

Osteoporosis is a novel risk factor of infections and sepsis: A cohort study

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Summary

Background Accumulating evidence suggests the interaction of bone metabolism and the immune system, but how bone health is associated with the risk of infections remains unknown.

Methods This study aimed to investigate the relationship of bone mineral density (BMD) with the risk of common infections and sepsis in Hong Kong Osteoporosis Study (HKOS). A prospective cohort study, initiated in 1995 and followed until 31 December 2020, of 5,717 participants examined the association of BMD at three skeletal sites (lumbar spine, femoral neck, and total hip) with common infections - pneumonia, urinary tract infection (UTI), skin infection, and sepsis. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI).

Findings During the median follow-up of 17 years, higher BMD T-scores at the femoral neck and total hip were significantly associated with the reduced risk of pneumonia (HRs 0.89 and 0.87; 95% CIs 0.82 to 0.98 and 0.81 to 0.95), UTI (HRs 0.85 and 0.86; 95% CIs 0.76 to 0.94 and 0.78 to 0.95), skin infection (HRs 0.85 and 0.82; 95% CIs 0.74 to 0.97 and 0.73 to 0.93), and sepsis (HRs 0.83 and 0.82; 95% CIs 0.71 to 0.97 and 0.72 to 0.94). A significant association was observed for the lumbar spine BMD T-score with the risk of skin infection (HR 0.86; 95% CI: 0.78 to 0.95) but not with other infections and sepsis. Similarly, participants with osteoporosis, but not osteopenia, were significantly associated with an increased risk of infections and sepsis compared to those with normal BMD.

Interpretation BMD is a novel risk factor of infections and sepsis. People with low BMD, particularly those with osteoporosis, are at higher risk of infections and sepsis than those with normal BMD. Further studies on whether improving bone health can reduce the risk of infections and sepsis are warranted.

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Introduction

Infections have been one of the leading causes of death globally,¹ and severe infection can lead to sepsis, the life-threatening organ dysfunction resulting from a dys-regulated host response to infections. In 2020, the World Health Organization (WHO) announced an official call for global action on sepsis by improving the

prevention, diagnosis, and treatment of sepsis.^{2,3} Therefore, it is crucial to identify the risk factors of infections and sepsis.

Osteoimmunology is the study of the interaction between the hematological system, immune system, and bone metabolism. Although bone is commonly considered as an inert organ, bone cells indeed can secrete several important molecules regulating multiple physiological processes, such as energy metabolism and the regulation of immune system.⁴ Osteoblasts, the bone formation cells, secrete interleukin-7 (IL-7) that is important for lymphocyte production. The deletion of osteoblast-specific IL-7 leads to lymphopenia with a reduced number of common lymphoid progenitors.⁵ Similarly, the deletion of

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Research in context

Evidence before this study

The immune system and bone metabolism interact with each other. We searched PubMed for research on osteoporosis, infections, and sepsis using the search terms ((osteoporosis[MeSH]) OR "bone mineral density" OR "BMD") AND (infections[MeSH] OR "pneumonia" OR "urinary tract infection" OR "skin infection" OR "sepsis") AND ("predict" OR "association" OR "associated") without language or date restrictions, up to Dec 31, 2021, and identified more than 800 studies. We found no research on the association of osteoporosis or low BMD, as the exposure, with the subsequent risk of infections and sepsis.

Added value of this study

We conducted the first prospective cohort analysis and examined the association of low BMD and osteoporosis with the subsequent risk of pneumonia, urinary tract infection (UTI), and skin infection, which are infectious diseases with relatively high incidence in Hong Kong. We also investigated the relationship of low BMD and osteoporosis with sepsis. This study suggests low BMD and osteoporosis as risk factors for infectious diseases and sepsis, which further supports the intimate interaction of bone and the immune system.

Implications of all available evidence

Low BMD is a novel risk factor for some common infections and sepsis. People with low BMD, particularly osteoporosis, should be aware of the potential increased risk of infections and sepsis.

osteoblasts and bone-specific deletion of delta-like 4 will reduce T-lineage competent progenitor.⁶ Lipocalin-2, another protein secreted by osteoblasts, can also mediate immune response and inhibit bacterial growth.⁷ These studies all demonstrate the regulatory role of bone metabolism in the immune system.

Considering the interplay between bone metabolism and the immune system, we hypothesized that higher BMD is associated with a reduced risk of infections and sepsis. We aimed to evaluate the association of BMD with pneumonia, urinary tract infection (UTI), skin infection, and sepsis in the Hong Kong Osteoporosis Study (HKOS), a prospective study of osteoporosis initiated in 1995.

Methods

Study design

The details of the HKOS have been described previously.⁸ In brief, the HKOS recruited 9,449 Southern Chinese community dwellers residing in Hong Kong

from 1995 to 2010 and collected their clinical, biomedical, BMD, and genetic data. The participants' lifestyle, physical activity, medical condition, smoking, and drinking habits were also collected through questionnaires. Ethics approval has been obtained by the Institutional Review Board (IRB) of The University of Hong Kong/HA HKW, Hong Kong Special Administrative Region. All participants gave informed consent to participate in the HKOS.

To follow up various clinical outcomes, participants (n=9,261) were linked to a territory-wide electronic health record database, Clinical Data Analysis Reporting System (CDARS), via an anonymized reference key. The CDARS is managed by the Hong Kong Hospital Authority (HKHA) that provides records of admission, prescription, diagnosis, procedures, laboratory test results, and deaths of participants. The database has been widely used in population-based studies.^{9–11} Among participants linked to the CDARS, 7,890 of them had BMD T-score available at all three skeletal sites studied (lumbar spine, femoral neck, and total hip). After excluding participants with missing records of the covariates (height, weight, smoking and drinking status, physical activeness, serum 25-Hydroxyvitamin D (25(OH)D), serum calcium, serum phosphate; n=1,967), and those having pneumonia (n=62), UTI (n=86), skin infection (n=65), or sepsis (n=10) diagnosis at the baseline, 5,717 subjects (4,072 women, 1,645 men) were included in the final analyses. We compared the distributions of various characteristics (age, sex, BMI, BMD, smoking and drinking status, physical activeness, 25(OH)D, calcium, and phosphate) between the cohorts with and without exclusion, the distribution of cohort characteristics after exclusion resembled those before the exclusion, which implied the randomness of missing records and justified the eligibility of our exclusion.

BMD measurement

The BMD of the participants in the study cohort were measured using a dual-energy X-ray absorptiometer (DXA) (Hologic Inc., Marlborough, MA, USA) by trained technicians using a standard protocol of measurement at three skeletal sites, including lumbar spine L1-L4, femoral neck, and total hip. Daily quality control scans were conducted using the spine phantom. BMD T-score was calculated as the difference between the individual BMD and the average BMD of young adults of the same sex and ethnicity in standard deviation (SD).

Outcome ascertainment and follow-up

All participants in the study cohort were followed until the outcome of interest, date of death, or December 31, 2020 (end of study), whichever came earlier. Among various infectious diseases, we selected common infections that have been captured by CDARS with high coverage (>80%) of all cases in Hong Kong according to

the Hospital Authority Statistical Report.¹² On this basis, the primary outcomes of this study were three infection groups (pneumonia, UTI, skin infection) and sepsis. The three infection groups and sepsis were defined in previous studies using the International Classification of Diseases 9th edition (ICD-9) codes: 480-487.0 for pneumonia,¹³ 599.0 for UTI,¹⁴ 680-686 for skin infection,¹⁵ and 038-038.9 for sepsis.¹⁶ The details of the ICD-9 codes are in Supplementary Table S1. Given that the definition of sepsis has been changing over time with the third international consensus definitions for sepsis and septic shock (Sepsis-3) became available in 2016¹⁷ and our cohort was initiated in 1995, we also evaluated the validity of sepsis' ICD-9 codes of 0.38-038.9 in CDARS. Sepsis is defined as organ dysfunction caused by a dysregulated host response to infection in the Sepsis-3, and organ dysfunction can be defined by an increase in the Sequential Organ Failure Assessment (SOFA) scores ≥ 2 . The sepsis case was considered true positive if the case had a SOFA score ≥ 2 . Positive predictive value (PPV) was defined as the number of true positives (cases with SOFA score ≥ 2) divided by the total number of true positives plus false positives (those with ICD-9 codes of 0.38-038.9). Among 100 potential sepsis cases randomly chosen, 77 of them had SOFA scores ≥ 2 , and the corresponding PPV was 0.77 (95% Confidence Interval [CI]: 0.67-0.85).

Statistical analysis

We compared the participant characteristics between females and males. The baseline characteristics of the study cohort were summarized as mean \pm standard deviation (SD) for continuous variables; frequency (n) and percentages (%) for categorical variables. Independent sample t-tests¹⁸ and chi-square tests were used to compare the differences between continuous and categorical variables, respectively.

We used the unadjusted and adjusted Cox proportional hazards models to determine the association of the BMD T-scores at the three different sites (lumbar spine L1-L4, femoral neck, and total hip) with the risk of infections and sepsis. Two models were used: Model 1 was the crude model. Model 2 was the fully adjusted model with adjustments: age, sex, height, weight, smoking status, drinking status, baseline physical activity, presence of comorbidities of infection (chronic obstructive pulmonary disease [COPD], congestive heart failure, chronic liver disease, chronic renal disease, cerebrovascular accident, diabetes mellitus, and cancer)¹⁹, serum 25(OH)D, serum calcium, serum phosphate, prescription of steroids and bisphosphonates within one year, and history of major osteoporotic fracture (at the spine, hip, wrist, and/or humerus) within one year prior to the baseline. The details of the covariates and ICD-9 codes used are provided in Supplementary Table S1. The proportional hazard assumptions

were verified by checking the plots of Schoenfeld residuals over time and no violation was observed. Interaction terms were used in the cox-regression to evaluate if the association was significantly differed by age (< 65 and ≥ 65), sex, and vitamin D deficiency/insufficiency (defined as < 50 nmol/L according to the Institute of Medicine definition).²⁰

In addition to BMD T-scores, we evaluated the association of osteoporosis status (osteoporosis: T-score < -2.5 , osteopenia: $-2.5 < \text{T-score} < -1$, and normal: T-score > -1) with the risk of infections and sepsis. Kaplan-Meier curves were used to display the cumulative survival probability for each of the clinical outcomes, and comparisons were performed with the log-rank tests. We also performed sensitivity analyses to test the robustness of our findings. First, the associations of raw BMD with different clinical outcomes were evaluated. Second, given that people with the history of fracture would have an increased risk of infections, we repeated the association analyses in the cohort excluding patients with the history of major osteoporotic fractures within one year prior to the baseline, instead of adjusting for the baseline history of fractures.

All statistical analyses were conducted using R version 4.1.0. (www.R-project.org). All statistical tests were two-sided, and P-value < 0.05 was considered statistically significant.

Role of the funding source

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Results

Cohort characteristics

A total of 5,717 HKOS cohort participants were included in the final analyses (Figure 1), in which 4,072 were females and 1,645 were males (Table 1). Males had higher average BMD, BMD T-scores, and incidence rate of pneumonia, skin infection, and sepsis than females. They also had higher mean height, weight, body mass index (BMI) and were more physically active than females, while females had a higher incidence rate of UTIs and were more likely to be non-drinkers and non-smokers than males. A lower incidence of chronic renal disease, stroke, diabetes, and cancer were observed in females (Table 1). Similar results were observed if the Mann-Whitney U test was used to evaluate the differences in continuous variables (Supplementary Table S2).

BMD and the risk of infections and sepsis

The number of participants who developed pneumonia, UTI, skin infection, and sepsis during the study period

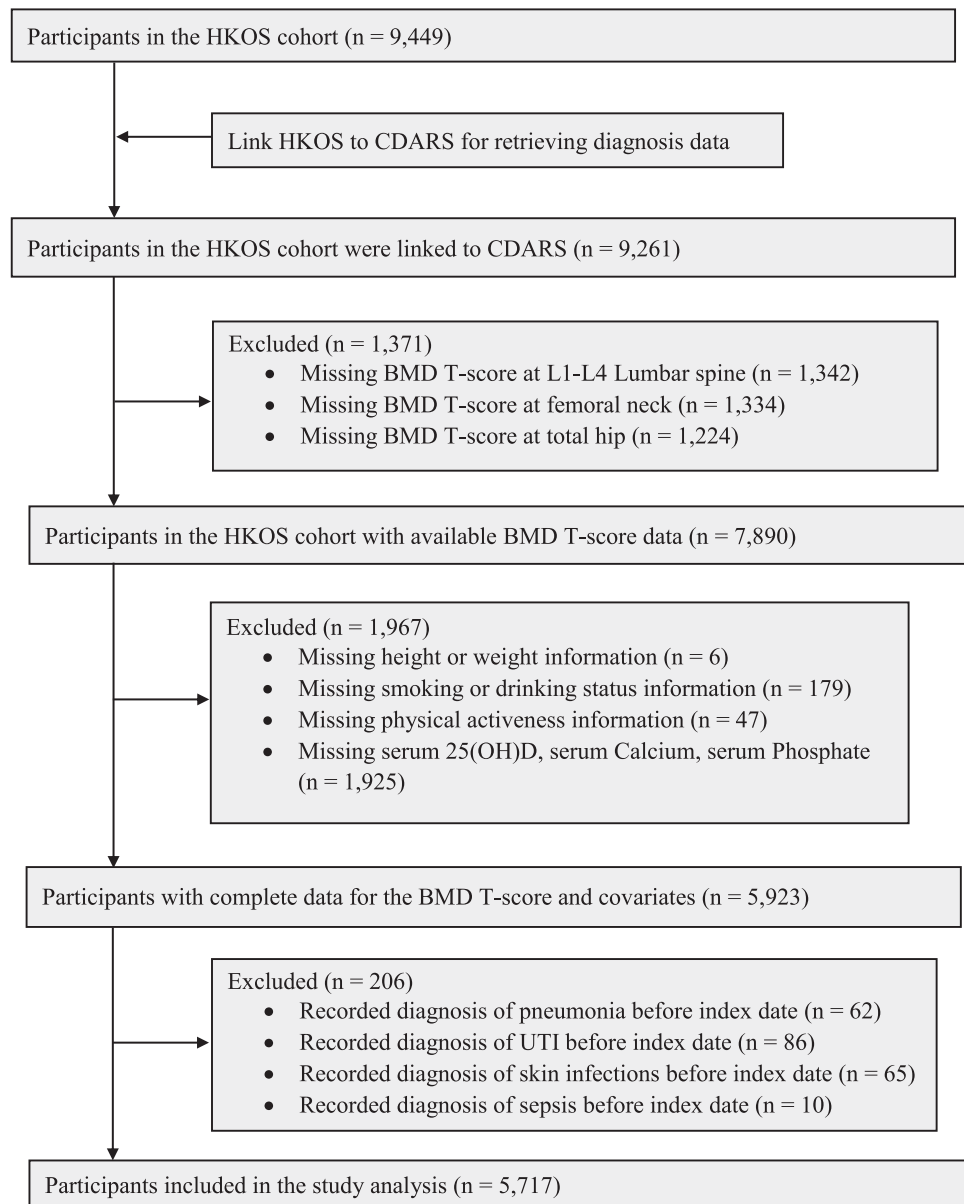


Figure 1. Selection of cohort.

was 700, 489, 298, and 252, respectively. The median follow-up time was 16.9 years (interquartile range, 14.4 – 18.3 years), 16.9 (14.2 – 18.3 years), 17.0 (14.5 – 18.3 years), and 17.1 years (14.7 – 18.3 years), resulting in an incidence rate of 7.77, 5.43, 3.29, and 2.74 per 1000 person-years for pneumonia, UTI, skin infection, and sepsis respectively (Supplementary Table S3). In the unadjusted model, BMD T-scores at the lumbar spine, femoral neck, and total hip were significantly associated with reduced risk of infections and sepsis (all $P < 0.001$). In the fully adjusted model, BMD T-scores at the femoral neck and total hip remained significantly associated with reduced risk of pneumonia (HRs 0.89 and

0.87; 95% CIs 0.82–0.98 and 0.81–0.95), UTI (HRs 0.85 and 0.86; 95% CIs 0.76–0.94 and 0.78–0.95), skin infection (HRs 0.85 and 0.82; 95% CIs 0.74–0.97 and 0.73–0.93), and sepsis (HRs 0.83 and 0.82; 95% CIs 0.71–0.97 and 0.72–0.94). We also evaluated the association of BMD with the 77 validated cases of sepsis by Sepsis-3 and found that the association was even more significant in terms of hazard ratio and p-value (Supplementary Table S4). The BMD T-score at the lumbar spine L1-L4 was still significantly associated with a reduced risk of skin infection (HR 0.86; 95% CI: 0.78–0.95), but its association with other outcomes became statistically insignificant (Table 2).

	Female	Male	P-value
Subjects, n (%)	4072 (71.2)	1645 (28.8)	
Pneumonia Incidence, n (%)	424 (10.41)	276 (16.78)	<0.001
UTI Incidence, n(%)	370 (9.09)	119 (7.23)	0.027
Skin Infection Incidence, n(%)	182 (4.47)	116 (7.05)	<0.001
Sepsis Incidence, n (%)	157 (3.86)	95 (5.78)	0.002
Age (years), mean ± SD	50.60 (16.14)	58.97 (16.16)	<0.001
Height (meters), mean ± SD	1.55 (0.07)	1.66 (0.07)	<0.001
Weight (kg), mean ± SD	54.13 (9.20)	64.65 (10.24)	<0.001
BMI, mean ± SD	22.61 (3.77)	23.36 (3.20)	<0.001
Drinking Status, n (%)			<0.001
Non-drinker	3826 (94.0)	1199 (72.9)	
Ex-drinker	62 (1.5)	146 (8.9)	
Current-drinker	184 (4.5)	300 (18.1)	
Smoking Status, n (%)			<0.001
Non-smoker	3887 (95.5)	1118 (68.0)	
Ex-smoker	87 (2.1)	327 (19.9)	
Current-smoker	98 (2.4)	200 (12.2)	
Physically Active, n (%)	1676 (41.2)	849 (51.6)	<0.001
Presence of Comorbidities, n (%)	185 (4.5)	157 (9.5)	<0.001
Presence of COPD, n (%)	29 (0.7)	23 (1.4)	0.020
Presence of Congestive Heart Failure, n (%)	13 (0.3)	10 (0.6)	0.183
Presence of Chronic Liver Disease, n (%)	7 (0.2)	3 (0.2)	1.000
Presence of Chronic Renal Disease, n (%)	1 (0.0)	4 (0.2)	0.042
Presence of Stroke, n (%)	32 (0.8)	38 (2.3)	<0.001
Presence of Diabetes, n (%)	78 (1.9)	65 (4.0)	<0.001
Presence of Cancer, n (%)	50 (1.2)	42 (2.6)	<0.001
Serum 25(OH)D (nmol/L), mean ± SD	54.16 (16.80)	53.28 (15.54)	0.089
Serum Calcium (mmol/L), mean ± SD	2.386 (0.089)	2.391 (0.090)	0.032
Serum Phosphate (mmol/L), mean ± SD	1.146 (0.151)	1.075 (0.155)	<0.001
Prescription of Steroids, n(%)	35 (0.9)	31 (1.9)	0.002
Prescription of Bisphosphonates, n (%)	22 (0.5)	0 (0.0)	0.006
History of Major Osteoporotic Fracture, n(%)	82 (2.0)	21 (1.3)	0.074
L1 - L4 BMD, mean ± SD	0.880 (0.166)	0.958 (0.165)	<0.001
Femoral Neck BMD, mean ± SD	0.678 (0.131)	0.727 (0.129)	<0.001
Total Hip BMD, mean ± SD	0.771 (0.138)	0.869 (0.139)	<0.001
L1 - L4 BMD T-score, mean ± SD	-0.994 (1.295)	-0.254 (1.295)	<0.001
Femoral Neck BMD T-score, mean ± SD	-1.005 (1.274)	-0.719 (0.888)	<0.001
Total Hip BMD T-score, mean ± SD	-0.853 (1.369)	-0.527 (0.979)	<0.001

Table 1: Demographic information of the study participants (N=5,717).

Adjusting for BMI instead of height and weight or adjusting for vitamin D deficiency/insufficiency instead of continuous serum 25(OH)D resulted in similar results (Supplementary Table S5 and S6).

Using raw BMD instead of BMD T-score in the sensitivity analyses resulted in a similar conclusion (Supplementary Table S7). Similar results were also observed by repeating the analyses in the cohort excluding participants with a history of osteoporotic fractures or in the original cohort but adjusted for the baseline history of osteoporotic fractures (Supplementary Table S8 and S9). Interaction terms in the regression model revealed that the association was not significantly

different by age, sex, and vitamin D deficiency/insufficiency (data not shown).

Osteoporosis status and the risk of infections and sepsis

Kaplan-Meier analysis showed an increased risk of infections and sepsis in participants with osteopenia and osteoporosis; the P values for the log-rank tests were <0.0001 (Figure 2). Compared to participants with normal BMD (Table 3), participants having osteoporosis at any sites were significantly associated with a higher risk of pneumonia (HR 1.39; 95% CI 1.07-1.81),

	Model 1: Hazard Ratio (95% CI)	P-value	Model 2: Hazard Ratio, (95% CI)	P-value
Pneumonia				
BMD T-score at				
L1-L4 Lumbar spine	0.74 (0.70, 0.78)	<0.001	0.99 (0.93, 1.06)	0.852
Femoral neck	0.57 (0.49, 0.56)	<0.001	0.89 (0.82, 0.98)	0.018
Total hip	0.57 (0.54, 0.60)	<0.001	0.87 (0.81, 0.95)	0.001
UTI				
BMD T-score at				
L1-L4 Lumbar spine	0.72 (0.67, 0.77)	<0.001	1.01 (0.93, 1.09)	0.892
Femoral neck	0.54 (0.49, 0.58)	<0.001	0.85 (0.76, 0.94)	0.002
Total hip	0.59 (0.55, 0.63)	<0.001	0.86 (0.78, 0.95)	0.002
Skin infection				
BMD T-score at				
L1-L4 Lumbar spine	0.82 (0.75, 0.89)	<0.001	0.86 (0.78, 0.95)	0.003
Femoral neck	0.75 (0.69, 0.82)	<0.001	0.85 (0.74, 0.97)	0.019
Total hip	0.75 (0.69, 0.82)	<0.001	0.82 (0.73, 0.93)	0.002
Sepsis				
BMD T-score at				
L1-L4 Lumbar spine	0.77 (0.70, 0.85)	<0.001	0.99 (0.89, 1.10)	0.820
Femoral neck	0.54 (0.48, 0.60)	<0.001	0.83 (0.71, 0.97)	0.020
Total hip	0.59 (0.54, 0.65)	<0.001	0.82 (0.72, 0.94)	0.005

Table 2: Cox proportional hazards models examining the relationship between the BMD T-scores and the risk of infections and sepsis.
 Model 1: Crude model.
 Model 2: Adjusted for age, sex, height, weight, smoking status, drinking status, physical activeness, presence of comorbidities of infection, serum 25(OH)D, serum calcium, serum phosphate, prescription of steroids and bisphosphonates within one-year, and history of major osteoporotic fracture within one-year.

UTI (HR 1.38; 95% CI 1.01-1.89), and skin infections (HR 1.60; 95% CI 1.07-2.40), while the association with sepsis was marginal (HR 1.48; 95% CI 0.95-2.33). When stratified the osteoporosis status by skeletal sites, osteoporosis at the femoral neck and total hip were significantly associated with a higher risk of all infections and sepsis, while participants with osteoporosis at the lumbar spine were only significantly associated with increased risk of skin infection (Table 3).

Discussion

We examined the association of BMD T-scores with the risk of infections and sepsis in the HKOS. We observed that patients with low BMD at the femoral neck and total hip had a higher risk of a range of common infections (pneumonia, UTI, and skin infection) and sepsis, suggesting that low BMD is a novel risk factor of infections and sepsis. The similar results obtained from the sensitivity analyses demonstrated the robustness of our models and strengthened the findings.

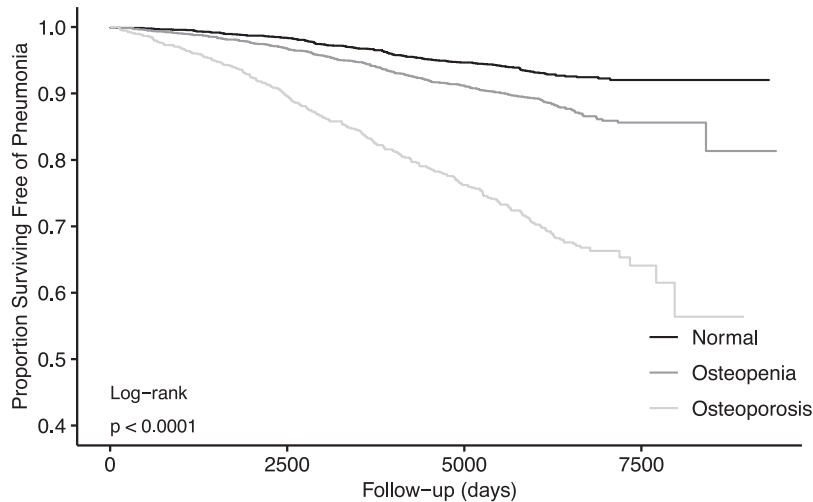
The associations of BMD with the risk of infections and sepsis were not reported before; thus, no comparison with literature can be made. Nevertheless, previous studies showed that BMD is a prognostic factor in patients with infections and sepsis. Low BMD is significantly associated with poor survival to pulmonary sepsis and respiratory infections. Schulze-Hagen et al. showed that low BMD is significantly associated with higher intensive care unit (ICU) mortality and the ICU patients

with pulmonary sepsis had the lowest BMD.²¹ In addition, recent studies also demonstrated that low BMD could be the predictor of the severe outcomes and mortality of the respiratory infections among patients with Coronavirus disease 2019 (COVID-19). The low vertebral BMD was significantly associated with the higher mortality of patients with COVID-19,²² and low BMD at thoracic vertebra can predict whether intensive care treatment is needed for patients with COVID-19.²³ Our study further showed that low BMD is not only a potential prognostic factor in patients with infections or sepsis, but also a novel risk factor of infections and sepsis.

In the current study, the association of BMD with the risk of infections and sepsis was mainly observed at the femoral neck and total hip but not the lumbar spine. Lumbar spine BMD is only significantly associated with skin infection but not the others. BMD at the lumbar spine is sensitive to environmental stimulation, e.g., treatment and hormonal change, while BMD at the hip is considered more robust in reflecting bone health. Thus, as observed in BMD at the hip, our findings suggest that bone health is associated with the risk of infections and sepsis.

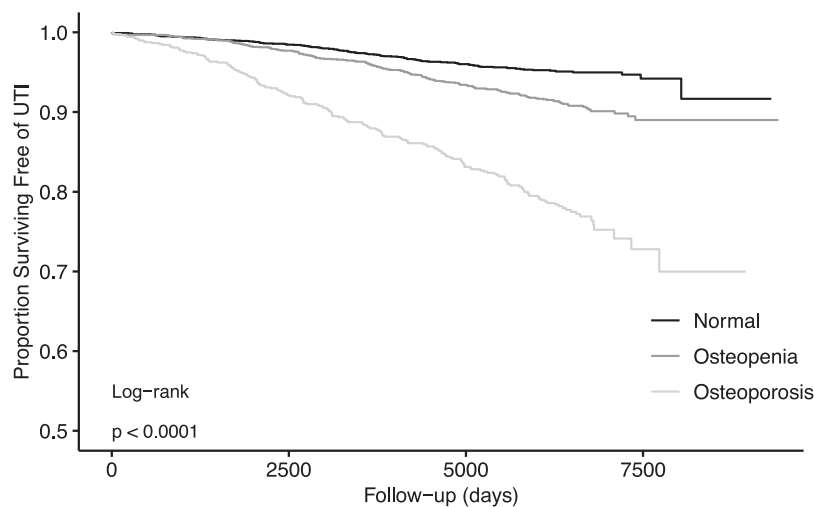
The interaction between bone metabolism and the immune system, i.e., osteoimmunology, could partially account for the association of BMD with the risk of infections and sepsis. For example, IL-7 secreted by osteoblasts can also positively regulate the immune system through ameliorating the loss of immune effector cells and enhancing lymphocyte production and

(a). K-M cumulative survival curves for the incidence of pneumonia



Number at risk (number censored)		0	2500	5000	7500
Normal	2398 (0)	2339 (39)	1962 (86)	156 (37)	
Osteopenia	2426 (0)	2294 (78)	1887 (128)	165 (71)	
Osteoporosis	893 (0)	749 (90)	559 (106)	33 (62)	

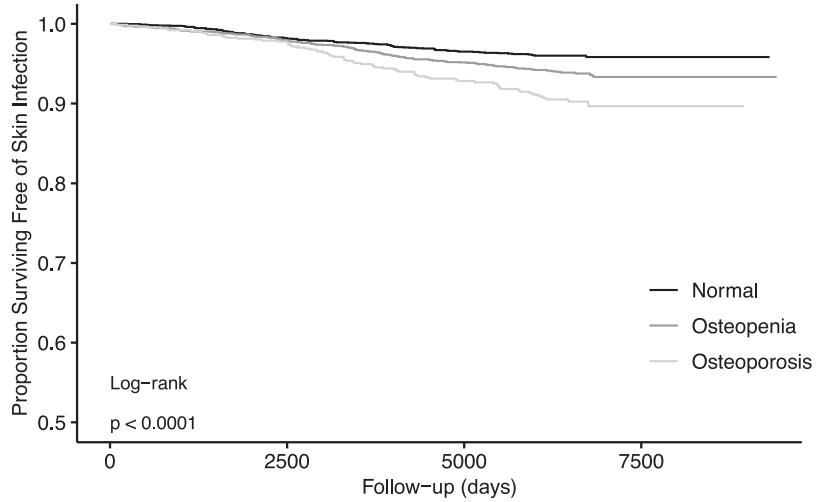
(b). K-M cumulative survival curves for the incidence of UTI



Number at risk (number censored)		0	2500	5000	7500
Normal	2398 (0)	2333 (37)	1949 (56)	154 (19)	
Osteopenia	2426 (0)	2295 (55)	1871 (96)	163 (49)	
Osteoporosis	893 (0)	748 (67)	572 (68)	32 (40)	

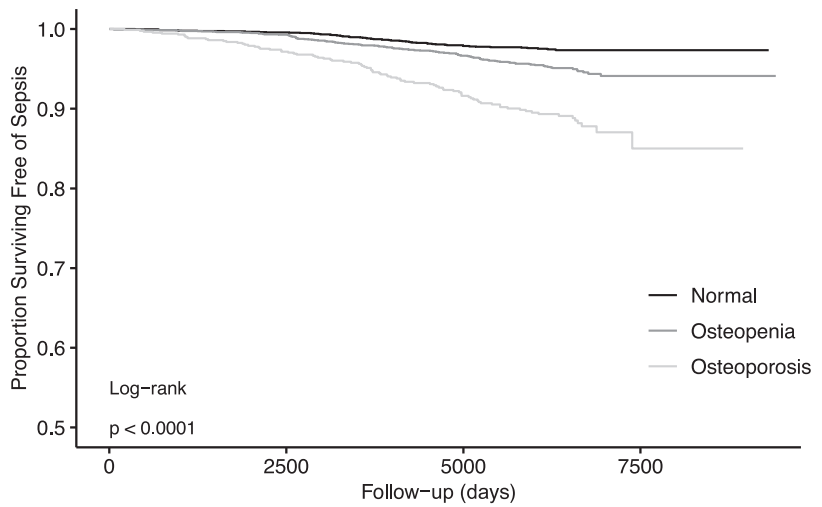
Figure 2. Kaplan–Meier (K-M) cumulative survival curves for the incidence of (a) pneumonia, (b) UTI, (c) skin infection, and (d) sepsis depending on BMD T-score groups. The number at risk and number censored were shown below the survival curves. Log-rank tests indicated a statistically significant difference in survival in all analyses ($P < 0.0001$). (a). K-M cumulative survival curves for the incidence of pneumonia. (b). K-M cumulative survival curves for the incidence of UTI. (c). K-M cumulative survival curves for the incidence of skin infection. (d). K-M cumulative survival curves for the incidence of sepsis.

(c). K-M cumulative survival curves for the incidence of skin infection



Number at risk (number censored)	0	2500	5000	7500
Normal	2398 (0)	2324 (44)	1948 (37)	157 (10)
Osteopenia	2426 (0)	2296 (50)	1890 (62)	164 (24)
Osteoporosis	893 (0)	783 (19)	600 (37)	35 (15)

(d). K-M cumulative survival curves for the incidence of sepsis



Number at risk (number censored)	0	2500	5000	7500
Normal	2398 (0)	2361 (10)	1991 (39)	159 (8)
Osteopenia	2426 (0)	2331 (17)	1930 (59)	173 (33)
Osteoporosis	893 (0)	783 (24)	609 (41)	35 (21)

Figure 2 Continued.

	Normal		Osteopenia		Osteoporosis	
	Hazard ratio (reference)	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	
Pneumonia						
BMD T-score at						
ANY	1	0.98 (0.80, 1.21)	0.855	1.39 (1.07, 1.81)	0.015	
L1-L4 Lumbar spine	1	1.04 (0.86, 1.26)	0.712	1.19 (0.94, 1.52)	0.156	
Femoral neck	1	1.04 (0.86, 1.26)	0.680	1.47 (1.12, 1.92)	0.006	
Total hip	1	1.04 (0.86, 1.25)	0.715	1.47 (1.14, 1.92)	0.003	
UTI						
BMD T-score at						
ANY	1	1.08 (0.84, 1.39)	0.529	1.38 (1.01, 1.89)	0.042	
L1-L4 Lumbar spine	1	1.07 (0.85, 1.34)	0.583	1.10 (0.82, 1.47)	0.529	
Femoral neck	1	1.06 (0.84, 1.33)	0.626	1.53 (1.11, 2.09)	0.008	
Total hip	1	1.09 (0.87, 1.37)	0.467	1.58 (1.16, 2.15)	0.003	
Skin Infection						
BMD T-score at						
ANY	1	1.31 (0.99, 1.75)	0.063	1.60 (1.07, 2.40)	0.022	
L1-L4 Lumbar spine	1	1.29 (0.98, 1.70)	0.072	1.51 (1.02, 2.22)	0.040	
Femoral neck	1	1.16 (0.88, 1.53)	0.277	1.73 (1.12, 2.66)	0.013	
Total hip	1	1.32 (1.00, 1.74)	0.053	1.92 (1.26, 2.92)	0.002	
Sepsis						
BMD T-score at						
ANY	1	1.20 (0.85, 1.69)	0.312	1.48 (0.95, 2.33)	0.085	
L1-L4 Lumbar spine	1	1.15 (0.84, 1.58)	0.386	1.21 (0.80, 1.84)	0.367	
Femoral neck	1	1.36 (0.98, 1.89)	0.063	1.81 (1.15, 2.85)	0.011	
Total hip	1	1.14 (0.83, 1.57)	0.416	1.81 (1.17, 2.78)	0.007	

Table 3: Multivariable-adjusted Hazard Ratio of infections and sepsis according to the osteoporosis status (Normal, Osteopenia, Osteoporosis).

Model was adjusted for age, sex, height, weight, smoking status, drinking status, physical activeness, and presence of comorbidities of infection, serum 25(OH) D, serum calcium, serum phosphate, prescription of steroids and bisphosphonates within one-year, and history of major osteoporotic fracture within one-year.

functions.²⁴ In particular, IL-7 can increase the absolute number of immune effector cells in the lung and spleen, improve immunity, and increase survival in secondary *Pseudomonas aeruginosa* pneumonia.²⁵ In addition, lipocalin 2 is a protein mediating the acute immune response to infections,⁷ and the previous study has shown that osteoblasts express lipocalin 2 at levels tenfold higher than that in white adipose tissue.²⁶ Therefore, the reduced osteoblast number and function could potentially impair human immunity and hence increase susceptibility to infections. Thus, future studies investigating if interleukins and lipocalin-2 are mediating the association are warranted. Emerging evidence showed that the gut microbiome is important in bone health and immune function. However, a recent study from the MrOS cohort showed that only four bacterial genera of the fecal microbiome were weakly associated with bone density, structure, or strength.²⁷ Meanwhile, a Mendelian Randomization study also showed marginal association of gut microbiota with bone health.²⁸ Thus, it is unlikely that the current association is confounded by gut microbiota. Notably, circulation cytokines may also explain the observed association.

Vitamin D could also potentially explain the association of BMD with infections and sepsis. Vitamin D levels lower than 50nmol/L were shown to be associated with an increased risk of infection and sepsis in a systematic review and meta-analysis.²⁹ The close relationship of vitamin D with BMD may explain the association.³⁰ However, BMD remained significantly associated with infection and sepsis even after adjusting for serum vitamin D levels or vitamin D deficiency/insufficiency. Similarly, no significant interaction between BMD and vitamin D deficiency/insufficiency was observed. These analyses suggested that the observed associations were independent of vitamin D.

In the face of the global pandemic of infectious diseases, e.g., COVID-19, improving immunity to prevent infection is important. Although it is still unclear whether BMD is a causal factor affecting immunity, our results support low BMD as a novel risk factor of infections and sepsis. People with low BMD, particularly osteoporosis, should be aware of the potential increased risk of infections and sepsis.

This study has several strengths, which include comprehensive baseline data, a relatively large sample size, and a long follow-up time (~17 years). However, our

results must be interpreted in light of limitations. First, this study was purely observational, so we cannot infer causality. Second, pneumonia, UTI, skin infections, and sepsis defined in this study were confined to their respective broad categories. No specific subtypes of pneumonia, UTI, skin infections, or sepsis were examined. Third, some incidence of events might not be captured by the CDARS, even though the CDARS database captured > 80% of the clinical outcomes. Nevertheless, this should lead to underestimation instead of overestimation of the association. Fourth, all participants of the HKOS were Southern Chinese and recruited by convenience sampling approach. Besides, considering the participants all resided in Hong Kong, the lifestyles, e. g., feeding, sports, and leisure activities, may be different from people in other areas. Thus, the generalisability of the findings to wider populations is unknown. Last, like other cohort studies, residual confounding is possible. However, we have adjusted for important confounders including the use of steroids that are known to be associated with low BMD and increased risk of infections. Physical activity was defined as a binary variable in the current study, insufficient to capture the effect of different activities on the association. Thus, future studies are warranted to investigate the effect of various activities and activity levels on the association.

In conclusion, this study reported that low BMD is a novel risk factor for infections and sepsis. Further study is warranted to examine whether improving bone health can reduce the risk of infections and sepsis.

Contributors

XZ and KWM contributed to literature search, figures, study design, data analyses, data curation, data interpretation, and writing - original draft.

GHYL contributed to writing - review & editing.

KCBT and AWCK contributed to resources, methodology and writing - review & editing.

CLC contributed to conceptualisation, resources, study design, methodology, data curation, data interpretation, supervision, validation, visualisation, and writing - review & editing.

All authors had the final responsibility for the decision to submit for publication.

Declaration of interests

Dr. Cheung reports grants and personal fees from Amgen, outside the submitted work. The other authors have nothing to declare.

Data sharing statement

The dataset used in the current study cannot be shared due to The Personal Data (Privacy) Ordinance (Cap. 486) in Hong Kong as stated in the patient consent

form. For all requests regarding data, please contact the corresponding authors at lung1212@hku.hk.

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References

- 1 Global Health Estimates 2020: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2019. World Health Organization; 2020. Available from: <https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death>. Accessed 10th September 2021.
- 2 Global report on the epidemiology and burden of sepsis: current evidence, identifying gaps and future directions. Geneva: World Health Organization; 2020.
- 3 WHO calls for global action on sepsis - cause of 1 in 5 deaths worldwide 2020. Available from: <https://www.who.int/news/item/08-09-2020-who-calls-for-global-action-on-sepsis-cause-of-1-in-5-deaths-worldwide>. Accessed 20 September 2021.
- 4 Terashima A, Takayanagi H. The role of bone cells in immune regulation during the course of infection. *Semin Immunopathol*. 2019;41(5):619-626.
- 5 Terashima A, Okamoto K, Nakashima T, Akira S, Ikuta K, Takayanagi H. Sepsis-Induced Osteoblast Ablation Causes Immunodeficiency. *Immunity*. 2016;44(6):1434-1443.
- 6 Yu VW, Saez B, Cook C, et al. Specific bone cells produce DLL4 to generate thymus-seeding progenitors from bone marrow. *J Exp Med*. 2015;212(5):759-774.
- 7 Flo TH, Smith KD, Sato S, et al. Lipocalin 2 mediates an innate immune response to bacterial infection by sequestering iron. *Nature*. 2004;432(7019):917-921.
- 8 Cheung CL, Tan KCB, Kung AWC. Cohort Profile: The Hong Kong Osteoporosis Study and the follow-up study. *Int J Epidemiol*. 2018;47(2):397-8f.
- 9 Sing CW, Wong AY, Kiel DP, et al. Association of Alendronate and Risk of Cardiovascular Events in Patients With Hip Fracture. *J Bone Miner Res*. 2018;33(8):1422-1434.
- 10 Wong AY, Wong IC, Chui CS, et al. Association Between Acute Neuropsychiatric Events and Helicobacter pylori Therapy Containing Clarithromycin. *JAMA Intern Med*. 2016;176(6):828-834.
- 11 Lau WCY, Chan EW, Cheung C-L, et al. Association Between Dabigatran vs Warfarin and Risk of Osteoporotic Fractures Among Patients With Nonvalvular Atrial Fibrillation. *JAMA*. 2017;317(11):1151-1158.
- 12 Hospital Authority Statistical Report (2016-2017). Hong Kong Hospital Authority; 2018. Available from: <https://www3.ha.org.hk/data/HASStatistics/DownloadReport/2>. Accessed 28 October 2021.
- 13 Sing CW, Kiel DP, Hubbard RB, et al. Nitrogen-Containing Bisphosphonates Are Associated With Reduced Risk of Pneumonia in Patients With Hip Fracture. *J Bone Miner Res*. 2020;35(9):1676-1684.
- 14 Fu AZ, Iglay K, Qiu Y, Engel S, Shankar R, Brodovick K. Risk characterization for urinary tract infections in subjects with newly diagnosed type 2 diabetes. *J Diabetes Complications*. 2014;28(6):805-810.
- 15 Lee CC, Lee MT, Chen YS, et al. Risk of Aortic Dissection and Aortic Aneurysm in Patients Taking Oral Fluoroquinolone. *JAMA Intern Med*. 2015;175(11):1839-1847.
- 16 Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. *Crit Care Med*. 2007;35(5):1244-1250.
- 17 Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801-810.

- 18 Fagerland MW. t-tests, non-parametric tests, and large studies—a paradox of statistical practice? *BMC Med Res Methodol*. 2012;12(78).
- 19 Luna CM, Palma I, Niederman MS, et al. The Impact of Age and Comorbidities on the Mortality of Patients of Different Age Groups Admitted with Community-acquired Pneumonia. *Ann Am Thorac Soc*. 2016;13(9):1519–1526.
- 20 Ross AC, Manson JE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab*. 2011;96(1):53–58.
- 21 Schulze-Hagen MF, Roderburg C, Wirtz TH, et al. Decreased Bone Mineral Density Is a Predictor of Poor Survival in Critically Ill Patients. *J Clin Med*. 2021;10(16).
- 22 Tahtabasi M, Kilicaslan N, Akin Y, et al. The Prognostic Value of Vertebral Bone Density on Chest CT in Hospitalized COVID-19 Patients. *J Clin Densitom*. 2021.
- 23 Kottlors J, Groe Hokamp N, Fervers P, et al. Early extrapulmonary prognostic features in chest computed tomography in COVID-19 pneumonia: Bone mineral density is a relevant predictor for the clinical outcome - A multicenter feasibility study. *Bone*. 2021;144:115790.
- 24 Unsinger J, Burnham CA, McDonough J, et al. Interleukin-7 ameliorates immune dysfunction and improves survival in a 2-hit model of fungal sepsis. *J Infect Dis*. 2012;206(4):606–616.
- 25 Shindo Y, Fuchs AG, Davis CG, et al. Interleukin 7 immunotherapy improves host immunity and survival in a two-hit model of *Pseudomonas aeruginosa* pneumonia. *J Leukoc Biol*. 2017;101(2):543–554.
- 26 Mosialou I, Shikhel S, Liu JM, et al. MC4R-dependent suppression of appetite by bone-derived lipocalin 2. *Nature*. 2017;543(7645):385–390.
- 27 Orwoll ES, Parimi N, Wiedrick J, et al. Analysis of the Associations Between the Human Fecal Microbiome and Bone Density, Structure, and Strength: The Osteoporotic Fractures in Men (MrOS) Cohort. *J Bone Miner Res*. 2022. <https://doi.org/10.1002/jbmr.4518>. Epub ahead of print.
- 28 Cheng S, Qi X, Ma M, et al. Assessing the Relationship Between Gut Microbiota and Bone Mineral Density. *Front Genet*. 2020;11:6. <https://doi.org/10.3389/fgene.2020.00006>.
- 29 de Haan K, Groeneveld AB, de Geus HR, Egal M, Struijs A. Vitamin D deficiency as a risk factor for infection, sepsis and mortality in the critically ill: systematic review and meta-analysis. *Crit Care*. 2014;18(6):660.
- 30 Leung RY, Cheung BM, Nguyen US, Kung AW, Tan KC, Cheung CL. Optimal vitamin D status and its relationship with bone and mineral metabolism in Hong Kong Chinese. *Bone*. 2017;97:293–298.