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Original Article

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Low bone mineral density and handgrip strength are associated with increased risk of all-cause mortality: A cohort study with primary analysis and replication in 16,282 adults

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Abstract

This study aimed to evaluate the modifying effects and joint associations of handgrip strength (HGS) and bone mineral density (BMD) with all-cause mortality, with an exploratory analysis of cardiovascular disease (CVD) mortality. A primary analysis cohort (n = 11 150) and a replication cohort (n = 5 952) were included. Cox proportional hazards regression, restricted cubic spline analysis, and interaction analysis were used to examine the associations of BMD with mortality across relative HGS groups. Relative HGS was defined as absolute HGS divided by body weight. The joint effects of BMD–HGS combinations were assessed. During a median follow-up of 9.75 and 6.59 years, the primary analysis and replication cohorts recorded 1 345 and 352 all-cause deaths, respectively. In the primary analysis cohort, low BMD was associated with an increased all-cause mortality risk in both the low and high relative HGS groups (hazard ratio [HR] = 1.26, 95% confidence interval [CI]: 1.04–1.52 and HR = 1.42, 95% CI: 1.16–1.74, respectively), with consistent findings in the replication cohort. No significant interaction was found between relative HGS and BMD (P > 0.05). Participants with low BMD and low relative HGS had a 59%–62% higher risk of all-cause mortality than those with high BMD and high relative HGS in both cohorts, and the estimated PAR% for this combined exposure was 10.8%–13.1%. Results for CVD mortality were inconsistent across cohorts. In conclusion, low BMD with low handgrip strength is consistently associated with increased all-cause mortality, suggesting combined screening may benefit high-risk individuals.

Keywords: muscle strength, bone mineral density, all-cause mortality, cardiovascular disease, cohort study

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Introduction

Bone mineral density (BMD) and muscle strength are essential diagnostic parameters for osteoporosis and sarcopenia, respectively, which together reflect overall musculoskeletal health[1-3]. Both parameters peak between the ages of 40 and 50 before declining progressively[4-6], and the associated health risks extend beyond the elderly to middle-aged adults[7-8]. Each standard deviation (SD) decrease in BMD is associated with a 17% higher risk of all-cause mortality and a 13% higher risk of cardiovascular disease (CVD). Similarly, a reduction of 5 kg in handgrip strength is linked to a 16% and 17% increased risk for these two outcomes, respectively[9-10].

Muscle and bone are anatomically and functionally connected as key components of the motor system[2]. Moreover, both tissues exert endocrine functions that contribute to systemic health by regulating nutrient storage and allocation, such as calcium in bone and glucose in muscle, as well as by secreting biochemical mediators like cardioprotective myokines and kidney-derived bone factors[11-12]. These complex interactions establish a strong correlation between muscle and bone across development, growth, and aging, and in various pathological conditions[13]. Greater muscle strength is positively correlated with higher bone density and slower bone loss[14]. The traditional view that muscle force mechanically controls bone strength is increasingly being challenged by a new model emphasizing biochemical crosstalk involving myokines, osteokines, and adipokines[13].

Previous studies have paid limited attention to how muscle strength might modify the link between BMD and all-cause or CVD mortality, and consequently, the combined effects of handgrip strength and BMD on long-term risks remain unclear. Furthermore, existing evidence is largely derived from older populations, with limited data representing the broader population. In addition, in cohort studies examining the association between handgrip strength (HGS) and long-term adverse outcomes, some studies have overlooked the influence of body weight or body mass index (BMI) on muscle strength and have not adequately evaluated the findings of both absolute and relative HGS[9-15-16].

Therefore, we conducted primary analyses in 11 150 adults and validated the findings in an independent subset of 5 952 adults. This study aims to evaluate both the modifying effects and the joint associations of HGS and BMD with all-cause mortality, with an exploratory analysis of CVD mortality. The findings will provide novel insights into the combined impact of muscle strength and BMD on all-cause mortality, underscoring the importance of integrated musculoskeletal assessments for early risk identification.

Methods

Study design and participants

This study used data from the Jurong Cohort, which was established using a multistage sampling method across 16 townships of Jurong City, Jiangsu Province, China. Participants were recruited in two stages, with stage 1 conducted from October to November 2015 and stage 2 from November to December 2018. The inclusion criteria were as follows: (1) age ⩾ 18 years; (2) local residence for more than 6 months within the past 12 months; and (3) voluntary completion of the survey after providing informed consent. The exclusion criteria were cognitive impairment, severe illness, or disability. The study was conducted according to the Declaration of Helsinki and was approved by the Ethics Committee of Nanjing Medical University (approval No. 2015111). All participants provided written informed consent.

The primary analysis was performed in the primary analysis cohort enrolled in 2015 (n = 11 150), and the findings were replicated in an independent replication cohort enrolled in 2018 (n = 5 952). Participants with missing BMD data were further excluded (primary analysis cohort: n = 230; replication cohort: n = 590). The final analytic sample comprised 10 920 participants in the primary analysis cohort and 5 362 participants in the replication cohort. A flowchart of participant selection for analysis is shown in ***Fig. 1***.

BMD measurement

BMD of the left heel was measured using the CM-200 quantitative ultrasound system (Furuno Electric Co., Ltd., Nishinomiya, Japan) while participants were seated. Age and sex were entered into the system prior to measurement, and T-scores were automatically generated. The classification of BMD was based on the criteria outlined in the WHO guidelines[17], osteoporosis was defined as T-score ⩽ −2.5, osteopenia as −2.5 < T-score < −1.0, and normal BMD as T-score ⩾ −1.0.

HGS measurement

HGS was measured using a hand-held dynamometer (Xiangshan CAMRY-EH101, Guangdong Senssun Weighing Apparatus Group Ltd.,

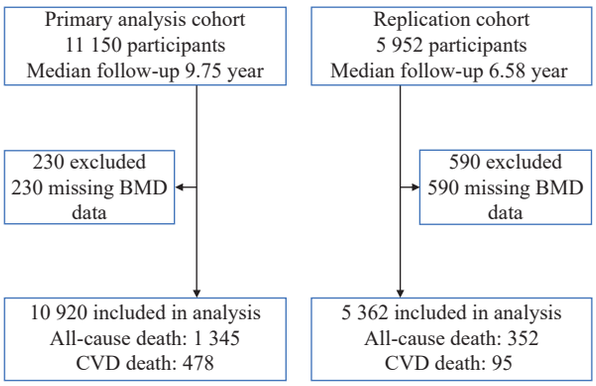

Fig. 1 **Flowcharts of the participants' selection for analysis.** Abbreviations: BMD, bone mineral density; CVD, cardiovascular disease.

Zhongshan, Guangdong, China). Participants stood upright with arms fully extended and held close to the body. They were instructed to exert maximum handgrip force alternately with each hand. The measurement was repeated twice per hand, and the highest value was recorded. The higher of the left and right maximum values was used in the analysis as the absolute handgrip strength. Since body weight is associated with maximal muscle strength performance, relative HGS was calculated as absolute HGS (kg) divided by body weight (kg)[18]. Given that body weight directly reflects the mechanical load during handgrip strength testing, we used it as the primary adjustment metric, with BMI-adjusted HGS included in sensitivity analyses[19]. For both absolute and relative HGS, higher values indicate a higher level of HGS and better physical function.

Outcome

Follow-up was conducted through July 2025. Mortality information was obtained from the death registration system. All-cause mortality was defined as death from any cause. The underlying cause of death was coded according to the International Classification of Diseases, Tenth Revision (ICD-10). CVD mortality was defined as death resulting from coronary heart disease or stroke. All records were reviewed and validated by qualified clinical experts.

Covariates

Data were collected through a standardized questionnaire, including demographics (age, sex, residence, marital status, and education), anthropometrics (height, body weight, and blood pressure), lifestyle factors (smoking, alcohol consumption, and physical activity), and previous medical history (cardiovascular disease, hypertension, and diabetes). BMI was calculated as weight (kg) divided by height (m^2). Smoking status was categorized as never-smoker, former smoker, or current smoker. Alcohol consumption was categorized as current drinker or nondrinker. Physical activity was systematically assessed using the International Physical Activity Questionnaire—Short Form (IPAQ-SF)[19]. Physical activity levels were quantified as metabolic equivalents (METs), with assigned MET values of 8.0 for vigorous activity, 4.0 for moderate activity, and 3.3 for walking. Hypertension was defined as a self-reported history of hypertension, elevated blood pressure (systolic blood pressure ⩾ 140 mmHg or diastolic blood pressure ⩾ 90 mmHg), or recent use of antihypertensive drugs. Diabetes was defined as fasting glucose ⩾ 7.0 mmol/L, a self-reported history of diabetes, or recent use of hypoglycemic agents. CVD was defined as a self-reported history of coronary heart disease or stroke.

Statistical analysis

Continuous variables were expressed as mean (standard deviation [SD]) and median with interquartile range, while categorical variables were presented as frequency and percentage. Between-group comparisons were performed using the χ^2 test for categorical variables, and ANOVA or the Kruskal-Wallis H test for continuous variables.

Considering the age- and sex-specific distributions of BMD and relative HGS[21-22], BMD T-scores were categorized into low, medium, and high tertiles, and relative HGS into low and high groups, using sex- and 5-year age-group-specific percentile cutoffs. Tertiles were chosen to ensure balanced statistical power across subgroups. Histograms were used to examine the distribution of BMD across HGS groups. To visualize the trends in BMD levels across different sex and age groups, we used generalized additive models for location, scale, and shape (GAMLSS). Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause and CVD mortality associated with BMD across relative HGS groups. The proportional hazards assumption was tested using Schoenfeld residuals. Both multiplicative and additive interactions between BMD and relative HGS were assessed. Additive interaction was quantified using the relative excess risk due to interaction (RERI) and the attributable proportion (AP). To examine non-linear relationships, restricted cubic spline (RCS) curves based on multivariable Cox regression were applied, with four knots placed at the 5th, 35th, 65th, and 95th percentiles of the BMD distribution. Six joint groups were defined based on relative HGS (low *vs.* high)

and BMD T-score (low, medium, and high). Kaplan-Meier curves were constructed for the cumulative incidence of all-cause mortality and CVD mortality across the six joint groups and were compared using the log-rank test. To estimate the contribution of combined low relative HGS and low BMD to all-cause mortality, we calculated the population attributable risk proportion (PAR%) and used bootstrap resampling to compute its 95% CI. Specifically, we performed 1 000 bootstrap replications with the individual as the resampling unit. For each bootstrap sample, the full model was refitted, and the PAR% was recalculated. The 95% CI was then constructed using the percentile bootstrap method. To further explore the relationship between joint groups and outcomes, subgroup analyses were performed according to age and sex.

Several sensitivity analyses were conducted to evaluate the robustness of the findings. First, analyses were repeated after excluding events that occurred within the first two years of follow-up to assess the potential impact of reverse causation. Second, to examine the consistency of the results across different exposure definitions, we used alternative measures of HGS, including absolute HGS alone and relative HGS defined as absolute HGS divided by BMI. In addition, BMD categories were redefined using standard T-score cutoffs (normal, osteopenia, and osteoporosis) rather than age- and sex-specific tertiles.

All data analyses were conducted in R version 4.0.2, with a two-sided $P < 0.05$ considered statistically significant.

Results

Baseline characteristics of participants

This study included 16 282 community-dwelling adults with a mean (SD) age of 60.31 (10.95) years, among whom 6 701 (41.16%) were men. The primary analysis cohort consisted of 10 920 participants (mean age 60.15 years), and the replication cohort comprised 5 362 participants (mean age 60.65 years). In the primary analysis cohort, the mean (SD) BMD T-score was −0.66 (0.89), mean (SD) absolute HGS was 29.21 (9.43) kg, and mean (SD) relative HGS was 0.47 (0.13) kg/kg. In the replication cohort, the mean (SD) BMD T-score was −1.66 (1.05), mean (SD) absolute HGS was 29.09 (10.54) kg, and mean (SD) relative HGS was 0.45 (0.14) kg/kg.

In the primary analysis and replication cohorts, median follow-up was 9.75 years and 6.59 years, respectively. During follow-up, all-cause death occurred in 1 345 (12.31%) participants in the primary analysis cohort and in 352 (6.56%) in the replication cohort; CVD death occurred in 478 (4.38%) and 95 (1.78%), respectively. The GAMLSS curves revealed that BMD T-score declined progressively with advancing age in both sexes across the primary analysis and replication cohorts (***Supplementary Fig. 1***). Using sex- and 5-year age-group-specific tertile cutoffs, BMD T-scores were categorized into low, medium, and high tertiles, and using sex- and 5-year age-group-specific median cutoffs, relative HGS was categorized into low and high groups (***Supplementary Table 1***). ***Table 1*** summarizes the characteristics of the two cohorts according to BMD tertile groups.

Distribution of BMD by relative HGS level

In the primary analysis cohort, the mean (SD) BMD T-scores for the low and high relative HGS groups were −0.69 (0.91) and −0.64 (0.87), respectively ($P = 0.02$). In the replication cohort, the mean (SD) BMD T-scores for the low and high relative HGS groups were −1.62 (1.07) and −1.69 (1.03), respectively ($P = 0.02$) (***Fig. 2***).

Association of BMD with all-cause and CVD death by relative HGS level

The proportional hazards assumption was satisfied for the main exposure variables in both cohorts (all $P > 0.05$). In the primary analysis cohort, compared with the high BMD tertile, the low BMD tertile was associated with a significantly higher risk of all-cause mortality in both the low relative HGS group and the high relative HGS group, with HRs of 1.26 (95% CI, 1.04–1.52) and 1.42 (95% CI, 1.16–1.74), respectively. Similar results were observed in the replication cohort (low relative HGS group: HR, 1.50; 95% CI, 1.04–2.14; high relative HGS group: HR, 1.75; 95% CI, 1.17–2.62). Each 1-SD decrease in BMD T-score was associated with a higher risk of all-cause mortality in the primary analysis cohort for both the low relative HGS group and the high relative HGS group, with HRs of 1.11 (95% CI, 1.01–1.20) and 1.24 (95% CI, 1.12–1.37), respectively. Consistent findings were obtained in the replication cohort (low relative HGS group: HR, 1.31; 95% CI, 1.12–1.52; high relative HGS group: HR, 1.30; 95% CI, 1.06–1.58). No statistically significant associations were observed between BMD and CVD mortality in either the primary analysis cohort or the replication cohort (both $P > 0.05$) (***Fig. 3***).

No statistically significant additive or multiplicative interaction between BMD and relative HGS was observed in either the primary analysis cohort or the

Table 1 **Baseline characteristics according to BMD tertiles in the primary analysis cohort and replication cohort**

Characteristics	Primary analysis cohort					Replication cohort				
	Overall (*n* = 10 920)	High BMD tertile (*n* = 3 569)	Medium BMD tertile (*n* = 3 652)	Low BMD tertile (*n* = 3 699)	*P*	Overall (*n* = 5 362)	High BMD tertile (*n* = 1 746)	Medium BMD tertile (*n* = 1802)	Low BMD tertile (*n* = 1814)	*P*
Age [years, mean (SD)]	60.15 (11.34)	59.51 (11.31)	60.04 (11.19)	60.88 (11.47)	< 0.001	60.65 (10.09)	60.68 (10.04)	60.59 (10.12)	60.68 (10.13)	0.957
Sex [*n* (%)]										
Men	4 291 (39.29)	1 486 (41.64)	1 460 (39.98)	1 345 (36.36)	< 0.001	2 410 (44.95)	784 (44.90)	812 (45.06)	814 (44.87)	0.993
Women	6 629 (60.71)	2 083 (58.36)	2 192 (60.02)	2 354 (63.64)		2 952 (55.05)	962 (55.10)	990 (54.94)	1 000 (55.13)	
Marital status [*n* (%)]										
Married	9 302 (85.18)	3 070 (86.02)	3 153 (86.34)	3 079 (83.24)	0.002	4 741 (88.42)	1 552 (88.89)	1 599 (88.73)	1 590 (87.65)	0.782
Singlehood	176 (1.61)	62 (1.74)	57 (1.56)	57 (1.54)		69 (1.29)	20 (1.15)	20 (1.11)	29 (1.60)	
Divorced	45 (0.41)	16 (0.45)	12 (0.33)	17 (0.46)		29 (0.54)	8 (0.46)	11 (0.61)	10 (0.55)	
Widowed	1 397 (12.79)	421 (11.80)	430 (11.77)	546 (14.76)		523 (9.75)	166 (9.51)	172 (9.54)	185 (10.20)	
Education [*n* (%)]										
Illiterate	3 299 (30.27)	1 021 (28.66)	1 092 (29.97)	1 186 (32.12)	0.011	1 406 (26.22)	476 (27.26)	453 (25.14)	477 (26.30)	0.462
Primary school	3 347 (30.71)	1 083 (30.40)	1 129 (30.98)	1 135 (30.74)		1 712 (31.93)	552 (31.62)	598 (33.19)	562 (30.98)	
Junior high school	3 126 (28.68)	1 063 (29.83)	1 066 (29.25)	997 (27.00)		1 681 (31.35)	535 (30.64)	552 (30.63)	594 (32.75)	
High school or higher	1 127 (10.34)	396 (11.11)	357 (9.80)	374 (10.13)		563 (10.50)	183 (10.48)	199 (11.04)	181 (9.98)	
Residing in urban areas [*n* (%)]	3 580 (32.78)	1 203 (33.71)	1 211 (33.16)	1 166 (31.52)	0.117	513 (9.57)	141 (8.08)	194 (10.77)	178 (9.81)	0.022
Smoking status [*n* (%)]										
Never	8 514 (77.97)	2 752 (77.11)	2 829 (77.46)	2 933 (79.29)	0.023	4 138 (77.17)	1 355 (77.61)	1 393 (77.30)	1 390 (76.63)	0.352
Former	200 (1.83)	78 (2.19)	73 (2.00)	49 (1.32)		101 (1.88)	40 (2.29)	26 (1.44)	35 (1.93)	
Current	2 206 (20.20)	739 (20.71)	750 (20.54)	717 (19.38)		1 123 (20.94)	351 (20.10)	383 (21.25)	389 (21.44)	
Drinking [*n* (%)]	3 025 (27.70)	1 072 (30.04)	1 060 (29.03)	893 (24.14)	< 0.001	1 498 (27.94)	506 (28.98)	508 (28.19)	484 (26.68)	0.298
BMI [kg/m^2, Median (IQR)]	24.71 (22.53, 27.04)	25.16 (23.07, 27.40)	24.69 (22.51, 27.03)	24.34 (22.08, 26.59)	< 0.001	25.06 (22.89, 27.31)	25.59 (23.54, 27.89)	25.21 (23.11, 27.44)	24.29 (22.20, 26.64)	< 0.001
Physical activity [MET-hours/week, Median (IQR)]	8.00 (2.86, 16.00)	8.67 (3.43, 17.14)	8.00 (2.86, 16.00)	8.00 (2.21, 14.83)	< 0.001	6.00 (2.00, 12.51)	6.86 (2.48, 12.86)	6.00 (2.00, 12.48)	5.33 (1.71, 12.00)	0.001
Hypertension [*n* (%)]	6 771 (62.01)	2 229 (62.45)	2 279 (62.40)	2 263 (61.18)	0.444	3 644 (67.96)	1 203 (68.90)	1 201 (66.65)	1 240 (68.36)	0.322
Diabetes [*n* (%)]	2031 (18.60)	757 (21.21)	667 (18.26)	607 (16.41)	< 0.001	1 227 (22.88)	463 (26.52)	405 (22.48)	359 (19.79)	< 0.001
CVD [*n* (%)]	813 (7.45)	273 (7.65)	257 (7.04)	283 (7.65)	0.516	315 (5.87)	110 (6.30)	102 (5.66)	103 (5.68)	0.654
SBP [mmHg, Median (IQR)]	139.67 (126.00, 154.33)	140.00 (126.67, 154.75)	140.67 (126.33, 155.00)	138.67 (125.08, 153.33)	0.001	140.00 (128.00, 153.00)	139.67 (128.33, 153.67)	139.33 (127.67, 152.67)	140.33 (127.67, 152.67)	0.725
DBP [mmHg, Median (IQR)]	80.33 (73.67, 87.33)	80.33 (74.00, 87.67)	80.67 (74.33, 87.67)	79.50 (72.67, 86.67)	< 0.001	80.00 (73.67, 87.00)	80.00 (73.67, 86.67)	80.67 (74.33, 87.33)	79.67 (73.33, 86.67)	0.165
Glucose [mmol/L, Median (IQR)]	5.67 (5.22, 6.32)	5.74 (5.25, 6.45)	5.67 (5.24, 6.33)	5.60 (5.16, 6.19)	< 0.001	5.82 (5.38, 6.56)	5.88 (5.41, 6.80)	5.81 (5.39, 6.54)	5.78 (5.35, 6.41)	< 0.001
Absolute HSG [kg, mean (SD)]	29.21 (9.43)	29.96 (9.43)	29.58 (9.25)	28.13 (9.50)	< 0.001	29.09 (10.54)	29.65 (10.81)	29.12 (10.51)	28.52 (10.27)	0.006
Relative HSG [kg/kg, mean (SD)]	0.47 (0.13)	0.47 (0.13)	0.47 (0.13)	0.46 (0.14)	< 0.001	0.45 (0.14)	0.45 (0.15)	0.45 (0.14)	0.46 (0.14)	0.169
BMD T-score [mean (SD)]	−0.66 (0.89)	0.23 (0.69)	−0.71 (0.43)	−1.48 (0.51)	< 0.001	−1.66 (1.05)	−0.64 (0.82)	−1.70 (0.55)	−2.59 (0.68)	< 0.001

Continuous variables expressed as mean (standard deviation) or median (interquartile range); categorical variables are expressed as n (%). Relative handgrip strength was defined as absolute handgrip strength (kg) divided by body weight (kg). Abbreviations: BMD, bone mineral density; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

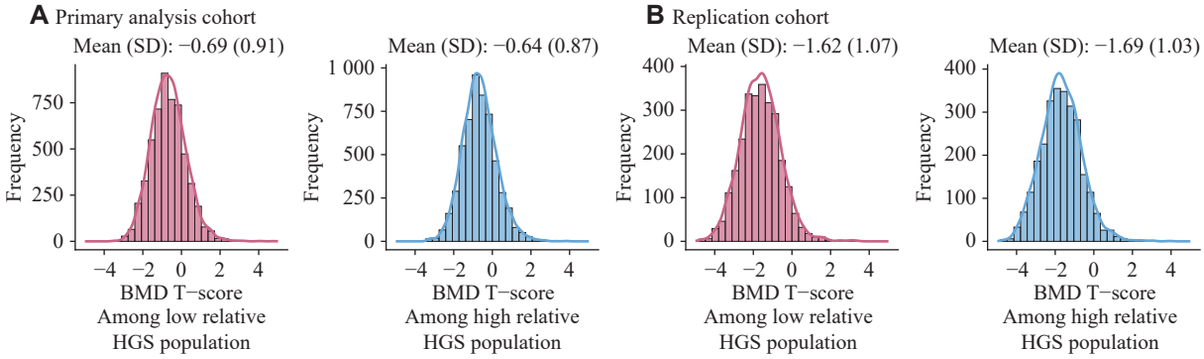

Fig. 2 **Distribution of BMD T-score by relative HGS groups.** A and B: Histograms showing the distribution of BMD T-score are presented for the primary analysis cohort (A) and the replication cohort (B). Relative handgrip strength was defined as absolute handgrip strength (kg) divided by body weight (kg) and relative HGS groups (high/low) were stratified by age- and sex-specific medians. Abbreviations: BMD, bone mineral density; HGS, handgrip strength; SD, standard deviation.

replication cohort (both $P > 0.05$) (***Table 2***).

Non-linear associations between BMD with all-cause and CVD mortality by relative HGS level

In the primary analysis cohort, a non-linear association between BMD T-score and all-cause mortality was observed in the high relative HGS group (P for non-linear < 0.05) but not in the low relative HGS group (P for non-linearity > 0.05). This finding was not validated in the replication cohort (both P for non-linearity > 0.05) (***Supplementary Fig. 2A***). For CVD mortality, no non-linear associations were found in either cohort (both P for non-linearity > 0.05) (***Supplementary Fig. 2B***).

Joint effects of relative HGS and BMD on all-cause and CVD mortality

Six subgroups were constructed to evaluate the joint effects of relative HGS and BMD on all-cause and CVD mortality (***Table 3***). In the primary analysis cohort, Kaplan–Meier analyses showed that the cumulative incidence of all-cause mortality differed significantly across the six groups (log-rank $P <$ 0.001), with the highest incidence observed in participants with both low relative HGS and low BMD. These findings were validated in the replication cohort (log-rank $P = 0.01$) (***Supplementary Fig. 3A***). For CVD mortality, a significant difference across groups was present in the primary analysis cohort (log-rank $P < 0.001$) but was not replicated in the validation cohort (log-rank $P = 0.4$) (***Supplementary Fig. 3B***). The cumulative PAR% of low relative HGS and low BMD was 10.8% (95% CI, 7.4% to 14.1%) for the primary analysis cohort and 13.1% (95% CI, 4.3% to 21.1 %) for the replication cohort.

After multivariable adjustment, the elevated risk of all-cause mortality associated with low relative HGS and low BMD remained consistent across both the primary analysis and replication cohorts. Compared with the high relative HGS and high BMD group, the low relative HGS with low BMD group showed a HR of 1.62 (95% CI, 1.35–1.96) for all-cause death in the primary analysis cohort. In the replication cohort, the corresponding HR was 1.59 (95% CI, 1.15–2.21). Low relative HGS with low BMD showed a higher risk of CVD death in the primary analysis cohort (HR, 1.84; 95% CI, 1.24–2.73), but the association was not statistically significant in the replication cohort (HR, 1.25; 95% CI, 0.57–2.75).

Subgroup analyses

Significant associations with all-cause mortality were observed across both age subgroups for the low relative HGS with low BMD group, with HRs of 1.73 (95% CI, 1.42–2.10) in participants aged ⩾ 65 years and 1.44 (95% CI, 1.01–2.05) in those aged < 65 years (***Fig. 4***). Further age-stratified analyses using four groups (40–54, 55–64, 65–74, and ⩾ 75 years) showed consistent results across all age groups, with no statistically significant association observed only in the 55-64 age group (***Supplementary Table 2***).

Significant associations with all-cause mortality were observed across both sex subgroups for the low relative HGS with high BMD group, with HRs of 1.73 (95% CI, 1.39–2.16) in men and 1.59 (95% CI, 1.21–2.08) in women (***Fig. 4***).

Sensitivity analysis

Multiple sensitivity analyses were performed to evaluate the robustness of the primary results. The associations of joint exposure to HGS and BMD with the risk of all-cause mortality remained consistent with the main findings after excluding participants with deaths occurring within the first two years of

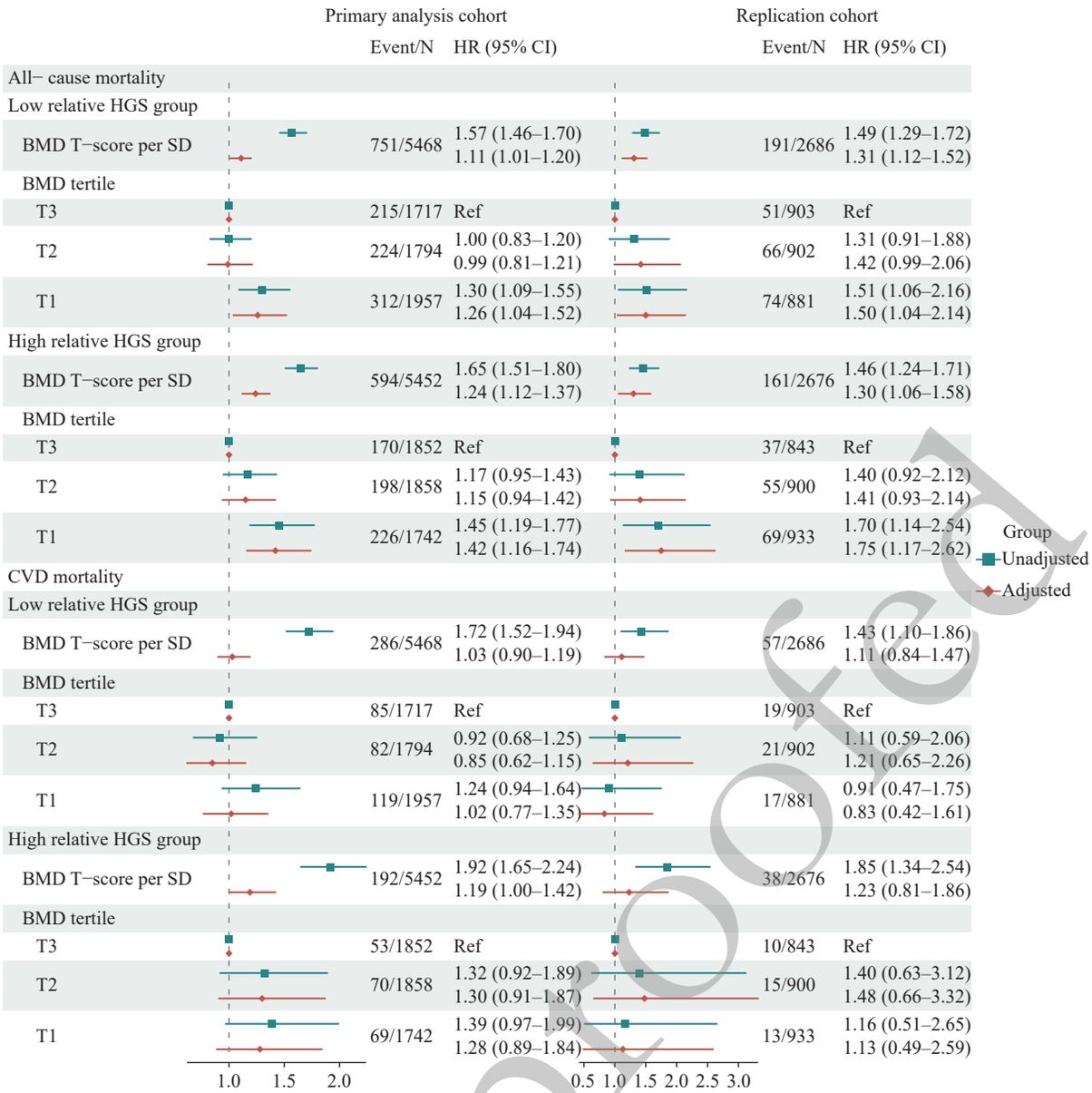

Fig. 3 **Association of BMD with all-cause and CVD mortality across different relative HGS groups in the primary analysis and replication cohort.** Adjusted model: adjusted for age, sex, smoking, drinking, hypertension, diabetes, physical activity, and CVD. Relative handgrip strength was defined as absolute handgrip strength (kg) divided by body weight (kg). Relative HGS groups (high/low) were stratified by age- and sex-specific medians. BMD tertiles (high/medium/low) were stratified by age- and sex-specific tertiles. T3: high BMD tertile; T2: medium BMD tertile; T1: low BMD tertile. Abbreviations: BMD, bone mineral density; CI, confidence interval; CVD, cardiovascular disease; HGS, handgrip strength; HR, hazard ratio.

follow-up (***Supplementary Tables 3*** and ***4***) or when using alternative measures of HGS, including absolute HGS alone and absolute HGS normalized by BMI (***Supplementary Tables 5–8***). Additionally, using the standard T-score cutoffs to classify BMD into three groups (normal, osteopenia, and osteoporosis) did not compromise the stability of the results (***Supplementary Tables 9*** and ***10***).

Discussion

In this cohort study of adults aged ≥18 years, we systematically evaluated the modifying and joint effects of muscle strength on the associations of BMD with all-cause mortality and, as an exploratory outcome, CVD mortality, with all analyses validated in independent datasets. We found no significant interaction between relative handgrip strength (HGS) and BMD for all-cause mortality ($P > 0.05$). However, the most consistent finding across both cohorts was that individuals with concurrently low BMD and low relative HGS had a 59% to 62% higher risk of all-cause mortality compared with those with neither risk factor. Overall, our findings suggest that the

Table 2 **Interaction between the BMD and relative HGS on all-cause and CVD mortality**

Characteristics	Additive effect		Multiplicative effect	
	RERI (95% CI)	AP (95% CI)	HR (95% CI)	*P* for interaction
Primary analysis cohort				
All-cause mortality				0.172
Medium BMD * Low relative HGS	0.17 (−0.05–0.40)	0.21 (–0.07–0.49)	1.24 (0.94–1.63)	
Low BMD * Low relative HGS	0.17 (–0.06–0.41)	0.17 (–0.06–0.41)	1.26 (0.97–1.65)	
CVD mortality				0.209
Medium BMD * Low relative HGS	0.34 (–0.01–0.69)	0.49 (–0.01–0.83)	1.53 (0.95–2.44)	
Low BMD * Low relative HGS	0.16 (–0.21–0.52)	0.19 (–0.26–0.64)	1.25 (0.79–1.96)	
Replication cohort				
All-cause mortality				0.764
Medium BMD * Low relative HGS	–0.08 (–0.69–0.53)	–0.07 (–0.60–0.46)	0.99 (0.57–1.73)	
Low BMD * Low relative HGS	0.11 (–0.48–0.72)	0.08 (–0.33–0.50)	1.16 (0.68–2.00)	
CVD mortality				0.786
Medium BMD * Low relative HGS	0.05 (–0.86–0.95)	0.05 (–0.95–1.06)	1.17 (0.42–3.21)	
Low BMD * Low relative HGS	0.30 (–0.45–1.05)	0.41 (–0.61–1.44)	1.44 (0.50–4.17)	

Multivariable Cox models were adjusted for age, sex, smoking, drinking, hypertension, diabetes, physical activity, and CVD. Relative HGS was defined as absolute handgrip strength (kg) divided by body weight (kg). Relative HGS groups (high/low) were stratified by age- and sex-specific medians. BMD groups (high/medium/low) were stratified by age- and sex-specific tertiles. Abbreviations: AP, attributable proportion due to interaction; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; RERI, relative excess risk due to interaction.

Table 3 **Association of joint exposure to relative HGS and BMD with all-cause mortality and CVD mortality in the primary analysis cohort and replication cohort**

Outcome	High relative HGS with high BMD	High relative HGS with medium BMD	High relative HGS with low BMD	Low relative HGS with high BMD	Low relative HGS with medium BMD	Low relative HGS with low BMD
Primary analysis cohort						
All-cause mortality						
Person-years	16 649.23	17 372.28	16 849.16	16 303.46	16 633.16	17 289.65
Event/total (*n*, %)	170/1852 (9.18%)	198/1858 (10.66%)	226/1 742 (12.97%)	215/1 717 (12.52%)	224/1 794 (12.49%)	312/1957 (15.94%)
Crude model	Ref	1.17 (0.95–1.43)	1.45 (1.19–1.77)	1.39 (1.14–1.70)	1.39 (1.14–1.69)	1.82 (1.51–2.19)
Adjusted model	Ref	1.16 (0.94–1.42)	1.44 (1.18–1.76)	1.43 (1.17–1.75)	1.35 (1.10–1.64)	1.62 (1.35–1.96)
CVD mortality						
Person-years	17 073.83	17 818.53	17 530.65	16 861.28	17 298.15	18 049.68
Event/total (*n*, %)	53/1852 (2.86%)	70/1858 (3.77%)	69/1 742 (3.96%)	85/1 717 (4.95%)	82/1 794 (4.57%)	119/1957 (6.08%)
Crude model	Ref	1.40 (0.92–2.12)	1.71 (1.14–2.54)	1.30 (0.85–1.98)	1.70 (1.13–2.54)	1.96 (1.32–2.91)
Adjusted model	Ref	1.41 (0.93–2.13)	1.76 (1.18–2.63)	1.22 (0.80–1.86)	1.72 (1.15–2.58)	1.84 (1.24–2.73)
Replication cohort						
All-cause mortality						
Person-years	5 464.88	5 809.32	5 985.47	5 818.25	5 768.93	5 605.63
Event/total (*n*, %)	37/843 (4.39%)	55/900 (6.11%)	69/933 (7.40%)	51/903 (5.65%)	66/902 (7.32%)	74/881 (8.40%)
Crude model	Ref	1.32 (0.92–1.89)	1.39 (0.97–1.99)	1.75 (1.24–2.46)	1.61 (1.14–2.27)	2.16 (1.57–2.99)
Adjusted model	Ref	1.30 (0.91–1.85)	1.28 (0.89–1.83)	1.56 (1.11–2.21)	1.33 (0.94–1.88)	1.59 (1.15–2.21)
CVD mortality						
Person-years	5 531.64	5 904.08	6 130.22	5 910.97	5 905.17	5 776.26
Event/total (*n*, %)	10/843 (1.19%)	15/900 (1.67%)	13/933 (1.39%)	19/903 (2.10%)	21/902 (2.33%)	17/881 (1.93%)
Crude model	Ref	1.40 (0.63–3.12)	1.16 (0.51–2.66)	1.78 (0.83–3.83)	1.97 (0.93–4.18)	1.62 (0.74–3.54)
Adjusted model	Ref	1.42 (0.64–3.17)	1.15 (0.50–2.62)	1.58 (0.73–3.41)	1.92 (0.90–4.08)	1.25 (0.57–2.75)

Adjusted model: adjusted for age, sex, smoking, drinking, hypertension, diabetes, physical activity, and CVD. Relative HGS was defined as absolute handgrip strength (kg) divided by body weight (kg). Relative HGS groups (high/low) were stratified by age- and sex-specific medians. BMD groups (high/medium/low) were stratified by age- and sex-specific tertiles. Abbreviations: BMD, bone mineral density; CI, confidence interval; CVD, cardiovascular disease; HGS, handgrip strength; HR, hazard ratio.

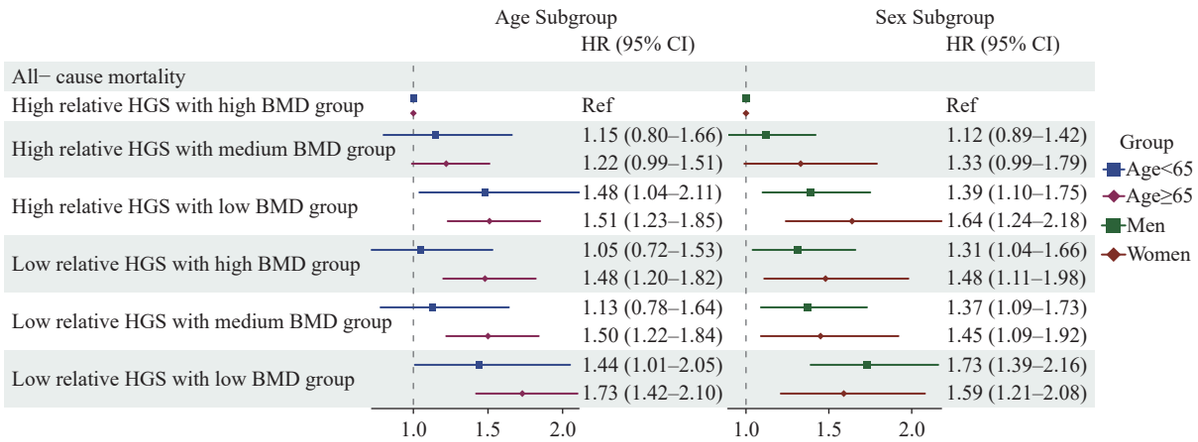

Fig. 4 **Subgroup analysis of associations between joint relative HGS and BMD exposure with all-cause and CVD mortality across age and sex subgroups.** For age-stratified analyses (< 65 vs. ≥65 years), models were adjusted for sex, smoking, drinking, hypertension, diabetes, physical activity, and CVD at baseline. For sex-stratified analyses (men vs. women), models were adjusted for age, smoking, drinking, hypertension, diabetes, physical activity, and CVD at baseline. Relative handgrip strength was defined as absolute handgrip strength (kg) divided by body weight (kg). Relative HGS groups (high/low) were stratified by age- and sex-specific medians. BMD tertiles (high/medium/low) were stratified by age- and sex-specific tertiles. Abbreviations: BMD, bone mineral density; CI, confidence interval; CVD, cardiovascular disease; HGS, handgrip strength; HR, hazard ratio.

concurrent presence of low BMD and low muscle strength defines a high-risk subgroup that may derive the greatest benefit from integrated musculoskeletal assessment.

Existing research has primarily focused on the association between sarcopenia and osteoporosis. Previous studies have suggested a potential additive effect of these two conditions on all-cause mortality in older adults, with individuals having both conditions facing a 282% increase in risk[23]. Within the sarcopenia diagnostic framework, muscle strength, a core and modifiable indicator for maintaining physical function and health, has gained increasing attention[24]. Although low muscle strength is known to be associated with low BMD[25], it remains unclear whether these two factors jointly associate with mortality, or whether muscle strength modifies the BMD–mortality relationship, particularly in the Chinese general population.

Previous studies have demonstrated that lower HGS and lower BMD are each independently associated with increased risks of all-cause mortality and cardiovascular disease, with risk increases ranging from 13% to 17%[9-10]. In our study, low BMD combined with low relative HGS was associated with a significantly increased risk of all-cause mortality, with the increase ranging from 78% to 133% in both cohorts. A study of 6 565 Norwegian adults aged 50 to 79 years reported that high HGS did not modify the association between low distal forearm BMD and all-cause mortality[26]. Similarly, our study, which included a larger sample of 16 282 adults, found no significant interaction between HGS and BMD, and the association between BMD and all-cause mortality was consistently observed in both low and high HGS groups. As a prespecified exploratory endpoint, the CVD mortality results were inconsistent between cohorts, with wide confidence intervals and failed replication; these findings should therefore be interpreted as hypothesis generating rather than confirmatory.

The mechanisms linking bone density and muscle strength to all-cause mortality are multifaceted and interconnected, spanning biomechanical, inflammatory, hormonal, nutritional, and endocrine pathways[11-12]. Osteokines and myokines secreted by bone and muscle, respectively, are known to interact with and regulate distal tissues, including the heart, brain, kidneys, and liver[27-28]. For instance, myokines interact with the immune system to exert anti-inflammatory effects[29]. Declining muscle strength is associated with mitochondrial dysfunction[30], reduced autophagy[31], and increased protein degradation[32]. Both muscle and bone contribute to health through distinct yet interconnected pathways, and preserving their function may reduce mortality risk by mediating the regulatory effects of osteokines and myokines on distal tissues and by protecting against acute and chronic diseases[33].

From a public health perspective, maintaining musculoskeletal health, encompassing both bone and muscle integrity, may contribute to healthy aging and is associated with lower mortality across the life course, as both bone and muscle are cornerstones of health throughout life. The Adult Health Examination Project Recommendation Guide (2025 Edition),

issued by the National Health Commission, recommends bone mineral density testing from age 40[34], and the Chinese Physical Activity Guidelines (2021) advise muscle strength training[35]. Current prevention strategies often target bone and muscle separately. Our findings for all-cause mortality are robust and demonstrate that the combination of low BMD and low muscle strength is associated with a substantially increased risk of all-cause mortality, with the estimated PAR% suggesting that 10.8% of all-cause deaths in the primary analysis cohort and 13.1% in the replication cohort were attributable to this high-risk musculoskeletal profile. Individuals presenting with both low BMD and low muscle strength constitute a high-risk subgroup with markedly increased mortality, and it is precisely within this subgroup that combined musculoskeletal screening may prove most valuable for early identification and risk stratification in community health examinations.

This study has several key strengths. First, the large sample size and long follow-up period provide adequate statistical power. Second, the use of an independent validation cohort enhances the reproducibility and reliability of the findings. Third, the inclusion of adults aged 18 years and older supports the generalizability of the conclusions to the entire adult population. Fourth, rigorous statistical methods were applied to assess the joint effects of BMD and handgrip strength, incorporating both absolute HGS and relative HGS adjusted for body weight and BMI.

This study has some limitations. First, heel quantitative ultrasound-derived T-scores are a surrogate marker, not DXA-measured BMD. As the WHO criteria were originally based on DXA, the present findings should be interpreted cautiously in light of this distinction. Second, the generalizability of the study is limited, as young adults (aged < 40 years) accounted for only 3.41% of the total sample. Third, baseline BMD differed markedly between the two cohorts. This marked difference is likely multifactorial, as the replication cohort had a higher prevalence of diabetes and reported lower levels of physical activity than the primary analysis cohort. In addition, between-cohort differences in sex distribution, device calibration, recruitment strategies, or secular changes over the study periods may have also contributed. Nonetheless, the consistent association across both cohorts reinforces the robustness of our findings despite baseline differences. Fourth, both HGS and BMD were measured only once at baseline, precluding the capture of dynamic trajectories, whereas rapid declines in muscle strength or accelerated bone loss may predict mortality risk more strongly than single measurements. Fifth, although we evaluated both absolute HGS and relative HGS adjusted for body weight and BMI, other functional muscle measures, such as gait speed or skeletal muscle mass, were not assessed. Sixth, the possibility of residual confounding cannot be fully ruled out, given that we lacked data on several key BMD determinants, including menopausal status, hormone replacement therapy, corticosteroid use, osteoporosis medication, and vitamin D/calcium supplementation, as well as comorbidities such as chronic kidney disease and rheumatoid arthritis. These limitations should be considered when interpreting the results. Future studies incorporating these covariates are needed.

In conclusion, low BMD combined with low handgrip strength is consistently associated with increased all-cause mortality. These findings support a combined musculoskeletal approach integrating bone and muscle assessment rather than addressing them separately. Combined screening for both low BMD and low muscle strength in community health examinations may facilitate early identification of high-risk individuals and inform targeted preventive strategies, with emphasis on early intervention beginning in middle age.

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Author contributions

Xinyi Huang: Conceptualization, Methodology,

Software, Formal Analysis, Investigation, Data curation, Writing —original draft, Visualization; **Ningli Han**: Validation, Formal analysis, Writing —original draft; **Kai Ling**: Project administration, Resources; **Yu Liu**: Resources; **Qun Li**: Resources; **Ting Zhao**: Investigation; **Jing Miao**: Investigation; **Jinxin Cai**: Resources; **Jiahui Liu**: Data curation; **Yao Fan**: Investigation; **Chong Shen**: Conceptualization, Writing —review & editing, Project administration, Funding acquisition, Supervision.

Data availability

Available upon request.

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