

Cardiovascular-Kidney-Metabolic Syndrome and Low Bone Mass: Dose-Response Association and the Mediating Role of Systemic Inflammation

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Abstract

Background

Cardiovascular-kidney-metabolic (CKM) syndrome, newly conceptualized by the American Heart Association (AHA), links metabolic disorders to multi-organ damage. However, its cumulative effect on bone loss and underlying inflammatory mechanisms remain unclear. We investigated the independent association between CKM stages and low bone mass risk in US adults, exploring the mediating role of inflammatory markers.

Methods

We analyzed 11,191 adults from the National Health and Nutrition Examination Survey (NHANES). Participants were categorized into CKM stages 0–4 per AHA criteria. Low bone mass was identified via dual-energy X-ray absorptiometry. We evaluated associations using multivariable logistic regression and assessed the bridging effect of systemic inflammation via causal mediation analysis.

Results

Low bone mass prevalence was 34.4%. After comprehensively adjusting for confounders, including body mass index, CKM syndrome progression exhibited a positive dose-response association with low bone mass risk (P for trend = 0.008). Compared to CKM stage 0, patients in stage 4 had a 43% higher risk of low bone mass (OR = 1.43, 95% CI: 1.10–1.86, P = 0.008). This risk was particularly pronounced in females and individuals < 50 years. Furthermore, an elevated neutrophil-to-lymphocyte ratio (NLR) independently mediated 3.58% of the CKM effect on low bone mass (P < 0.001).

Conclusions

Advanced CKM syndrome stages are independently associated with a higher prevalence of low bone mass. This cross-sectional association is partially mediated by systemic immune-inflammatory imbalance (elevated NLR). Integrating routine hematological risk stratification into CKM management may facilitate comprehensive multiorgan protection.

Introduction

With the accelerating global aging process and steadily rising obesity rates, the co-prevalence of chronic metabolic conditions—such as cardiovascular disease (CVD), chronic kidney disease (CKD), and type 2 diabetes mellitus (T2DM)—has significantly increased^{1,2}. Recognizing the profound pathophysiological interplay among these conditions, the American Heart Association (AHA) formally issued a Presidential Scientific Statement in 2023, establishing the systemic clinical concept of "cardiovascular-kidney-metabolic (CKM) syndrome" for the first time³. This framework not only highlights the pathological "crosstalk" linking adipose tissue toxicity and chronic systemic low-grade inflammation to target organ damage, but also

constructs a comprehensive risk staging model ranging from a healthy state (Stage 0) to end-stage clinical cardiovascular events (Stage 4)³.

Concurrently, osteoporosis and subsequent fragility fractures have emerged as a major public health challenge causing substantial morbidity and mortality in the middle-aged and elderly populations⁴. Classic endocrinological studies have previously established that isolated metabolic abnormalities (e.g., accumulation of advanced glycation end products in diabetic bone disease)^{5,6} or declining renal function (e.g., CKD-MBD)⁷ independently elevate fracture risk. More recently, accumulating epidemiological evidence has unveiled shared pathogenic mechanisms between atherosclerosis and declining bone mineral density, known as the "bone-vascular axis" theory^{8,9}. However, within the novel and systemic CKM framework, it remains unclear how multidimensional, cascading metabolic perturbations cumulatively affect skeletal homeostasis, highlighting a lack of empirical studies based on large-scale populations.

Systemic chronic low-grade inflammation is not only the core pathological basis driving CKM-related multiorgan damage¹⁰, but also plays a key role in the aberrant activation of osteoclasts¹¹. In clinical practice, the neutrophil-to-lymphocyte ratio (NLR) has been widely validated as a reliable biomarker for evaluating the systemic immune-inflammatory microenvironment due to its convenience and low cost^{12,13}. Therefore, utilizing the nationally representative National Health and Nutrition Examination Survey (NHANES) database, the present study aimed to evaluate the independent association between CKM syndrome staging and the risk of low bone mass among US adults, and to explore the potential mediating pathways of peripheral blood inflammatory indices (such as NLR).

Materials and Methods

Study Design and Participants

This study utilized a cross-sectional observational design, with data sourced from the National Health and Nutrition Examination Survey (NHANES) led by the US Centers for Disease Control and Prevention (CDC)¹⁴. Data for this study were accessed for research purposes on March 15, 2026. We extracted and integrated datasets from the 2005–2010 and 2013–2014 survey cycles. These specific cycles were selected because they represent the most comprehensive and recent NHANES periods where standardized and complete dual-energy X-ray absorptiometry (DXA) data for the femoral neck and lumbar spine were publicly available for adult populations. The final analysis included 11,191 adult participants with complete demographic information, clinical histories, laboratory biochemical indices, and bone densitometry data.

Clinical Biochemical and Anthropometric Measurements

To operationalize the AHA definitions for CKM stages 3 and 4, we estimated the participants' glomerular filtration rate (eGFR) and their 10-year risk of developing CVD in accordance with current clinical guidelines:

1. Calculation of estimated Glomerular Filtration Rate (eGFR):

eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI 2009) Eq. 1⁵, based on the subject's serum creatinine (Scr, mg/dL), age (Age, years), sex, and race. For non-Hispanic Black individuals, a racial correction factor of 1.159 was uniformly applied. The calculation formula is as follows:

Female:

$$\text{Scr} \leq 0.7, \text{eGFR} = 144 \times (\text{Scr}/0.7)^{-0.329} \times 0.993^{\text{Age}}$$

$$\text{Scr} > 0.7, \text{eGFR} = 144 \times (\text{Scr}/0.7)^{-1.209} \times 0.993^{\text{Age}}$$

Male:

$$\text{Scr} \leq 0.9, \text{eGFR} = 141 \times (\text{Scr}/0.9)^{-0.411} \times 0.993^{\text{Age}}$$

$$\text{Scr} > 0.9, \text{eGFR} = 141 \times (\text{Scr}/0.9)^{-1.209} \times 0.993^{\text{Age}}$$

1. 2. AHA 10-Year CVD Risk Prediction Model:

The participants' 10-year cardiovascular risk probabilities were estimated using the Pooled Cohort Equations (PCEs) recommended by the AHA/ACC or an analogous validated model¹⁶. This multivariable logistic regression model incorporated clinical characteristics including age, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP), history of diabetes (DM, binary), smoking status (SMK, binary), eGFR, as well as the use of antihypertensive medications (BPMed) and statins. The final 10-year CVD incident risk was derived through exponential function transformation. Participants with an estimated 10-year risk > 20% were classified as having an extremely high cardiovascular risk. The calculation formula is as follows:

$$\text{Risk}_{10y} = \frac{e^{\log \text{Odds}}}{1 + e^{\log \text{Odds}}}$$

$$\begin{aligned}\log\text{Odds}_F = & -3.307728 + 0.7939329 \times \frac{\text{Age}-55}{10} + 0.0305239 \times (\text{TC}-\text{HDL}-3.5) \\ & -0.1606857 \times \frac{\text{HDL}-1.3}{0.3} - 0.2394003 \times \frac{\min(\text{SBP},110)-110}{20} \\ & + 0.360078 \times \frac{\max(\text{SBP},110)-130}{20} + 0.8667604 \times \text{DM} + 0.5360739 \times \text{SMK} \\ & + 0.6045917 \times \frac{\min(\text{eGFR},60)-60}{-15} + 0.0433769 \times \frac{\max(\text{eGFR},60)-90}{-15} \\ & + 0.3151672 \times \text{BPMed} - 0.1477655 \times \text{Statin} - 0.0663612 \times \text{BPMed} \times \frac{\max(\text{SBP},110)-130}{20} \\ & + 0.1197879 \times \text{Statin} \times (\text{TC}-\text{HDL}-3.5) - 0.0819715 \times \frac{\text{Age}-55}{10} \times (\text{TC}-\text{HDL}-3.5) \\ & + 0.0306769 \times \frac{\text{Age}-55}{10} \times \frac{\text{HDL}-1.3}{0.3} - 0.0946348 \times \frac{\text{Age}-55}{10} \times \frac{\max(\text{SBP},110)-130}{20} \\ & - 0.27057 \times \frac{\text{Age}-55}{10} \times \text{DM} - 0.078715 \times \frac{\text{Age}-55}{10} \times \text{SMK} \\ & - 0.1637806 \times \frac{\text{Age}-55}{10} \times \frac{\min(\text{eGFR},60)-60}{-15}\end{aligned}$$

$$\begin{aligned}\log\text{Odds}_M = & -3.031168 + 0.7688528 \times \frac{\text{Age}-55}{10} + 0.0736174 \times (\text{TC}-\text{HDL}-3.5) \\ & - 0.0954431 \times \frac{\text{HDL}-1.3}{0.3} - 0.4347345 \times \frac{\min(\text{SBP},110)-110}{20} \\ & + 0.3362658 \times \frac{\max(\text{SBP},110)-130}{20} + 0.7692857 \times \text{DM} + 0.4386871 \times \text{SMK} \\ & + 0.5378979 \times \frac{\min(\text{eGFR},60)-60}{-15} + 0.0164827 \times \frac{\max(\text{eGFR},60)-90}{-15} \\ & + 0.288879 \times \text{BPMed} - 0.1337349 \times \text{Statin} + 0.0475924 \times \text{BPMed} \times \frac{\max(\text{SBP},110)-130}{20} \\ & + 0.150273 \times \text{Statin} \times (\text{TC}-\text{HDL}-3.5) - 0.0517874 \times \frac{\text{Age}-55}{10} \times (\text{TC}-\text{HDL}-3.5) \\ & + 0.0191169 \times \frac{\text{Age}-55}{10} \times \frac{\text{HDL}-1.3}{0.3} - 0.1049477 \times \frac{\text{Age}-55}{10} \times \frac{\max(\text{SBP},110)-130}{20} \\ & - 0.2251948 \times \frac{\text{Age}-55}{10} \times \text{DM} - 0.0895067 \times \frac{\text{Age}-55}{10} \times \text{SMK} \\ & - 0.1543702 \times \frac{\text{Age}-55}{10} \times \frac{\min(\text{eGFR},60)-60}{-15}\end{aligned}$$

Definition of CKM Syndrome Clinical Staging

- Integrating the aforementioned objective indicators with self-reported clinical histories, and adhering to the AHA's step-down diagnostic principles, we categorized the population into five mutually exclusive clinical stages (individuals meeting the criteria for a higher stage were assigned to that respective stage and were not retrospectively assessed):
- CKM Stage 4 (Clinical CVD): Confirmed clinical history of established CVD (including congestive heart failure, coronary heart disease, angina, myocardial infarction, or ischemic/hemorrhagic stroke).
 - CKM Stage 3 (Subclinical CVD or Very High-Risk CKD): Excluding those in Stage 4, this encompasses individuals meeting the diagnostic criteria for very high-risk CKD (urinary albumin-to-creatinine ratio [UACR] ≥ 300 mg/g with eGFR < 60 ; or UACR ≥ 30 mg/g with eGFR < 45 ; or severe eGFR decline < 30).

mL/min/1.73m²); or possessing an AHA 10-year CVD risk > 20% as computed by the aforementioned equation.

3. CKM Stage 2 (Underlying Metabolic Disease or Moderate-to-High-Risk CKD): Presence of definitive pathological hypertriglyceridemia (≥ 135 mg/dL), diagnosed hypertension, or diagnosed diabetes; or fulfilling the criteria for clinical metabolic syndrome (MetS) (meeting at least three of five traits: central obesity, elevated blood pressure, impaired fasting glucose, reduced HDL-C, and elevated triglycerides); or presenting with moderate-to-high-risk CKD.
4. CKM Stage 1 (Early Increased Metabolic Risk): Characterized merely by excessive adiposity (overweight/obesity: BMI ≥ 25 kg/m², or ≥ 23 kg/m² for Asians; or abdominal obesity) or a prediabetic state (impaired fasting glucose or impaired glucose tolerance).
5. CKM Stage 0 (Healthy State): After sequentially excluding the conditions above, this stage comprises individuals with normal clinical biochemical and anthropometric parameters, devoid of any known cardiorenal or metabolic aberrations. During epidemiological data processing, participants with missing core pivotal parameters precluding definitive disease staging were excluded to maximally minimize potential confounding biases at baseline.

Definition of the Low Bone Mass Outcome

The primary outcome was defined as low bone mass. It was evaluated using bone mineral density of the femoral neck or lumbar spine measured by dual-energy X-ray absorptiometry (DXA). According to World Health Organization standards, the diagnosis of low bone mass is based on the internationally recognized T-score. The reference mean BMD for calculating the T-score was derived from 20- to 29-year-old non-Hispanic White women in the NHANES III report. According to the standards set by the World Health Organization (WHO), a T-score ≤ -1.0 based on DXA scanning is defined as low bone mass¹⁷.

Mediation Analysis

To further explore the potential bridging role of the systemic immune-inflammatory microenvironment between CKM syndrome and low bone mass, a causal mediation analysis was performed using the mediation package in R. With CKM syndrome as the exposure variable and low bone mass as the outcome variable, eight routine peripheral blood cell-derived inflammatory indices (focusing specifically on the NLR) were evaluated as potential mediators, given their clinical feasibility and translational value. We constructed a crude model (Model 1) unadjusted for covariates, and a fully adjusted model (Model 2) controlling for the aforementioned confounding factors. The average causal mediation effect (ACME/Indirect Effect), average direct effect (ADE), and total effect were robustly estimated via 1,000 quasi-Bayesian Monte Carlo simulations¹⁸. Moreover, sensitivity analyses were graphically depicted by varying the correlation coefficient (ρ) between the error terms of the mediator and outcome models to rigorously evaluate the robustness of the mediation estimates against unmeasured confounders. A two-sided P-value < 0.05 was considered statistically significant.

Statistical Analysis

Continuous variables are presented as medians with interquartile ranges (IQRs) based on their distribution characteristics, while categorical variables are expressed as frequencies and percentages (%). Intergroup differences were assessed using weighted linear regression or Chi-square tests. Multivariable logistic regression models were employed to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CIs). Model 1 was the crude model; Model 2 was adjusted for basic demographic covariates including age, sex, and race; Model 3 (the fully adjusted model) further controlled for education level, family poverty income ratio (PIR), smoking history, alcohol consumption, dietary calcium intake, and the biomechanical influence of baseline BMI. Stratified analyses and interaction testing (P for interaction) were conducted to explore the heterogeneity of effect characteristics across diverse clinical subgroups.

Results

Baseline Characteristics of the Study Population

Among the 11,191 participants included in this study(Fig. 1), 7,337 (65.6%) had normal bone mass, while 3,854 (34.4%) were diagnosed with low bone mass. The baseline clinical characteristics of the two cohorts are compared in Table 1.

Table 1
Baseline Characteristics by Low Bone Mass Status

Characteristics	Overall (n = 11191)	Normal bone mass (n = 7337)	Low bone mass (n = 3854)	p- value
Age, years	53.00 [40.00, 66.00]	47.00 [35.00, 61.00]	63.00 [51.00, 74.00]	< 0.001
Age group, years, n (%)				< 0.001
< 50	4855 (43.38)	4018 (54.76)	837 (21.72)	
50–64	3233 (28.89)	2017 (27.49)	1216 (31.55)	
>=65	3103 (27.73)	1302 (17.75)	1801 (46.73)	
Sex, n (%)				< 0.001
Male	5879 (52.53)	4475 (60.99)	1404 (36.43)	
Female	5312 (47.47)	2862 (39.01)	2450 (63.57)	
Race and ethnicity, n (%)				< 0.001
Mexican American	1837 (16.41)	1285 (17.51)	552 (14.32)	
Other Hispanic	900 (8.04)	605 (8.25)	295 (7.65)	
Non-Hispanic White	5733 (51.23)	3411 (46.49)	2322 (60.25)	
Non-Hispanic Black	2095 (18.72)	1676 (22.84)	419 (10.87)	
Other Race/Multi-Racial	626 (5.59)	360 (4.91)	266 (6.90)	
PIR	2.30 [1.20, 4.33]	2.40 [1.21, 4.46]	2.15 [1.18, 4.08]	0.001
Education level, n (%)				0.006
Less than 9th grade	1193 (10.66)	729 (9.94)	464 (12.04)	
9-11th grade	1686 (15.07)	1107 (15.09)	579 (15.02)	
High school graduate/GED	2657 (23.74)	1731 (23.59)	926 (24.03)	
Some college or AA degree	3157 (28.21)	2119 (28.88)	1038 (26.93)	
College graduate or above	2498 (22.32)	1651 (22.50)	847 (21.98)	
Marital status, n (%)				< 0.001
Married/Living with partner	6969 (62.27)	4753 (64.78)	2216 (57.50)	
Widowed/Divorced/Separated	2674 (23.89)	1361 (18.55)	1313 (34.07)	

Characteristics	Overall (n = 11191)	Normal bone mass (n = 7337)	Low bone mass (n = 3854)	p-value
Never married	1548 (13.83)	1223 (16.67)	325 (8.43)	
Smoking status, n (%)				0.018
Yes	5462 (48.81)	3521 (47.99)	1941 (50.36)	
No	5729 (51.19)	3816 (52.01)	1913 (49.64)	
Alcohol consumption, n (%)				< 0.001
Yes	8191 (73.19)	5654 (77.06)	2537 (65.83)	
No	3000 (26.81)	1683 (22.94)	1317 (34.17)	
Dietary calcium intake, mg/day	797.00 [519.00, 1161.00]	825.00 [537.00, 1208.00]	740.50 [487.00, 1075.00]	< 0.001
BMI, kg/m²	27.44 [24.06, 31.44]	28.44 [25.08, 32.51]	25.70 [22.60, 29.10]	< 0.001
Waist circumference, cm	97.10 [87.00, 107.30]	99.20 [89.10, 109.20]	93.45 [84.00, 103.00]	< 0.001
Systolic blood pressure, mmHg	122.67 [112.00, 136.00]	120.67 [112.00, 133.33]	125.33 [113.33, 140.67]	< 0.001
Diastolic blood pressure, mmHg	70.67 [62.67, 78.00]	71.33 [63.33, 78.00]	69.00 [60.67, 76.67]	< 0.001
HbA1c, %	5.50 [5.20, 5.90]	5.50 [5.20, 5.90]	5.60 [5.30, 5.90]	< 0.001
HDL-C, mg/dL	51.00 [42.00, 63.00]	50.00 [41.00, 60.00]	55.00 [45.00, 68.00]	< 0.001
UACR, mg/g	7.21 [4.53, 14.83]	6.58 [4.20, 12.81]	8.57 [5.38, 18.53]	< 0.001
Serum creatinine, mg/dL	0.90 [0.74, 1.02]	0.90 [0.76, 1.02]	0.85 [0.72, 1.02]	< 0.001
CVD, n (%)				< 0.001
No	9878 (88.27)	6667 (90.87)	3211 (83.32)	
Yes	1313 (11.73)	670 (9.13)	643 (16.68)	
CKM stages, n (%)				< 0.001
Stage 0	1322 (11.81)	862 (11.75)	460 (11.94)	
Stage 1	1820 (16.26)	1399 (19.07)	421 (10.92)	

Characteristics	Overall (n = 11191)	Normal bone mass (n = 7337)	Low bone mass (n = 3854)	p-value
Stage 2	5438 (48.59)	3839 (52.32)	1599 (41.49)	
Stage 3	1298 (11.60)	567 (7.73)	731 (18.97)	
Stage 4	1313 (11.73)	670 (9.13)	643 (16.68)	

Demographically, the low bone mass group exhibited a markedly older profile (median age 63 vs. 47 years, $P < 0.001$), with seniors aged ≥ 65 years constituting a substantial 46.73%. Furthermore, sex disparities driven by menopausal factors were evident, as females predominated in the low bone mass group (63.57%).

Clinically, a distinct phenotype emerged: on one hand, their absolute median BMI (25.70 kg/m²) and waist circumference (93.45 cm) were lower than those of the normal bone mass group; on the other hand, their indicators of vascular and organ damage were significantly more severe. Patients with low bone mass not only had a higher prevalence of preexisting CVD (16.68% vs. 9.13%, $P < 0.001$) but also demonstrated significantly elevated renal microalbuminuria (median UACR 8.57 mg/g vs. 6.58 mg/g). Examining the overarching CKM syndrome stages, individuals with low bone mass were disproportionately concentrated in the advanced stages accompanied by substantial target organ damage, with CKM Stage 3 accounting for 18.97% (vs. 7.73% in the normal bone mass group) and CKM Stage 4 comprising 16.68% (vs. 9.13%) (differences were statistically significant, $P < 0.001$).

Association Analysis Between CKM Stages and Low Bone Mass

To investigate the independent impact of CKM syndrome severity on bone metabolism, we established three progressive logistic regression models (Table 2). In Models 1 and 2, which did not adequately adjust for key biomechanical factors like somatic physical load (BMI), early-stage CKM seemingly exhibited a "protective" phenotype, likely attributable to the mechanical stimulation exerted by an overweight physique itself on bone remodeling.

Table 2
Association between CKM Stages and Low Bone Mass

Characteristic	Model 1			Model 2			Model 3		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
CKM (per 1-stage increase)	1.24	1.18, 1.31	< 0.001	0.87	0.83, 0.92	< 0.001	1.09	1.02, 1.16	0.014
CKM stages (Categorical)									
Stage 0 (Reference)	—	—		—	—		—	—	
Stage 1	0.58	0.48, 0.69	< 0.001	0.56	0.45, 0.69	< 0.001	1.07	0.85, 1.35	0.60
Stage 2	0.75	0.64, 0.89	0.001	0.46	0.39, 0.55	< 0.001	1.09	0.88, 1.35	0.40
Stage 3	2.53	2.07, 3.08	< 0.001	0.60	0.48, 0.75	< 0.001	1.20	0.91, 1.56	0.20
Stage 4	1.73	1.43, 2.08	< 0.001	0.63	0.51, 0.77	< 0.001	1.43	1.10, 1.86	0.008
P for trend	< 0.001			< 0.001			0.008		
Model 1: No adjusted.									
Model 2: Adjusted for Age group, Gender, Race.									
Model 3: Adjusted for Age group, Gender, Race, PIR, Education, Marital Status, Smoke, Alcohol, Dietary calcium intake, Waist circumference and BMI.									

However, after comprehensively adjusting for the confounding effects of demographic characteristics, lifestyle factors, and baseline BMI in the multivariable model (Model 3), a significant positive association became evident. When CKM stage was incorporated as a continuous variable, each 1-stage advancement in disease progression corresponded to a significant 9% increase in the risk of concurrent low bone mass (OR = 1.09, 95% CI: 1.02–1.16, P = 0.014). Analysis of CKM stages as categorical variables revealed a robust dose-response gradient (P for trend = 0.008). Specifically, compared with healthy adults in CKM Stage 0, those in CKM Stage 4 had a 43% higher likelihood of exhibiting low bone mass (OR = 1.43, 95% CI: 1.10–1.86, P = 0.008).

Subgroup Analyses

To assess the applicability of the association between CKM and low bone mass risk across specific clinical populations, we performed comprehensive subgroup analyses (Table 3 and Fig. 2).

Table 3
Subgroup Analyses of the Association Between CKM Stages and Low Bone Mass

Subgroups	OR	95%CI Low	95%CI High	P for interaction
Age group				0.058
< 50	1.20	1.09	1.32	
50–64	1.09	0.99	1.20	
>=65	1.12	1.02	1.23	
Sex				< 0.001
Male	1.10	1.02	1.19	
Female	1.17	1.08	1.26	
Race and ethnicity				0.478
Mexican American	1.10	0.95	1.27	
Other Hispanic	1.20	0.98	1.48	
Non-Hispanic White	1.09	1.02	1.17	
Non-Hispanic Black	1.18	1.03	1.36	
Other Race/Multi-Racial	1.28	1.02	1.60	
BMI Group				0.399
< 25	1.11	1.02	1.20	
25-29.9	1.21	1.09	1.34	
>=30	1.19	1.06	1.35	
PIR Group				0.358
< 1.3	1.14	1.03	1.26	
1.3–3.5	1.12	1.03	1.23	
>=3.5	1.10	1.00	1.21	
Education				0.629
Less than 9th grade	1.23	1.03	1.47	
9-11th grade	1.02	0.89	1.17	
High school graduate/GED	1.22	1.09	1.37	
Some college or AA degree	1.07	0.96	1.18	
College graduate or above	1.14	1.02	1.27	
Marital Status				0.077

Subgroups	OR	95%CI Low	95%CI High	P for interaction
Married/Living with partner	1.11	1.04	1.19	
Widowed/Divorced/Separated	1.22	1.09	1.35	
Never married	1.02	0.87	1.21	
Smoking status				0.399
Yes	1.12	1.04	1.20	
No	1.14	1.05	1.23	
Alcohol consumption				0.49
Yes	1.13	1.06	1.20	
No	1.12	1.01	1.24	

The results demonstrated that sex played a highly significant effect-modifying role in this pathogenic pathway (P for interaction < 0.001). With the progressive advancement of CKM, the risk of exacerbated bone loss was substantially higher in females (OR = 1.17, 95% CI: 1.08–1.26) than in males (OR = 1.10, 95% CI: 1.02–1.19). Concurrently, age also exhibited a marginally significant interaction (P for interaction = 0.058). Notably, in the relatively younger cohort (< 50 years), the strength of the association between CKM and low bone mass risk (OR = 1.20) was modestly higher than that in the elderly cohort ($\geq$ 65 years, OR = 1.12), implying that age might exert a potential modifying effect (P for interaction = 0.058).

Conversely, no significant heterogeneity was observed across subgroups stratified by race/ethnicity, baseline BMI categories (normal, overweight, obese), poverty income ratio, education level, or lifestyle factors such as smoking and alcohol consumption (all P for interaction > 0.05). This strongly suggests that the CKM-associated skeletal burden is consistent across diverse demographics.

Mediation Analysis of Systemic Inflammatory Indices

Systemic chronic low-grade inflammation is considered the pivotal pathological substrate driving the progression of CKM syndrome toward end-stage disease. To elucidate the clinically accessible mechanisms underlying CKM-induced bone loss triggered by deep metabolic toxicity, we conducted a systematic causal mediation analysis of eight routine peripheral blood cell-derived immune-inflammatory indices (Table 4).

Table 4
Mediation Analysis of Systemic Inflammatory Markers on the Association Between CKM Syndrome and Low Bone Mass

Model	Mediator	Indirect Effect	P value	Direct Effect	P value	Proportion Mediated (%)	P value
Model 1 (Unadjusted)	SII	4e-04	0.54	0.0538	< 0.001	0.0082	0.54
	SIRI	0.0016	< 0.001	0.0523	< 0.001	0.0297	< 0.001
	PLR	-1.00E-04	0.44	0.0544	< 0.001	-0.0036	0.44
	NLR	0.0027	< 0.001	0.0511	< 0.001	0.0496	< 0.001
	MLR	0.0026	< 0.001	0.0511	< 0.001	0.0461	< 0.001
	dNLR	-1.00E-04	0.22	0.0544	< 0.001	-0.0029	0.22
	NMLR	0.003	< 0.001	0.0508	< 0.001	0.0542	< 0.001
	PIV	3e-04	0.68	0.0538	< 0.001	0.0063	0.68
Model 2 (Adjusted)	SII	2e-04	0.58	0.0192	< 0.001	0.0064	0.58
	SIRI	5e-04	0.12	0.0188	< 0.001	0.022	0.12
	PLR	0	0.68	0.0193	< 0.001	3e-04	0.68
	NLR	7e-04	< 0.001	0.0186	< 0.001	0.0358	< 0.001
	MLR	0	0.76	0.0194	< 0.001	-0.0032	0.76
	dNLR	2e-04	0.12	0.0192	< 0.001	0.0102	0.12
	NMLR	7e-04	< 0.001	0.0186	< 0.001	0.0348	< 0.001
	PIV	1e-04	0.82	0.0192	< 0.001	0.0032	0.82

In the unadjusted crude model (Model 1), several inflammatory indices demonstrated statistically significant mediating effects, but this may be attributable to confounding bias; however, in the fully adjusted model (Model 2) which strictly eliminated powerful confounders such as age, sex, and baseline BMI, the neutrophil-

to-lymphocyte ratio (NLR) withstood robust testing and exhibited a significant and independent mediating role.

As depicted in the path model in Fig. 3A, CKM syndrome not only demonstrated a significant independent association with low bone mass (Direct Effect = 0.0186, $P < 0.001$) but also further escalated the risk of low bone mass by precipitating a systemic immune-inflammatory imbalance (i.e., driving up NLR levels) (Indirect Effect = 0.0007, $P < 0.001$). Within this pathological cascade, the immune-inflammatory state, represented by the NLR, independently mediated 3.58% of the total effect of CKM syndrome on bone loss. The forest plot (Fig. 3B) visually confirms that the confidence interval for the indirect effect did not encompass zero, verifying the pathway's significance. Furthermore, as a mechanistic validation, the neutrophil-to-monocyte+lymphocyte ratio (NMLR), which is highly homologous to the NLR, displayed a perfectly consistent and significant mediation proportion (3.48%). Sensitivity analysis (Fig. 3C) corroborated that the estimated mediation effect remained relatively robust despite certain fluctuations in the residual correlation (ρ) induced by unmeasured confounders. This finding not only establishes immune imbalance as a central bridge in CKM osteotoxicity but also provides direct evidence for utilizing routine blood count screening to identify populations at high risk of bone loss in clinical settings

Discussion

This large-scale epidemiological analysis involving over 10,000 US adults substantiates, from a multisystem integration perspective, a significant and independent positive association between the stage progression of CKM syndrome and the risk of low bone mass. This association proved exceptionally robust after rigorously adjusting for biomechanical confounders such as baseline BMI. We postulate that the deep pathophysiological mechanisms by which CKM syndrome induces bone loss predominantly involve the following three clinical dimensions:

1. **Impaired Glucose Metabolism and Bone Matrix Degradation:** Patients in CKM stages 2–3 universally present with insulin resistance and impaired glucose tolerance. A 2022 multicenter study indicated that long-term chronic hyperglycemia not only suppresses osteoblast proliferation and mineralization but also accelerates the non-enzymatic glycation of collagen proteins¹⁹. The excessive cross-linking of advanced glycation end products (AGEs) within the bone matrix leads to an insidious deterioration of "bone quality," which explains the "diabetic bone paradox" where some patients with metabolic syndrome exhibit acceptable bone density on DXA measurement but have a significantly increased actual fracture risk^{20,21}.
2. **Mineral Remodeling Triggered by Target Organ Decline:** As CKM advances to the moderate-to-high-risk CKD stages, the progressive loss of nephrons triggers complex secondary hyperparathyroidism and abnormal compensation of fibroblast growth factor 23 (FGF23)²². The KDIGO clinical practice guidelines (and their recent updates) indicate that this CKD-MBD state can promote osteoclastic bone resorption via imbalances in the RANKL/OPG pathway^{23,24,25}.
3. **Systemic Immune-Inflammatory Imbalance Mediated by the NLR:** Systemic low-grade inflammation triggered by ectopic adipose remodeling is a hallmark feature of CKM²⁶. The mediation analysis in this study confirms for the first time that immune-inflammatory imbalance, characterized by an elevated NLR,

independently mediates a portion of the CKM-induced bone loss risk (proportion mediated: 3.58%). This is consistent with previous epidemiological data linking elevated peripheral NLR to reduced BMD.^{27,28} Pathomechanistically, a sustained high load of neutrophils can secrete copious amounts of proinflammatory cytokines (e.g., TNF- α and IL-6), which act as potent stimuli inducing aberrant osteoclast differentiation²⁹; concurrently, relative lymphopenia reflects a blunting of the adaptive immune system's protective regulatory effects on osteoblasts^{30,31}.

Confounding Effect of Biomechanical Load: Our results additionally unveiled a critical epidemiological phenomenon: in the unadjusted models, a high BMI portrayed a superficial "protective" effect on bone mass. This finding conforms to the classic Wolff's Law, positing that the accrual of absolute body weight can passively stimulate bone remodeling via mechanical stress^{32,33}. Nonetheless, only after strictly controlling for BMI in the multivariable model (Model 3) was the latent destructive impact of CKM fully exposed. This implies that in clinical practice, the mechanical benefits of absolute body weight can easily mask the "true metabolic toxicity" driven by visceral adiposity and systemic inflammation^{34,35}.

Clinical Implications and Study Limitations

Our findings carry important clinical implications. Primarily, it strongly advocates that multidisciplinary physicians—spanning endocrinology, cardiology, and nephrology—must broaden their therapeutic strategies beyond mere glycemic control, blood pressure management, and delaying renal function decline when managing patients in advanced CKM stages. Routine bone mineral density screening and personalized fall-prevention strategies must be integrated early into the comprehensive assessment algorithms for CKM.

Crucially, this study underscores the unique prognostic value of the NLR. Given that the NLR is a readily accessible, inexpensive biomarker obtained from a routine complete blood count (CBC), it provides primary healthcare facilities with a highly convenient clinical early-warning metric. Clinicians can track dynamic NLR changes in CKM patients to proactively identify immune-imbalanced subpopulations at high risk of bone loss. This not only offers a novel perspective for optimizing multidisciplinary chronic disease management but also suggests that future interventions targeting the systemic immune microenvironment (e.g., intensive lifestyle modifications or the introduction of novel anti-inflammatory agents) might delay or even halt the trajectory of bone loss in CKM patients.

This study also has certain limitations. First, the inherent nature of a cross-sectional design restricts our ability to establish definitive causality between CKM progression and bone loss. Second, despite utilizing rigorous mediation sensitivity testing, observational data cannot entirely preclude all unmeasured residual confounding from dietary or gene-environment factors. Future large-scale, prospective follow-up cohorts, coupled with in-depth in vitro bone biology experiments, are urgently warranted to validate the causal sequence of our findings and decipher the precise molecular pathological pathways.

Conclusions

In summary, higher stages of cardiovascular-kidney-metabolic (CKM) syndrome are independently associated with an increased prevalence of low bone mass in the adult population, and a systemic immune-

inflammatory imbalance, marked by an elevated NLR derived from routine clinical blood counts, plays a critical pathological mediating role in this process. As the global burden of multisystem chronic diseases grows, integrating routine inflammatory prognostication and proactive bone health management into comprehensive CKM care pathways may prove essential for preserving patient mobility and overall quality of life.

Declarations

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Author Contribution

YL conceptualized the study, performed the statistical analysis, and wrote the main manuscript text. JS, XZ, and TC extracted the data, conducted the literature review, and prepared the figures and tables. LZ and XP provided methodological guidance, validated the data, and critically reviewed the manuscript. GJ conceptualized and supervised the entire project, acquired the funding, and provided critical revisions to the manuscript. All authors reviewed and approved the final manuscript.

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Not applicable.

Data Availability

The datasets generated and/or analysed during the current study are available in the official NHANES repository, which can be accessed at <https://www.cdc.gov/nchs/nhanes/>.

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Figures

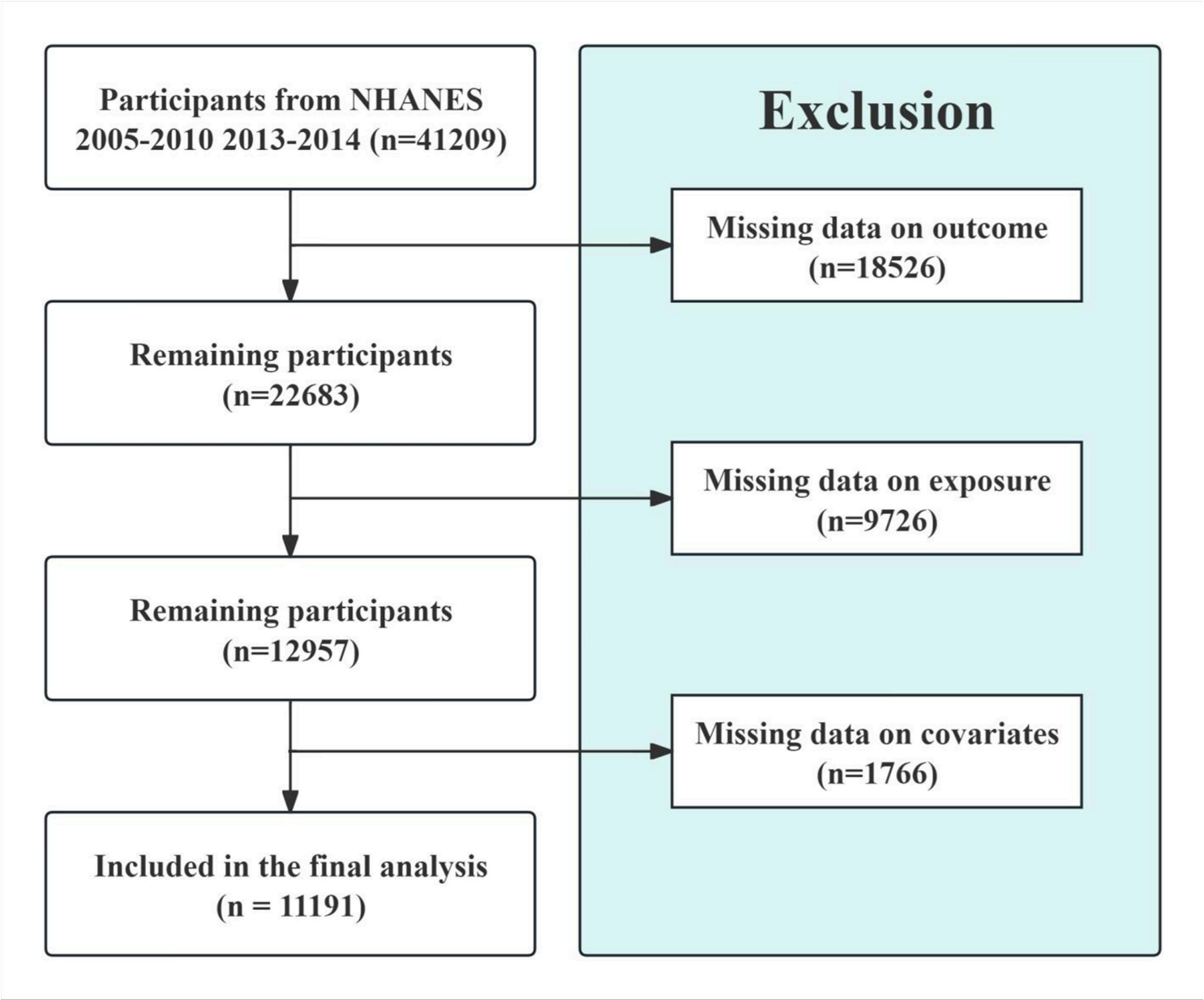


Figure 1

Flowchart of participant selection from the NHANES 2005-2010 and 2013-2014.

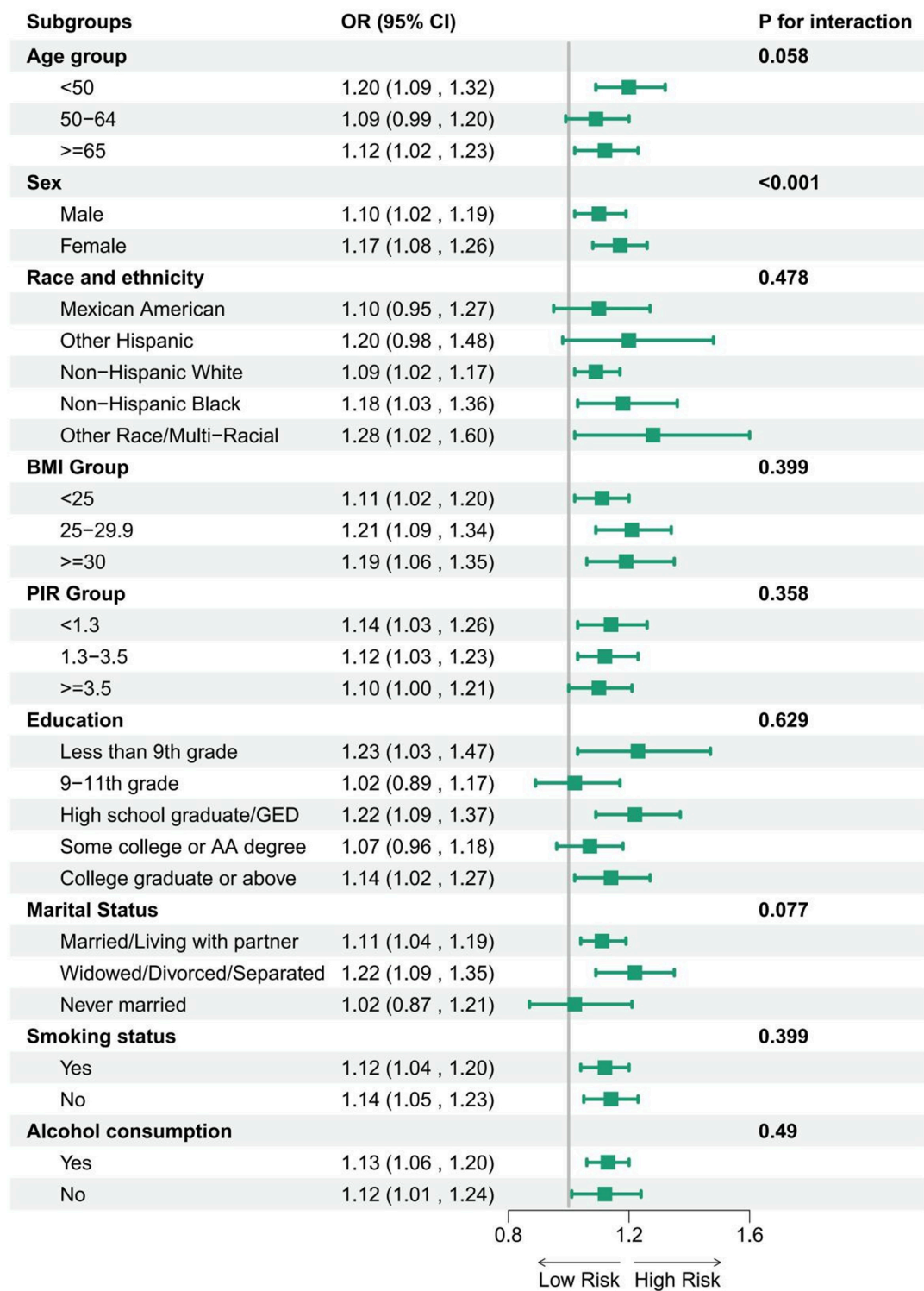


Figure 2

Subgroup analyses of the association between CKM stages and low bone mass.

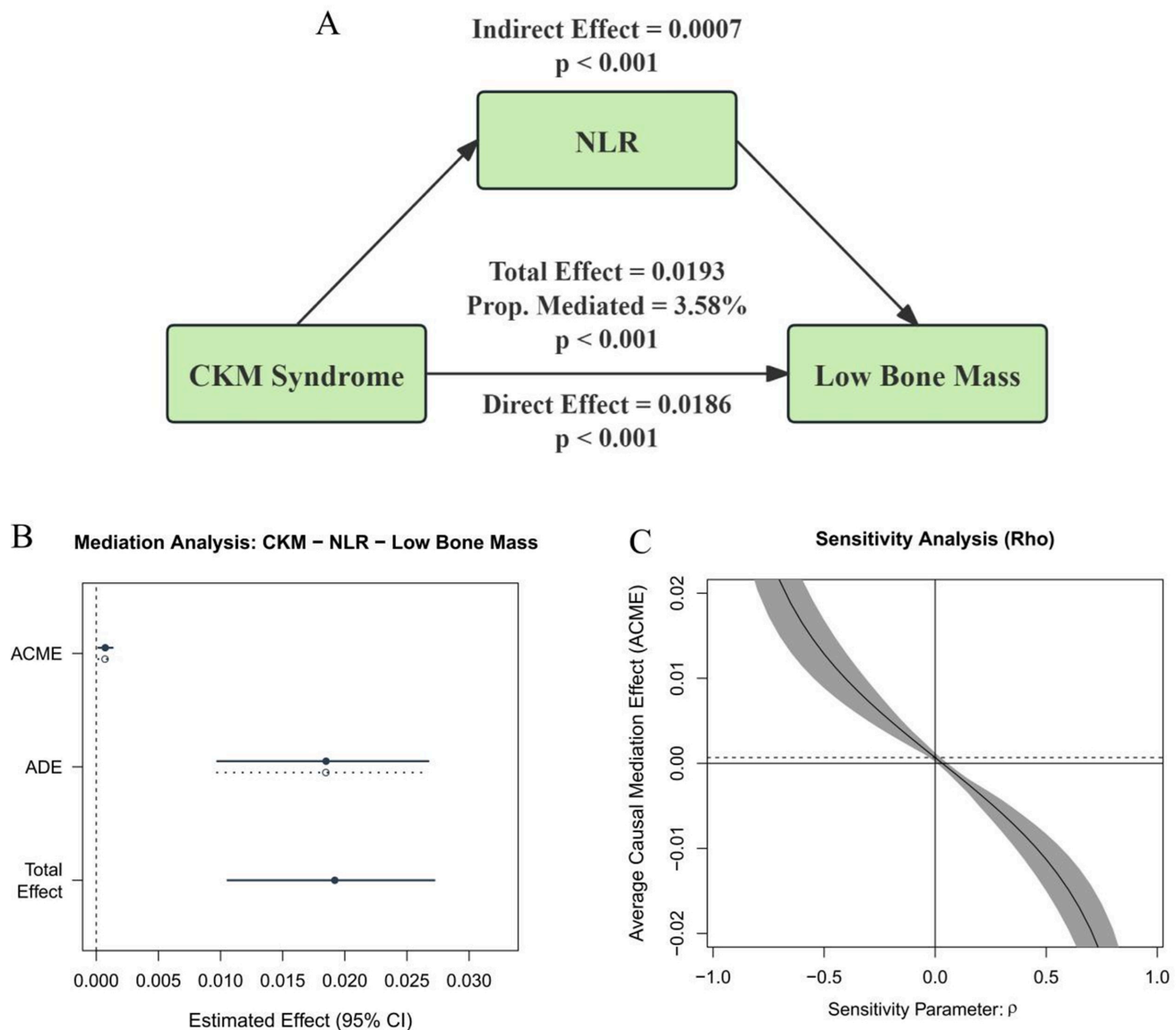


Figure 3

Causal mediation analysis of the neutrophil-to-lymphocyte ratio (NLR) on the association between CKM syndrome and low bone mass.