant of bone health status: what properties of bone does it reflect? *Int J Med Sci.* (2013) 10:1778–83. doi: 10.7150/ijms.6765

20. Mei J, Hu H, Ding H, Huang Y, Zhang W, Chen X, et al. Investigating the causal relationship between ankylosing spondylitis and osteoporosis in the European population: a bidirectional Mendelian randomization study. *Front Immunol.* (2023) 14:1163258. doi: 10.3389/fimmu.2023.1163258

21. Cheng HH, Carmona F, McDavitt E, Wigmore D, Perez-Rossello JM, Gordon CM, et al. Fractures related to metabolic bone disease in children with congenital heart disease. *Congenital Heart Dis.* (2016) 11:80–6. doi: 10.1111/chd.12293

22. Burgess S, Small DS, Thompson SG. A review of instrumental variable estimators for Mendelian randomization. *Stat Methods Med Res.* (2017) 26:2333–55. doi: 10.1177/0962280215597579

23. Papadimitriou N, Dimou N, Tsilidis KK, Banbury B, Martin RM, Lewis SJ, et al. Physical activity and risks of breast and colorectal cancer: a Mendelian randomisation analysis. *Nat Commun.* (2020) 11:597. doi: 10.1038/s41467-020-14389-8

24. Burgess S, Davey Smith G, Davies NM, Dudbridge F, Gill D, Glymour MM, et al. Guidelines for performing Mendelian randomization investigations: update for summer 2023. *Wellcome Open Res.* (2019) 4:186. doi: 10.12688/wellcomeopenres.15555.3

25. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synthesis Methods*. (2010) 1:97–111. doi: 10.1002/jrsm.12

26. 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: 10.1002/gepi.21965

27. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol.* (2015) 44:512–25. doi: 10.1093/ije/dyv080

28. Bowden J, Del Greco MF, Minelli C, Davey Smith G, Sheehan N, Thompson J. A framework for the investigation of pleiotropy in two-sample summary data Mendelian randomization. *Stat Med.* (2017) 36:1783–802. doi: 10.1002/sim.7221

29. Chen S, Zhou G, Han H, Jin J, Li Z. Causal effects of specific gut microbiota on bone mineral density: a two-sample Mendelian randomization study. *Front Endocrinol (Lausanne).* (2023) 14:1178831. doi: 10.3389/fendo.2023.1178831

30. Verbanck M, Chen C-Y, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet.* (2018) 50:693–8. doi: 10.1038/s41588–018-0099–7

31. Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. *Eur J Epidemiol.* (2017) 32:377–89. doi: 10.1007/s10654-017-0255-x

32. Gua C, Li T, Wang J. Causal association between heart failure and bone mineral density: Insights from a two-sample bidirectional Mendelian randomization study. *Genomics.* (2022) 114:110522. doi: 10.1016/j.ygeno.2022.110522

33. Yu Y, Chu T, Dong J, Deng H, Pan Y, Wang Y. A Mendelian randomization study on the association of bone mineral density with periodontitis. *Oral Dis.* doi: 10.1111/odi.14582

34. Bhatta L, Cepelis A, Vikjord SA, Malmo V, Laugsand LE, Dalen H, et al. Bone mineral density and risk of cardiovascular disease in men and women: the HUNT study. *Eur J Epidemiol.* (2021) 36:1169–77. doi: 10.1007/s10654-021-00803-y

35. Campos-Obando N, Kavousi M, Roeters van Lennep JE, Rivadeneira F, Hofman A, Uitterlinden AG, et al. Bone health and coronary artery calcification: The Rotterdam Study. *Atherosclerosis.* (2015) 241:278–83. doi: 10.1016/j.atherosclerosis.2015.02.013

36. Gebre AK, Lewis JR, Leow K, Szulc P, Scott D, Ebeling PR, et al. Abdominal aortic calcification, bone mineral density, and fractures: A systematic review and metaanalysis of observational studies. *J Gerontol A Biol Sci Med Sci.* (2023) 78:1147–54. doi: 10.1093/gerona/glac171

37. Myint PK, Clark AB, Kwok CS, Loke YK, Yeong JK-Y, Luben RN, et al. Bone mineral density and incidence of stroke: European prospective investigation into cancer-norfolk population-based study, systematic review, and meta-analysis. *Stroke*. (2014) 45:373–82. doi: 10.1161/STROKEAHA.113.002999

38. Pickering M-E, Oris C, Chapurlat R. Periostin in osteoporosis and cardiovascular disease. J Endocr Soc. (2023) 7:bvad081. doi: 10.1210/jendso/bvad081

39. Veronese N, Stubbs B, Crepaldi G, Solmi M, Cooper C, Harvey NC, et al. Relationship between low bone mineral density and fractures with incident cardiovascular disease: A systematic review and meta-analysis. *J Bone Miner Res.* (2017) 32:1126–35. doi: 10.1002/jbmr.3089

40. Wiklund P, Nordström A, Jansson J-H, Weinehall L, Nordström P. Low bone mineral density is associated with increased risk for myocardial infarction in men and women. *Osteoporos Int.* (2012) 23:963–70. doi: 10.1007/s00198–011-1631–0

41. Yang Y, Huang Y. Association between bone mineral density and cardiovascular disease in older adults. *Front Public Health.* (2023) 11:1103403. doi: 10.3389/ fpubh.2023.1103403

42. Zhang Y, He B, Wang H, Shi J, Liang H. Associations between bone mineral density and coronary artery disease: a meta-analysis of cross-sectional studies. *Arch Osteoporos.* (2020) 15:24. doi: 10.1007/s11657-020-0691-1

43. Broussard DL, Magnus JH. Coronary heart disease risk and bone mineral density among U.S. Women and men. *J Women's Health*. (2008) 17:479–90. doi: 10.1089/ jwh.2007.0593

44. Azeez TA. Osteoporosis and cardiovascular disease: a review. Mol Biol Rep. (2023) 50:1753–63. doi: 10.1007/s11033–022-08088–4

45. Thompson B, Towler DA. Arterial calcification and bone physiology: role of the bone-vascular axis. *Nat Rev Endocrinol.* (2012) 8:529–43. doi: 10.1038/nrendo.2012.36

46. Li J, Shi L, Sun J. The pathogenesis of post-stroke osteoporosis and the role oxidative stress plays in its development. *Front Med (Lausanne)*. (2023) 10:1256978. doi: 10.3389/fmed.2023.1256978

47. Manubolu VS, Mao S, Kinninger A, Dahal S, Ahmad K, Havistin R, et al. Association between coronary artery calcium and thoracic spine bone mineral density: Multiethnic Study of Atherosclerosis (MESA). *Nutrition Metab Cardiovasc Dis.* (2023) 33:532–40. doi: 10.1016/j.numecd.2022.12.006

48. Aronow WS. Osteoporosis, osteopenia, and atherosclerotic vascular disease. Arch Med Sci. (2011) 7:21–6. doi: 10.5114/aoms.2011.20599

49. den Uyl D, Nurmohamed MT, van Tuyl LH, Raterman HG, Lems WF. (Sub) clinical cardiovascular disease is associated with increased bone loss and fracture risk; a systematic review of the association between cardiovascular disease and osteoporosis. *Arthritis Res Ther.* (2011) 13:R5. doi: 10.1186/ar3224

50. Lv F, Cai X, Yang W, Gao L, Chen L, Wu J, et al. Denosumab or romosozumab therapy and risk of cardiovascular events in patients with primary osteoporosis: Systematic review and meta- analysis. *Bone.* (2020) 130:115121. doi: 10.1016/j.bone.2019.115121

51. Alkaissi H, McFarlane SI. Hyperhomocysteinemia and accelerated aging: the pathogenic role of increased homocysteine in atherosclerosis, osteoporosis, and neurodegeneration. *Cureus.* (2023) 15:e42259. doi: 10.7759/cureus.42259

52. Signorelli SS, Scuto S, Marino E, Giusti M, Xourafa A, Gaudio A. Anticoagulants and osteoporosis. Int J Mol Sci. (2019) 20:5275. doi: 10.3390/ijms20215275

53. Kittithaworn A, Toro-Tobon D, Sfeir JG. Cardiovascular benefits and risks associated with calcium, vitamin D, and antiresorptive therapy in the management of skeletal fragility. *Womens Health (Lond).* (2023) 19:17455057231170059. doi: 10.1177/17455057231170059

54. Anagnostis P, Florentin M, Livadas S, Lambrinoudaki I, Goulis DG. Bone health in patients with dyslipidemias: an underestimated aspect. *Int J Mol Sci.* (2022) 23:1639. doi: 10.3390/ijms23031639

55. García-Gómez MC, Vilahur G. Osteoporosis and vascular calcification: A shared scenario. *Clínica e Investigación en Arterioscler (English Edition)*. (2020) 32:32–41. doi: 10.1016/j.artere.2019.03.008

56. Gilbert ZA, Muller A, Leibowitz JA, Kesselman MM. Osteoporosis prevention and treatment: the risk of comorbid cardiovascular events in postmenopausal women. *Cureus*. 14:e24117. doi: 10.7759/cureus.24117

57. Chai H, Ge J, Li L, Li J, Ye Y. Hypertension is associated with osteoporosis: a case-control study in Chinese postmenopausal women. *BMC Musculoskelet Disord*. (2021) 22:253. doi: 10.1186/s12891-021-04124-9

58. LeBoff MS, Greenspan SL, Insogna KL, Lewiecki EM, Saag KG, Singer AJ, et al. The clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int.* (2022) 33:2049–102. doi: 10.1007/s00198-021-05900-y

59. He B, Yin L, Zhang M, Lyu Q, Quan Z, Ou Y. Causal effect of blood pressure on bone mineral density and fracture: A mendelian randomization study. *Front Endocrinol (Lausanne)*. (2021) 12:716681. doi: 10.3389/fendo.2021.716681

60. Sandberg C, Johansson K, Christersson C, Hlebowicz J, Thilén U, Johansson B. Low bone mineral density in adults with complex congenital heart disease. *Int J Cardiol.* (2020) 319:62–6. doi: 10.1016/j.ijcard.2020.06.053

61. Truong T-H, Thi Nguyen M-N, Kim N-T, Thi Nguyen T-H, Do D-L, Le T-T, et al. Low bone mineral density and its related factors in adults with congenital heart disease in Vietnam: A cross-sectional study. *Health Sci Rep.* (2022) 5:e732. doi: 10.1002/hsr2.732