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Osteoporosis and Trabecular Bone Score in Relation to Rose Questionnaire Angina: Evidence from the Bushehr Elderly Health (BEH) Program

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Article

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Abstract

Osteoporosis and ischemic heart disease share several risk factors and biological pathways, but their relationship remains uncertain. We examined whether angina defined by the Rose Angina Questionnaire (RAQ) was associated with bone mineral density (BMD), osteoporosis, and trabecular bone score (TBS) in 1,989 community-dwelling adults aged ≥ 50 years participating in the Bushehr Elderly Health Program in Iran. Angina was assessed using the validated Persian RAQ. BMD was measured by dual-energy X-ray absorptiometry at the lumbar spine, femoral neck, and total hip, and TBS was derived from lumbar spine images. Multivariable logistic regression assessed associations with overall and site-specific osteoporosis and abnormal TBS.

Overall, 10.2% were RAQ-positive and 27.5% had osteoporosis. RAQ positivity was not independently associated with overall osteoporosis (adjusted OR 0.98, 95% CI 0.67–1.44; P = 0.932), lumbar-spine osteoporosis, total-hip osteoporosis, or abnormal TBS. In sex-specific analyses, RAQ positivity was associated with femoral-neck osteoporosis among men (adjusted OR 2.17, 95% CI 1.07–4.38; P = 0.032), but not women. These findings do not support a generalized association between RAQ-defined angina and skeletal health. The observed sex- and site-specific association in men is hypothesis-generating and requires confirmation in prospective studies.

Introduction

Osteoporosis and ischemic heart disease (IHD) are among the leading chronic conditions of later life. Each one imposes a heavy burden of morbidity, mortality, disability and healthcare cost, and the two frequently coexist [1, 2]. Over the past decade interest has grown in the idea that skeletal and vascular health may be biologically connected. Proposed shared mechanisms include chronic low-grade inflammation, oxidative stress, endothelial dysfunction, disordered mineral metabolism, shifts in the hormonal milieu and accelerated biological aging [3–6]. Despite considerable interest in the concept of a common bone–vascular axis, epidemiological findings remain inconsistent. Although many studies have reported inverse associations between bone mineral density (BMD) and cardiovascular disease [7–10], others have demonstrated substantial attenuation or complete disappearance of these relationships after rigorous adjustment for shared cardiometabolic risk factors [11–13]. The common occurrence of the two conditions may therefore owe more to shared upstream determinants than to a direct causal pathway that operates uniformly.

Part of the inconsistency arises from the different ways cardiovascular disease is defined. Many investigations rely on objective markers such as coronary artery calcium score (CACS), angiographically confirmed coronary disease or adjudicated clinical events. On the other hand, the Rose Angina Questionnaire (RAQ) takes a different approach. It is a validated, inexpensive, WHO-endorsed instrument developed specifically for detecting symptoms of stable angina in large population studies where imaging is impractical. The tool has high specificity (80–90%) and moderate sensitivity (roughly 50%) for IHD [14–17], and it has shown acceptable reliability and prognostic value in Iranian cohorts [18–20].

Because the RAQ records symptoms rather than confirmed coronary pathology, the phenotype it identifies is broader and more heterogeneous than other objective diagnostic measures. Whether this symptom-based phenotype carries the same skeletal associations as objectively verified coronary disease remains an open question, one that matters in practice, because symptom assessment is often the only feasible method in large-scale epidemiological research.

Shared risk factors further cloud our interpretation. Aging, obesity, diabetes, hypertension, declining sex hormones, smoking, physical inactivity and socioeconomic disadvantage are all strongly linked to both conditions and may explain a substantial fraction of the crude associations reported in the literature [1–3, 6, 21]. In addition, any relationship between vascular and skeletal health is unlikely to be the same at every skeletal site. The femoral neck, a weight-bearing region with mixed cortical–trabecular architecture, differs from the lumbar spine in mechanical loading and in susceptibility to age-related artifacts on dual-energy X-ray absorptiometry (DXA) [22, 23]. Sex differences in hormonal status, bone remodeling rates and cardiovascular risk profiles may also modify the picture [6, 24]. Many earlier studies treated osteoporosis as a single composite outcome and paid little attention to trabecular bone score (TBS), a texture index derived from lumbar-spine DXA images that provides an indirect assessment of trabecular microarchitecture independent of BMD and improves fracture-risk prediction beyond conventional densitometry [25, 26].

Few population-based studies have examined RAQ-defined angina in relation to both overall and site-specific osteoporosis and to trabecular microarchitecture within a single analytical framework, or have formally tested whether associations differ by skeletal site or by sex. Filling these gaps may help clarify some of the apparent contradictions in the existing literature. Using data from the Bushehr Elderly Health (BEH) Program [27, 28], we therefore asked whether RAQ-defined angina was independently associated with overall osteoporosis, with osteoporosis at the lumbar spine, femoral neck and total hip, and with TBS after adjustment for shared confounders, and whether any such associations varied by site or by sex.

Methods

Study Design

This analytical cross-sectional study was conducted using baseline data of the second sampling phase from the Bushehr Elderly Health (BEH) study. The BEH study is a population-based investigation of cardiovascular, metabolic, musculoskeletal and cognitive outcomes among older adults living in Bushehr. In 2018, the second recruitment, PoCOsteo study, engaged new population aged 50 years or older residing in Bushehr through a stratified multistage cluster random sampling proportional to household numbers across 75 municipal strata in Bushehr. [27–29].

Study Population and Setting

The study population comprised men and women aged ≥ 50 participating in the second recruitment of the BEH program. In this sampling, 2,000 eligible individuals were selected. Inclusion criteria were: age ≥ 50 years; both sexes; residence in Bushehr for at least one year prior to enrollment; no intention to leave the city within two years; adequate physical and mental capacity to participate; and provision of written informed consent. Exclusion criteria included non-residence in Bushehr, unwillingness to participate, and residence in nursing homes. For the present analysis, participants were additionally required to have complete data on BMD, TBS, and responses to the RAQ. Individuals with missing data on key exposures, outcomes, or essential covariates were excluded from the respective analyses.

Measurements and Data Collection

Data were collected through structured, validated questionnaires administered by trained interviewers, clinical and anthropometric assessments performed by trained nurses according to standardized protocols, blood sampling for laboratory analyses, and DXA. All procedures followed quality-control standards.

Angina symptoms were evaluated using the Persian version of the RAQ, based on the full World Health Organization–recommended instrument. The questionnaire included seven core items, supplemented by two additional questions to improve characterization of chest pain and identify a possible history of myocardial infarction within the previous year. Participants were classified as RAQ-positive (RAQ+) or RAQ-negative (RAQ−) according to standard scoring criteria. The RAQ is widely validated across populations, including Middle Eastern cohorts, for epidemiological identification of angina pectoris [16–20].

BMD was measured using dual-energy X-ray absorptiometry (DXA) with a Hologic Discovery WI system (Hologic, Bedford, Virginia, USA), following standardized protocols. Measurements were obtained at the lumbar spine (L1–L4), femoral neck, and total hip with appropriate positioning. All scans were performed on the same day by a trained operator, with each assessment requiring approximately 20 minutes. Results were reported as mean density values for each site along with corresponding T-scores, calculated relative to a reference population of young Caucasian women [30].

TBS was derived from lumbar spine (L1–L4) DXA images using TBS iNsight® software (version 2.2; Medimaps Group, Switzerland) and expressed as a quantitative index of trabecular microarchitecture. TBS values were analyzed both as continuous variables and as categorical variables using standard cut-off values: normal (> 1.31) and abnormal (all other values). TBS was used to complement BMD by capturing skeletal characteristics not reflected by bone quantity alone.

Osteoporosis was defined according to World Health Organization criteria as a T-score ≤ − 2.5 at any of the three measured skeletal sites, with T-scores calculated using a reference population of Caucasian women aged 20 to 29 years [30]. Site-specific osteoporosis outcomes (lumbar spine, femoral neck, and

total hip) were also evaluated. Continuous BMD values were retained for analyses comparing mean BMD across exposure groups.

Variable Definitions

Variables were selected based on biological plausibility and prior literature and included demographic, anthropometric, clinical, lifestyle, and socioeconomic factors.

Hypertension was defined as systolic blood pressure (BP) ≥ 140 mmHg or diastolic BP ≥ 90 mmHg (averaged from three measurements) or use of antihypertensive medication. Diabetes mellitus was defined as fasting plasma glucose ≥ 126 mg/dL, Hemoglobin A1c (HbA1c) level ≥ 6.5%, or use of antidiabetic medication. Dyslipidemia was defined by abnormal lipid profile, defined according to the NCEP ATP III criteria that is Total cholesterol (TC) ≥ 200 mg/dL, LDL cholesterol (LDL-C) ≥ 130 mg/dL, HDL cholesterol (HDL-C) < 40 mg/dL in men and < 50 mg/dL in women, Triglycerides (TG) ≥ 150 mg/dL, or lipid-lowering therapy. Current smoking, defined as the use of cigarettes and/or hookah, was assessed by self-report. Physical activity was evaluated using the International Physical Activity Questionnaire (IPAQ) and categorized into tertiles based on MET-minutes/week. Socioeconomic status (SES) was assessed across multiple domains (education, income, assets, housing) and divided into quintiles. Laboratory measures included lipid profile and vitamin D levels.

Statistical Analysis

Participant characteristics were summarized using means ± standard deviation for continuous variables and frequencies/percentages for categorical variables. Group comparisons used independent t-tests (continuous) and χ^2 tests (categorical). Mean BMD values were compared between RAQ + and RAQ− groups using t-tests.

Potential confounders included age, sex, BMI, SES, smoking, physical activity, and cardiometabolic conditions (diabetes, hypertension, dyslipidemia).

Logistic regression was used to examine the associations between RAQ status and the osteoporosis outcomes. Univariable models came first; multivariable models were then built by stepwise selection, with a variable allowed to enter if its p-value was less than 0.20 and retained only if the p-value stayed below 0.05. We also tested for effect modification by sex by including interaction terms. A p-value under 0.10 for the interaction was taken as a signal that stratification by sex might be worthwhile, and we proceeded accordingly when that threshold was met.

Every test was two-sided. We considered $p < 0.05$ statistically significant. All analyses were performed in Stata 17 (StataCorp, College Station, Texas).

Ethical Considerations

The PoCOsteo study was conducted in accordance with the principles of the Declaration of Helsinki. The original study obtained informed consent from all participants. Ethical approval for the present secondary analyses was obtained from the Ethics Committee of Tehran University of Medical Sciences (Ethics Code: IR.TUMS.EMRI.REC.1403.139).

Results

Of the 2000 participants recruited in the PoCOsteo study, 1989 (99.5%) had complete data on BMD, TBS, RAQ status, and key covariates and were included in the present analysis. Table 1 presents the baseline characteristics of the participants. 202 (10.2%) of the participants had a positive RAQ and 546 (27.5%) were osteoporotic.

Table 1
Baseline characteristics of the study participants

Variable	Overall
Age, mean ± SD (years)	62.1 ± 8.1
Female sex, n (%)	1138 (57.2)
BMI, mean ± SD (kg/m²)	28.3 ± 4.9
Hypertension, n (%)	1196 (60.1)
Diabetes mellitus, n (%)	680 (34.2)
Current smoking, n (%)	362 (18.2)
Low physical activity (lowest MET tertile), n (%)	661 (33.2)
Lowest SES quintile, n (%)	401 (20.1)
RAQ Positive, n (%)	202 (10.2)
Overall Osteoporosis, n (%)	546 (27.5)
Lumbar Spine Osteoporosis, n (%)	397 (20)
Total Hip Osteoporosis, n (%)	87 (4.4)
Femoral Neck Osteoporosis, n (%)	345 (17.3)
Abnormal TBS, n (%)	887 (44.6)

Compared with RAQ-negative participants, those with RAQ-positive status were slightly older (63.8 ± 8.4 vs. 61.9 ± 8.0 years), had higher BMI (29.4 ± 5.1 vs. 28.1 ± 4.8 kg/m²), and had a higher prevalence of hypertension (68.3% vs. 59.3%) and diabetes mellitus (42.6% vs. 33.1%), all $p < 0.05$. RAQ-positive participants were also more likely to have low physical activity (40.1% vs. 32.3%, $p < 0.001$) and belonged to higher socioeconomic status quintiles ($p < 0.001$). There were no significant differences in sex distribution or smoking status between the groups.

Figure 1 shows the comparison of mean BMD values by RAQ status overall and separately by sex (Fig. 1). In the overall population, RAQ-positive participants had higher lumbar spine BMD than RAQ-negative participants (0.969 ± 0.170 vs. 0.926 ± 0.165 g/cm², $p < 0.001$), with no significant differences at the total hip ($p = 0.257$) or femoral neck ($p = 0.440$).

Considering the relation in each sex, RAQ positivity was associated with higher BMD at the lumbar spine (mean difference 0.041 g/cm², 95% CI: 0.011–0.071, $p = 0.007$), total hip (0.041 g/cm², 95% CI: 0.012–0.070, $p = 0.006$), and femoral neck (0.031 g/cm², 95% CI: 0.004–0.058, $p = 0.023$) in women. In men, RAQ positivity was associated with lower BMD at the total hip (− 0.031 g/cm², 95% CI: −0.062 to − 0.001, $p = 0.045$) and femoral neck (− 0.027 g/cm², 95% CI: −0.055 to 0.001, $p = 0.059$), whereas lumbar spine BMD was non-significantly higher (0.032 g/cm², 95% CI: −0.004 to 0.068, $p = 0.079$). Mean TBS did not differ between RAQ-positive and RAQ-negative participants overall (1.3186 ± 0.1199 vs. 1.3175 ± 0.1086, $p = 0.898$) or in sex-stratified analyses (women: $p = 0.544$; men: $p = 0.910$) (Fig. 1).

In unadjusted analyses, RAQ positivity was not significantly associated with overall osteoporosis (OR = 0.83, 95% CI: 0.59–1.17, $p = 0.284$). Site-specific comparisons revealed no significant differences in osteoporosis prevalence at the total hip ($p = 0.763$) or femoral neck ($p = 0.701$). RAQ-positive participants had a lower prevalence of lumbar spine osteoporosis ($p = 0.026$). RAQ positivity was similar between the normal and abnormal TBS groups (9.72% vs. 10.37%, $p = 0.629$).

After adjustment for potential confounders, RAQ positivity was not independently associated with overall osteoporosis (adjusted OR 0.98, 95% CI: 0.67–1.44, $p = 0.932$). No significant sex interaction was observed ($p = 0.533$). Similar null results were found for lumbar spine osteoporosis (adjusted OR 0.81, 95% CI: 0.52–1.27, $p = 0.354$) and total hip osteoporosis (adjusted OR 1.21, 95% CI: 0.52–2.82, $p = 0.656$).

For femoral neck osteoporosis, a possible sex interaction was suggested ($p = 0.097$); hence, sex-stratified multivariable models were applied. RAQ positivity was not associated with femoral neck osteoporosis in women (adjusted OR 0.99, 95% CI: 0.57–1.72, $p = 0.969$). However, among men, RAQ positivity remained independently associated with higher odds of femoral neck osteoporosis (adjusted OR 2.17, 95% CI: 1.07–4.38, $p = 0.032$) after controlling for confounders. Univariable and multivariable logistic regression analyses examining factors associated with osteoporosis at the lumbar spine, total hip, and femoral neck are presented in detail in Table 2.

Table 2
Univariable and multivariable logistic regression analyses of factors associated with osteoporosis at different skeletal sites

		Variables	Univariable (Crude)		Multivariable (Adjusted)	
			OR (95%CI)	P-value	OR (95% CI)	P-value
Osteoporosis Site	**Lumbar Spine**	Age	1.06 (1.05–1.08)	**< 0.001**	1.06 (1.04–1.07)	**< 0.001**
		Sex	0.51 (0.40–0.64)	**< 0.001**	0.28 (0.21–0.37)	**< 0.001**
		BMI	0.87 (0.85–0.90)	**< 0.001**	0.86 (0.83–0.88)	**< 0.001**
		DM	0.68 (0.53–0.86)	**0.002**	0.69 (0.53–0.90)	**0.006**
		HTN	0.99 (0.79–1.24)	0.975	NR	
		Current Smoking	1.41 (1.08–1.85)	**0.013**	1.34 (0.98–1.82)	0.062
		PA (MET) (T3)	1.07 (0.82–1.41)	0.600	NR	
		SES (Q5)	0.31 (0.21–0.44)	**< 0.001**	0.62 (0.41–0.93)	**0.021**
		Dyslipidemia	0.94 (0.74–1.20)	0.640	NR	
		Vitamin D	1.05 (0.83–1.31)	0.699	NR	
		RAQ	0.62 (0.41–0.94)	**0.026**	0.81 (0.52–1.27)	0.354
	Total Hip	Age	1.15 (1.12–1.19)	**< 0.001**	1.18 (1.14–1.21)	**< 0.001**
		Sex	0.22 (0.12–	**< 0.001**	0.08 (0.04–0.16)	**< 0.001**

		0.40)				
	BMI	0.87 (0.82–0.92)	**< 0.001**	0.87 (0.82–0.92)		**< 0.001**
	DM	0.85 (0.53–1.34)	0.485	NR		
	HTN	1.78 (1.10–2.87)	**0.018**	NR		
	Current Smoking	1.46 (0.88–2.42)	0.138	1.81 (1.01–3.24)		**0.048**
	PA (MET) (T3)	0.37 (0.21–0.67)	**0.001**	NR		
	SES (Q5)	0.08 (0.03–0.22)	**< 0.001**	0.43 (0.15–1.25)		0.121
	Dyslipidemia	1.14 (0.71–1.85)	0.578	NR		
	Vitamin D	1.08 (0.69–1.69)	0.721	NR		
	RAQ	0.89 (0.42–1.87)	0.763	1.21 (0.52–2.82)		0.656
Femoral Neck	Age	1.12 (1.10–1.14)	**< 0.001**	M	1.07 (1.04–1.10)	**< 0.001**
				F	1.17 (1.14–1.20)	**< 0.001**
	Sex	0.30 (0.23–0.39)	**< 0.001**	Stratified into **M** & **F**		
	BMI	0.92 (0.90–0.95)	**< 0.001**	M	0.82 (0.75–0.88)	**< 0.001**
				F	0.91 (0.88–0.94)	**< 0.001**

	DM	0.86 (0.67–1.1)	0.224	NR		
	HTN	1.62 (1.26–2.07)	**< 0.001**	M	1.67 (0.93–3.02)	0.088
				F	NR	
	Current Smoking	1.19 (0.89–1.60)	0.238	NR		
	PA (MET) (T3)	0.63 (0.47–0.84)	**0.001**	NR		
	SES (Q5)	0.25 (0.17–0.38)	**< 0.001**	M	0.44 (0.20–0.95)	**0.037**
				F	NR	
	Dyslipidemia	1.04 (0.81–1.34)	0.755	NR		
	Vitamin D	1.17 (0.92–1.49)	0.202	NR		
	RAQ	1.08 (0.74–1.57)	0.701	**M**	**2.17 (1.07–4.38)**	**0.032**
				F	0.99 (0.57–1.72)	0.969

Abbreviations in Table 2

NR, Not Retained in the final multivariable model; OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; HTN, hypertension; BMI, body mass index; PA, physical activity; MET, metabolic equivalent; T3, third tertile; SES, socioeconomic status; Q5, fifth quintile; RAQ, Rose Angina Questionnaire; M, Male (Men); F, Female (Women).

RAQ positivity was not associated with abnormal TBS in the overall population (adjusted OR 0.976, 95% CI: 0.699–1.363, p = 0.887). No significant sex interaction was observed (p = 0.994). Table 3 presents the crude and adjusted logistic regression analyses of factors associated with abnormal TBS.

Table 3
Univariable and multivariable logistic regression analyses of variables associated with abnormal trabecular bone score

	Variables	Univariable (Crude)		Multivariable (Adjusted)	
		OR (95%CI)	P-value	OR (95% CI)	P-value
Abnormal Trabecular Bone Score (TBS)	Age	1.050 (1.037–1.063)	**< 0.001**	1.065 (1.050–1.080)	**< 0.001**
	Sex	0.276 (0.228–0.332)	**< 0.001**	0.268 (0.215–0.335)	**< 0.001**
	BMI	1.078 (1.057–1.1)	**< 0.001**	1.068 (1.044–1.094)	**< 0.001**
	DM	1.128 (0.933–1.364)	0.215	NR	
	HTN	1.465 (1.22–1.76)	**< 0.001**	1.245 (1.006–1.542)	**0.044**
	Current Smoking	1.195 (0.944–1.51)	0.139	1.663 (1.265–2.187)	**< 0.001**
	PA (MET) (T3)	1.03 (0.83–1.28)	0.771	NR	
	SES (Q5)	0.430 (0.322–0.576)	**< 0.001**	0.651 (0.467–0.907)	**0.011**
	Dyslipidemia	1.278 (1.05–1.55)	**0.013**	NR	
	RAQ	0.93 (0.69–1.25)	0.616	0.976 (0.699–1.363)	0.887

Abbreviations in Table 3: NR, Not Retained in the final multivariable model; OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; HTN, hypertension; BMI, body mass index; PA, physical activity; MET, metabolic equivalent; T3, third tertile; SES, socioeconomic status; Q5, fifth quintile; RAQ, Rose Angina Questionnaire

Discussion

The relationship between cardiovascular disease and skeletal health is of growing interest given their shared age-related rise, frequent coexistence, and overlapping biological pathways. The epidemiological evidence, however, is still mixed. Much of the inconsistency seems to come from differences in how the cardiovascular phenotype is defined, which skeletal sites are examined, how thoroughly shared risk factors are controlled, and the overall study design.

In this population-based sample of older adults living in the community, RAQ-defined angina showed no statistically significant association with overall osteoporosis once the main confounders were taken into account. An apparent link with lumbar-spine osteoporosis largely disappeared after adjustment. The only

association that remained was between RAQ-defined angina and femoral neck osteoporosis in men; nothing comparable was seen in women or at the lumbar spine or total hip. RAQ-defined angina was also unrelated to trabecular bone score, whether treated as a continuous or a categorical variable. The absence of an independent association with overall osteoporosis after multivariable adjustment is consistent with previous evidence that shared upstream determinants may contribute substantially to observed bone–vascular relationships. Although mechanistic studies highlight common pathways, observational, meta-analytic, and Mendelian randomization studies frequently show substantial attenuation or elimination of associations after rigorous adjustment for related confounders [11–13].

Crude comparisons of continuous BMD provided additional insight into the role of confounding. Before adjustment, women with RAQ-defined angina exhibited significantly higher BMD at all evaluated skeletal sites, whereas men showed a contrasting pattern characterized by lower hip and femoral neck BMD. The apparently paradoxical findings among women are consistent with confounding by adiposity and other cardiometabolic factors, including diabetes and hypertension, which are closely linked to cardiovascular risk and may also influence BMD [31–33]. These differences largely disappeared after adjustment, supporting the interpretation that shared cardiometabolic factors may partly explain a substantial portion of the observed relationships.

In unadjusted analyses, RAQ positivity was associated with lower lumbar spine osteoporosis prevalence and higher BMD; however, these associations disappeared after adjustment, indicating they may reflect differences in baseline risk profiles rather than an independent relationship. Another possible explanation might be the susceptibility of the Lumbar spine DXA to degenerative artifacts that can overestimate BMD [34, 35]. In addition, due to RAQ capturing a symptom-based phenotype rather than cumulative atherosclerosis, non-differential misclassification may attenuate associations. The cross-sectional design and potential adjustment for mediators limit causal interpretation; therefore, absence of statistical association does not exclude biological interaction. These findings highlight the need to identify specific cardiovascular phenotypes and skeletal outcomes in relevant populations.

The most novel finding of the present study was the independent association between RAQ-defined angina and femoral neck osteoporosis that persisted in men but not at other sites or in women. This observation suggests that the interaction between angina pectoris and skeletal health may be site-specific and sex-specific rather than generalized across the skeleton. These findings are consistent with recent studies that have reported stronger links between objective cardiovascular measures and femoral neck BMD than with lumbar spine measurements [36–39].

Several explanations may account for this apparent site specificity. Compared with lumbar spine BMD, femoral neck BMD is less susceptible to artifactual elevation from degenerative changes such as osteophytes, osteoarthritis, and aortic calcification in older adults [34]. The femoral neck has distinct structural and biomechanical characteristics. As a cortical-rich, weight-bearing region subjected to complex mechanical loading, it undergoes substantial age- and hormone-related cortical thinning, trabecular deterioration, and increased cortical porosity. These age-related changes contribute to

impaired bone strength and are closely associated with hip fracture risk [22, 23, 40–42]. Its mixed cortical–trabecular architecture means that even modest deterioration may substantially impair skeletal strength, suggesting vulnerability specific to this site rather than generalized bone loss. One possible explanation for the male-specific association is that sex differences in bone remodeling trajectories may influence how vascular disease is reflected in skeletal health [24, 42]. In women, postmenopausal estrogen deficiency is the predominant driver of bone loss [6, 24, 42] and may obscure more modest vascular influences, whereas the more gradual pattern of bone loss in men [24, 42] may allow chronic cardiometabolic and vascular factors to contribute more detectably to skeletal deterioration. Although biologically plausible and consistent with emerging literature, the femoral neck association was the only significant site-specific finding after multiple analyses; therefore, causality cannot be inferred and replication in longitudinal cohorts is needed to confirm sex-specific mechanisms.

The null findings for TBS further suggest that RAQ-defined angina may not be linked to detectable deterioration in trabecular microarchitecture in this population. Combined with the site-specific BMD results, the lack of association with TBS indicates that symptom-defined angina does not appear to affect all aspects of skeletal aging uniformly. Although lower TBS has been associated with adverse cardiovascular outcomes in the cohort studied by Ye et al. [43], that study examined objective cardiovascular endpoints rather than symptom-based angina. Overall, these results highlight the importance of carefully matching the precision of both the skeletal and the cardiovascular phenotype under investigation.

From a practical public-health perspective the results do not support using RAQ-defined angina as a flag for osteoporosis screening. Existing risk-assessment tools and clinical guidelines should continue to guide practice. The femoral-neck association seen in men is worth exploring further but is not strong enough to change current recommendations. Overall, the attenuation of associations after adjustment highlights the contribution of shared modifiable risk factors to the relationship between RAQ-defined angina and skeletal outcomes.

The study has several strengths: a large, population-based cohort recruited by multistage sampling, detailed skeletal phenotyping that included both multi-site BMD and TBS, use of a validated Persian version of the RAQ, and a rich set of confounders enabling rigorous adjustment. Examining a symptom-based cardiovascular phenotype also extends the existing literature. Limitations are equally clear. The cross-sectional design prevents any conclusion about temporal sequence or causality. Symptom-based classification, although validated for epidemiological work, inevitably involves more misclassification than imaging-based definitions. Residual confounding remains possible because inflammatory markers, sex-hormone levels and direct measures of vascular calcification were not available. As a secondary analysis the sample size and variable set were fixed in advance, which limited power in some subgroups. The male femoral neck finding, while plausible, should be viewed as hypothesis-generating given multiple testing. Finally, generalizability is primarily to community-dwelling older adults in similar Middle Eastern settings.

Conclusion

In this study, RAQ-defined angina was not independently associated with overall osteoporosis or TBS after multivariable adjustment. However, a selective independent association with femoral neck osteoporosis was observed in men. These findings suggest that the bone–vascular relationship is context-dependent, varying by cardiovascular phenotype, skeletal site, sex, shared risk-factor architecture and methodological aspects.

By demonstrating the prominent role of shared risk factors and the importance of phenotypic specificity, this study refines our understanding of why associations between cardiovascular disease and osteoporosis appear in some contexts but not others. Rather than treating cardiovascular disease and osteoporosis as homogeneous entities, future research should recognize their biological heterogeneity to provide a more informative framework for investigating bone–vascular interactions. In particular, longitudinal studies integrating objective cardiovascular imaging, circulating biomarkers, and serial skeletal assessments will be needed to determine whether the observed femoral neck association represents a reproducible biological signal or a chance finding, and to clarify the mechanisms underlying site-specific skeletal vulnerability.

Declarations

Competing Interests

The authors declare no competing interests.

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Author Contribution

1- Kasra Sotoodeh: Conceptualization; Methodology; Visualization; Writing – original draft; Writing – review & editing2- Noushin Fahimfar: Supervision; Conceptualization; Methodology; Writing – review & editing; Project administration3- Fatemeh Mogharrar: Investigation; Data curation; Formal analysis4- Elahe Hesari: Investigation; Writing – review & editing5- AmirAli Soltani: Visualization; Writing – review & editing6- Kazem Khalagi: Supervision; Methodology; Writing – review & editing7- Sasan Salehi Nezamabadi: Writing – review & editing8- Mahnaz Sanjari: Supervision; Methodology; Writing – review & editing9- Gita Shafiee: Methodology; Validation10- Hamid Reza Aghaei Meybodi: Methodology11- Iraj Nabipour: Methodology12- Akram Farhadi: Investigation; Methodology; Validation; Writing – review & editing.13- Bagher Larijani: Supervision14- Afshin Ostovar: Supervision

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Data Availability

The data that support the findings of this study are not publicly available because they contain participant-level information and are subject to ethical and institutional restrictions. The data may be available from the corresponding author upon reasonable request and with permission from the Bushehr Elderly Health (BEH) study investigators, subject to applicable ethical and data-access requirements.

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Figures

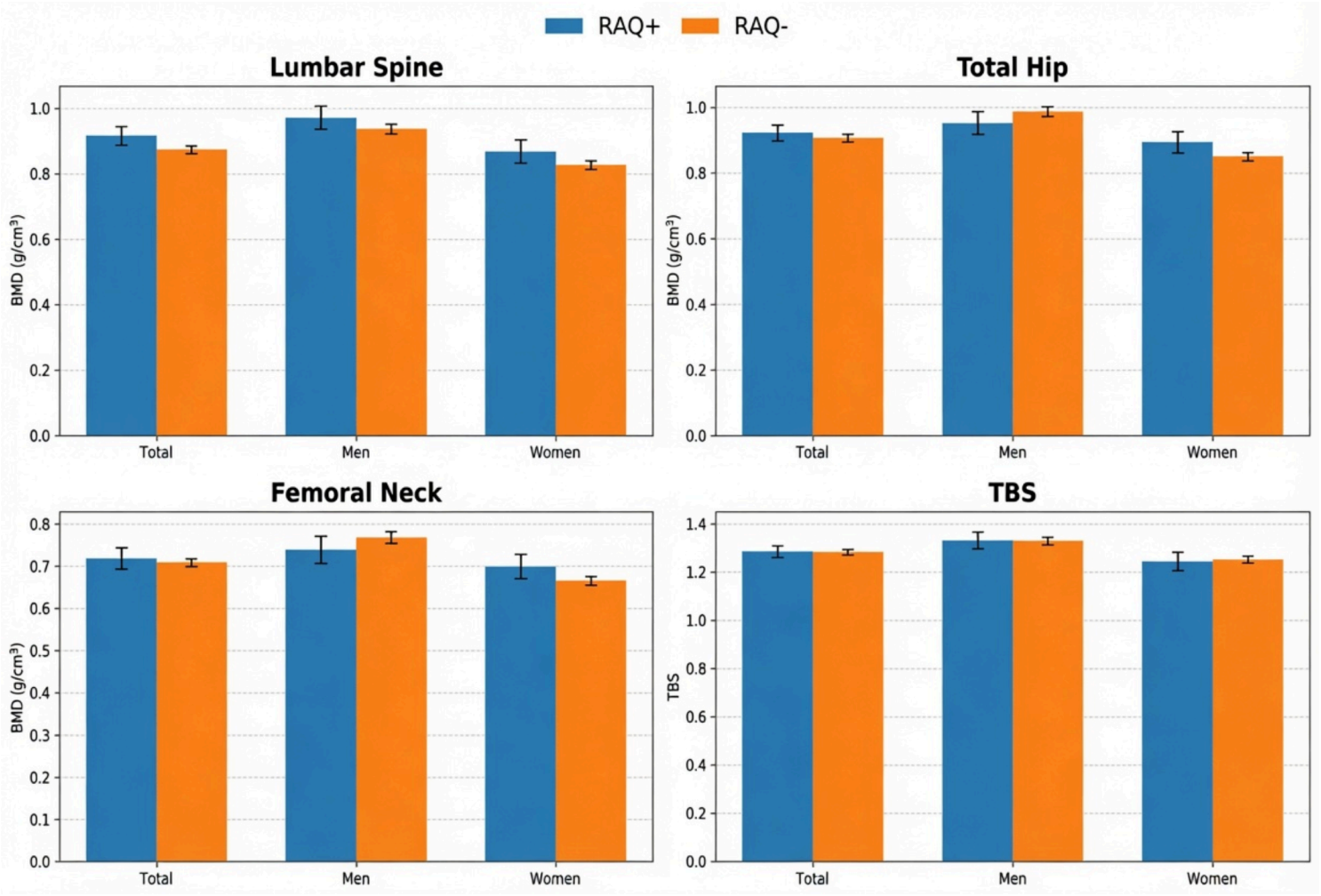


Figure 1

Bone mineral density (BMD) at the lumbar spine, total hip, and femoral neck, and trabecular bone score (TBS) according to Rose Angina Questionnaire (RAQ) status in the overall population and stratified by sex. Bars represent means and error bars indicate 95% confidence intervals. RAQ+ = RAQ positive; RAQ− = RAQ negative.