Association of low bone mineral density and dementia in older women: insights from the Longevity Improvement and Fair Evidence Study

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Abstract

Background: Both osteoporosis and dementia have emerged as important public health challenges in Japan's aging population. This study aimed to investigate the impact of low bone mineral density (BMD) on the subsequent risk of dementia in older Japanese women aged ≥65 years, given the overlapping demographics of individuals affected by these two conditions. **Methods**: This cohort study was conducted using osteoporosis screening data and insurance claims data from a municipality. We identified 8618 women (median age: 73 years) who underwent osteoporosis screening between April 2019 and March 2021. Participants with a BMD <80% of the young adult mean were assigned to a low-BMD group (n=2297), whereas those with a BMD ≥80% were assigned to a control group (n=6321). The study outcomes were new-onset all-cause dementia and Alzheimer's disease. To estimate the risk of low BMD on these outcomes, we constructed Cox proportional hazards models that adjusted for covariates (age, care needs, year of cohort entry, comorbidities, and medications) using inverse probability of treatment weighting. **Results**: The low-BMD group had a significantly higher risk of developing both all-cause dementia (adjusted hazard ratio: 1.58, 95% confidence interval: 1.20–2.08) and Alzheimer's disease (1.61, 1.11–2.36) than the control group over approximately 30 months of follow-up. **Conclusions**: These findings suggest that low BMD is associated with medium-term onset of dementia. Osteoporosis screenings could be useful not only for the secondary prevention of osteoporosis, but also for the primary prevention of dementia.

Keywords

Osteoporosis, Osteoporosis screening, Bone mineral density, Dementia, Alzheimer’s disease, Older people.

Key Points

- Women with low bone mineral density had a 1.58 times higher risk of developing all-cause dementia compared to those with normal bone mineral density.
- This research highlights the importance of bone health not only for skeletal diseases but also as a significant factor in neurodegenerative conditions, expanding the scope of preventive strategies in aging populations.
- Health policies can integrate osteoporosis screenings as part of a broader approach to dementia prevention in older populations.

Introduction

Osteoporosis is a skeletal disorder characterized by decreased bone strength and an elevated risk of fracture [1], whereas dementia is a neurological disorder characterized by memory impairment and cognitive dysfunction [2]. National surveys conducted by the Japanese government in 2016 and 2022 found that dementia and falls/fractures were among the leading causes of long-term care (LTC) certification [3, 4]. These trends highlight that both osteoporosis and dementia have recently emerged as significant public health challenges in Japan's aging population.

Osteoporosis and dementia share a common patient demographic, i.e., they mainly affect older persons [1, 5-7]. Some studies have proposed a potential association between these two conditions [8, 9], while others have extended beyond mere association to infer potential causal relationships [10-15]. Overall, these studies suggest that patients with low bone mineral density (BMD) have a significantly higher risk of developing dementia later in life. However, conclusions remain elusive due to issues related to generalizability and study limitations.

The aim of this study was to investigate the association between low BMD and dementia in older Japanese women, a population for which this relationship has not been extensively studied. As many countries are projected to become aging societies in the near future [16], this study sought to provide evidence that can inform public health strategies, particularly in consideration of the potential added value of osteoporosis screening as a tool for the primary prevention of dementia.

Methods

Study design and data source

This cohort study was conducted using osteoporosis screening data and insurance claims data acquired from the Longevity Improvement and Fair Evidence (LIFE) Study, which is a longitudinal database project managed by Kyushu University (Fukuoka, Japan). The LIFE Study collects inpatient, outpatient, pharmacy, and LTC claims data from more than 3 million individuals residing in over 30 participating municipalities [17]. The target population includes individuals enrolled in the following public insurance schemes: National Health Insurance (for the self-employed, irregularly employed, unemployed, and primary sector workers aged ≤74 years), Latter-Stage Older Persons Health Care System (for persons aged ≥75 years), and LTC Insurance (for persons aged ≥65 years with certified care needs and persons aged 40–64 years with specific debilitating diseases such as cancer). In these public insurance schemes, municipal governments fulfil the role of insurer. Some municipalities participating in the LIFE Study also provide health examination data, such as osteoporosis screening data, in addition to the claims data. These data are linked at the individual level using a common identification code. Further details on the LIFE Study have been previously published [18].

Study population

We acquired data from a municipality that provided osteoporosis screening data in addition to claims data. In Japan, osteoporosis screenings are conducted with specific eligibility criteria varying by municipality. In the municipality that provided data for this study, the target population comprised women aged ≥30 years who were eligible to

undergo the municipal-subsidized screening using a voucher. Osteoporosis screening is not mandatory, and is conducted only for those who wish to participate.

We identified women who had undergone osteoporosis screening during fiscal years (FYs: April–March) 2019 and 2020. The cohort entry date for participants was defined as the date of their osteoporosis screening, and the 12 months prior to the cohort entry date were set as the baseline period. The reason for selecting a 12-month baseline period was to accommodate the dosing intervals of denosumab (6 months) and zoledronic acid (Reclast®, 12 months). Diseases were defined according to International Classification of Diseases, 10th revision (ICD-10) codes, and medications were identified using Anatomical Therapeutic Chemical (ATC) Classification System codes.

We excluded the following from analysis: (1) No medical claims between FY2018 and FY2022; (2) Last recorded claim before FY2021; (3) First recorded claim after the baseline period start; (4) Age <65 years at the cohort entry; (5) Diagnosis of dementia (ICD-10 codes: F00, G30, F01, F02, F03), osteoporosis (M80, M81), or fracture likely caused by osteoporosis (S720, S721, S722, S220, S221, S32) during the baseline period; and (6) Osteoporosis treatment during the baseline period, including the use of selective oestrogen receptor modulators (ATC code: G03XC), bisphosphonates (M05BA), denosumab (M05BX04), teriparatide (H05AA02), and romosozumab (M05BX06).

Exposure and outcomes

During the osteoporosis screenings, participants were categorized into the following three groups based on their

results: “No abnormal findings”, “Requires guidance”, and “Requires further examination”. The study data only provided screening results using these three categories, and did not include quantitative BMD values.

The study exposure was low BMD, which was defined as an osteoporosis screening result of “Requires further examination”. Participants classified as “Requires guidance” or “No abnormal findings” were analysed as a control group. According to Japanese clinical guidelines, individuals with a BMD <80% of the young adult mean (YAM) are considered to have low BMD [19]. During osteoporosis screenings, individuals with a BMD <80% of the YAM are classified as “Requires further examination”, which matched the clinical guidelines for low BMD. Participants who underwent screening in both FY2019 and FY2020 were included in the analysis based on the earliest year in which they were classified as “Requires further examination”. Participants who were consistently classified as “Requires guidance” or “No abnormal findings” were considered as being enrolled in FY2020. BMD measurement was performed using one of the following methods: dual energy X-ray absorptiometry, quantitative ultrasound, or microdensitometry. Typically, dual energy X-ray absorptiometry is performed at the femur, lumbar spine, or forearm; quantitative ultrasound is performed at the calcaneus; and microdensitometry is performed at the metacarpal [19]. However, detailed information regarding each patient’s measurement was not available in the study data.

The primary outcome was defined as a new diagnosis of all-cause dementia, and the secondary outcome was defined as a new diagnosis of Alzheimer’s disease (AD; ICD-10 codes: F00, G30). The follow-up period extended from the cohort entry date until the occurrence of an outcome event or right-censoring. Participants were censored at the time of the final medical claims; for the control group, censoring also included the date of

osteoporosis diagnosis after cohort entry.

Covariates

We selected the following comorbidities and medications as potential confounders based on theoretical considerations. These, along with age (years), LTC needs status, and the FY of cohort entry, were included as covariates. All covariates were assessed based on information available during the baseline period. The comorbidities are listed in **Supplementary Table S1**. The medications listed in **Supplementary Table S2** were included if prescribed at least once in the claims data during the baseline period. LTC needs status was categorized into four groups based on LTC needs certifications: “Support Levels and Care Level 1”, “Care Levels 2 and 3”, “Care Levels 4 and 5”, and “No certification”. If an individual received multiple LTC needs certifications during the baseline period, the highest level was used in the analysis. The timeline for participant exclusion, covariate assessment, and follow-up is presented in **Supplementary Figure S1**.

Statistical analysis

We first compared the comorbidities, medications, and LTC needs status at baseline between the low-BMD group and the control group. The differences in variables between the groups were expressed as unadjusted standardised mean differences (SMDs). To assess the effect of low BMD on the primary and secondary outcomes, we used cumulative incidence function and performed log-rank tests. Additionally, we constructed Cox proportional hazards regression models to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of this effect.

Next, we adjusted for covariates using inverse probability of treatment weighting (IPTW) [20], and assessed covariate balance using adjusted SMDs (**Supplementary Figure S2**). The IPTW was based on propensity scores obtained from logistic regression models for low BMD. Subsequently, we performed Cox proportional hazards regression analyses to estimate the effect of low BMD on the study outcomes as average treatment effects.

In addition, we conducted subgroup analyses to consider the influence of participant background and treatment effects. Here, we comparatively assessed the risk of dementia and AD in the low-BMD group between those who initiated osteoporosis treatment (i.e., selective oestrogen receptor modulators, bisphosphonates, denosumab, teriparatide, or romosozumab) within six months of cohort entry and those who did not. The subgroup analyses used the same control group as the main analysis. To further understand the differences in participant background between those who initiated treatment early and those who did not, we estimated the IPTW-adjusted HR for osteoporotic fractures between these two groups.

For the survival analysis, we used a cause-specific hazard model. This approach acknowledges the potential for competing risks arising from death for all-cause dementia and other types of dementia for AD. We performed a sensitivity analysis (unadjusted) using a Fine–Gray subdistribution hazard model to account for competing risks. However, we adopted the interpretation that the cause-specific hazard model is more appropriate than the subdistribution hazard model for analysing risk factors and causes of clinical events [21, 22], and thus did not apply the latter to all adjusted analyses.

All data processing and statistical analyses were performed using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $p < 0.05$.

Results

Participant characteristics

A total of 30 708 women underwent osteoporosis screening in FY2019 and FY2020 (**Figure 1**). After applying the exclusion criteria, 8618 women aged ≥65 years were included in the study cohort. Of these, 2297 and 6321 were classified into the low-BMD group and control group, respectively.

The characteristics of the study cohort are presented in **Table 1**. The median age was 75 years (interquartile range [IQR]: 71–80) in the low-BMD group and 73 years (IQR: 69–77) in the control group. The median observation period was 37 months (IQR: 29–42) for the low-BMD group and 29 months (IQR: 25–34) for the control group. During the follow-up period, 267 women (3.1%) developed all-cause dementia, including 135 (5.9%) in the low-BMD group and 132 (2.1%) in the control group. Among those who developed all-cause dementia, 50.7% were diagnosed with AD.

Risk of low BMD for developing dementia

In the unadjusted survival analysis, the low-BMD group had a significantly higher risk of developing both all-cause dementia (HR: 2.16, 95% CI: 1.70–2.75) and AD (HR: 2.05, 95% CI: 1.45–2.88) than the control group (**Figure 2**). After adjusting for covariates using IPTW, the low-BMD group still exhibited a significantly higher risk of developing both all-cause dementia (HR: 1.58, 95% CI: 1.20–2.08) and AD (HR: 1.61, 95% CI: 1.11–2.36) (**Figure 3**).

Subgroup and sensitivity analyses

The results of the subgroup analyses are shown in **Figure 3**. Similar to the main analysis, the low-BMD group had a significantly higher risk for all-cause dementia (adjusted HR: 1.59, 95% CI: 1.01–2.51 with treatment) regardless of whether or not osteoporosis treatment was initiated within six months. While the low-BMD group without treatment had a significantly higher risk of developing AD (adjusted HR: 1.62, 95% CI: 1.05–2.51), this association was not observed in the low-BMD group with treatment (adjusted HR: 1.61, 95% CI: 0.84–3.07). Notably, the incidence of all-cause dementia within three months (4 cases) and six months (9 cases) of cohort entry in the low-BMD group was very low, and their impact on the results was considered negligible. Additionally, the low-BMD group that initiated osteoporosis treatment within six months demonstrated a significantly higher risk of osteoporotic fractures (adjusted HR: 1.72, 95% CI: 1.28–2.32) than the group that did not.

Finally, the analysis using the subdistribution hazard model showed that the low-BMD group had a significantly higher risk of developing AD (HR: 2.04, 95% CI: 1.46–2.84) than the control group, which was similar to the cause-specific hazard model. The competing risk for death in all-cause dementia showed similar results, with death occurring in 94 cases (1.1% of those without events) and an HR of 2.16 (95% CI: 1.70–2.75).

Discussion

Principal findings

Using osteoporosis screening data and insurance claims data, this cohort study investigated the association between

low BMD and dementia in older Japanese women. The results revealed that women with low BMD had a higher risk of developing dementia than those with normal BMD.

As Japan's population rapidly ages, osteoporosis has emerged as a significant public health concern [3, 4, 23]. Therefore, the prevention of osteoporosis—a major cause of fractures—is a pressing issue in Japan for improving and maintaining the quality of life, extending healthy life expectancy, and reducing medical costs in older adults [24]. Similarly, dementia is the most common cause of LTC certification in Japan [3, 4], and therefore poses a major public health challenge in an aging society. Clarifying the relationship between low BMD or osteoporosis and dementia could provide valuable evidence to inform public health policies.

Comparison with other studies

Several studies have analysed osteoporosis as a risk factor for dementia [10-15]. Studies using claims data reported an HR of 1.5 in a Taiwanese population [10] and an HR of 1.2 in German women [11]. The results align with these previous findings. However, our study defined low BMD based on the YAM, which provided greater reliability in identifying the low-BMD group when compared to previous studies that relied solely on claims data. Furthermore, our use of the IPTW method, not employed in earlier studies, yielded results consistent with those of prior research. On the other hand, a recent cohort study reported that low BMD was not a significant risk factor for dementia in women [25], which contrasts with the findings of our study. Nonetheless, while the CIs in their results were not statistically significant, the HRs suggested a trend that low BMD may be associated with an increased risk of dementia. Moreover, their adjustment for comorbidities was limited to a small number of conditions, leaving the

potential influence of other confounding factors (particularly those associated with sex differences) unresolved. Notably, this is the only study that did not show a significantly higher risk of low BMD for dementia in women, and we believe it does not completely refute the findings of our study.

In recent years, two Mendelian randomization studies examined the causal relationship between low BMD and AD [26, 27]. While they found no evidence of causality, an association could not be rule out. These studies used genome-wide association study data from European populations, providing no evidence for other populations, particularly Asians. Their assessments of confounding by single-nucleotide polymorphisms were also limited. Although Mendelian randomization is a robust tool for causal inference, its findings on BMD and AD remain inconclusive. In contrast, numerous observational studies, including ours, have reported an association between low BMD and dementia. While our study suggests low BMD may be a risk factor for dementia in Japanese individuals, it does not establish causality. Nonetheless, the accumulating evidence underscores the need for further research to clarify this relationship.

Possible explanations

The biological mechanisms by which low BMD increases the risk of dementia are thought to involve several factors common to both conditions. Apolipoprotein E4 (ApoE4), which binds to amyloid-beta peptides and linked to AD, is associated with lower vitamin K levels [28], leading to higher fracture risk [29]. However, a study found that low BMD remained a significant risk factor for dementia even after adjusting for the presence of the ApoE4 allele [12], suggesting other mechanisms. Additionally, hypovitaminosis D, common in patients with dementia [30],

is also associated with impaired cognitive function [31, 32] and contributes to low BMD [29]. However, the mechanisms linking vitamin D deficiency to dementia require further exploration.

Since osteoporosis takes years to improve with treatment, its impact on fracture risk was likely minimal within the study's follow-up period (median of 30 months). Even with teriparatide or denosumab, which substantially increase BMD, the two-year improvements are modest (e.g., lumbar spine +8–10%, femoral neck +3–4%) [33, 34]. Thus, most patients initiating treatment were unlikely to reach BMD levels associated with lower fracture risks within two years. In this study, low-BMD (YAM <80%) encompassed a wide range of values, And those starting treatment early had lower BMD at cohort entry, explaining their higher fracture risk. This highlights the heterogeneity within the low-BMD group.

One possible reason for the lack of a significant increase in AD risk in the low-BMD group with treatment could be that osteoporosis treatment may have mitigated the risk of AD. Selection bias may also be a factor, as more health-conscious women were more likely to undergo treatment. Additionally, subgroup division reduced cases numbers, potentially lowering the statistical power. A study in Taiwan found a lower risk of developing dementia in those treated with selective oestrogen receptor modulators or bisphosphonates [10]. However, another study conducted in the US reported that hormone replacement therapy did not significantly reduce AD risk unless the therapy had exceeded 10 years [35]. Given that oxidative stress and inflammation contribute to dementia [36], and that bisphosphonates have antioxidant and anti-inflammatory properties [37, 38], osteoporosis treatment may reduce the risk of dementia. Bisphosphonates interact with iron to suppress oxidative stress-related processes like lipid peroxidation [37]. Furthermore, non-aminobisphosphonates inhibit the release of

inflammatory mediators (interleukin-6, tumour necrosis factor-α, and interleukin-1) from activated macrophages [38]. This anti-inflammatory effect is thought to be mediated by specific metabolites produced when non-aminobisphosphonates are metabolized within macrophages. While evidence remains insufficient, osteoporosis treatment unlikely to increase AD risk, and early treatment initiation may be beneficial.

Limitations

This study has several limitations. First, the study population comprised individuals who voluntarily underwent health screenings, which may not be representative of the general population. As a result, our findings might reflect a lower estimated risk of dementia than would be observed in the general population. Second, the study was limited to women, and the findings may not be applicable to men. Third, osteoporosis screening data and claims data were only available from FY2018 to FY2022. Consequently, setting a two-year enrolment period and a one-year baseline period inevitably restricted the follow-up period to two years. Therefore, our study was unable to analyse further cognitive changes in patients after two years. Fourth, the methods for measuring BMD, including the equipment and measurement sites, were not standardised across all screening facilities. However, since this study utilised screening data, there were likely to be few false negatives for low BMD. On the other hand, the low-BMD group may have included some healthy individuals, which could lead to underestimating the risk of dementia associated with low BMD. Fifth, we were unable to analyse non-AD dementia subtypes, such as vascular dementia and dementia with Lewy bodies, due to the limited number of cases and insufficient diagnostic information. However, most previous studies had focused their analyses and discussions exclusively on all-cause dementia and AD.

Following this precedent, our study adopted a similar design. Lastly, our study could not account for lifestyle factors, which are potential confounders, due to the lack of data.

Implications

Despite the aforementioned limitations, this study has several strengths. These include the definition of low BMD based on the YAM and the use of a causal inference method (IPTW) that had not been previously applied to this particular topic. Japan has become an aging society ahead of most other countries, and is currently dealing with both osteoporosis and dementia as major public health challenges. Therefore, the findings of this study may contribute to the formulation of effective policies in Japan. Furthermore, such policies could serve as valuable references for other countries facing similar challenges in the near future.

Conclusion

Low BMD was associated with dementia in older Japanese women, and may be linked to an increased medium-term risk of dementia. Osteoporosis screenings could be useful not only for the secondary prevention of osteoporosis, but also for the primary prevention of dementia.

Research data transparency and availability

This study was based on a contract between the municipal government, which provided the data, and Kyushu

University. The contract prohibits public access to the data to protect personal information and ensure the anonymity of the municipal government.

Declaration of Conflicts of Interest

None

Declaration of Sources of Funding

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Figure legends

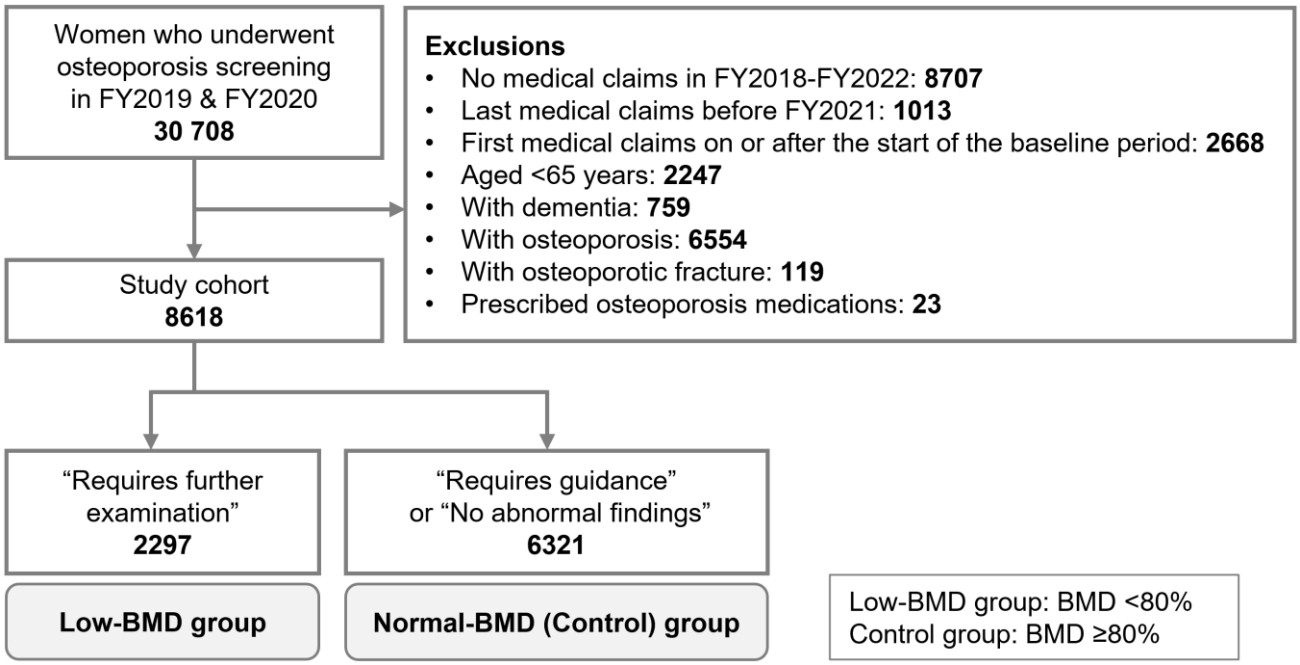

Figure 1. Flowchart of study participant selection

This figure illustrates the selection process of the study participants. Initially, 30,708 women who underwent osteoporosis screening in FY2019 and FY2020 were identified. After applying the exclusion criteria, 8,618 women remained in the study cohort. These women were categorized into two groups: the low-BMD group (Classified as "Requires further examination"; BMD <80%) and the control group (Classified as "Requires guidance" or "No abnormal findings"; BMD ≥80%).

Abbreviations: BMD, bone mineral density; FY, fiscal year.

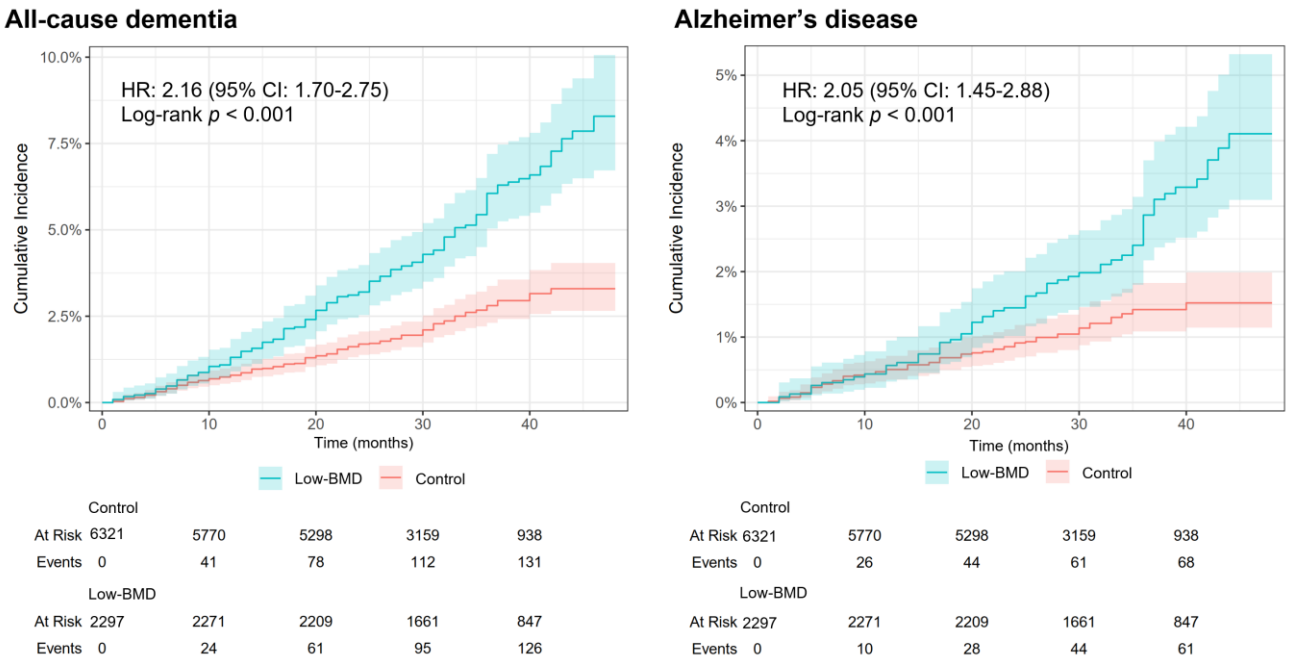

Figure 2. Unadjusted survival analyses of dementia occurrence

This figure presents the unadjusted survival analyses for all-cause dementia and AD using cumulative incidence function. The left panel shows the cumulative incidence for all-cause dementia, with the low-BMD group (green) demonstrating a significantly higher HR (2.16, 95% CI: 1.70–2.75; Log-rank $p < 0.001$) than the control group (red). The right panel shows the cumulative incidence for AD, with the low-BMD group (green) again demonstrating a significantly higher HR (2.05, 95% CI: 1.45–2.88; Log-rank $p < 0.001$) than the control group (red).

Abbreviations: AD, Alzheimer's disease; BMD, bone mineral density; CI, confidence interval; HR, hazard ratio.

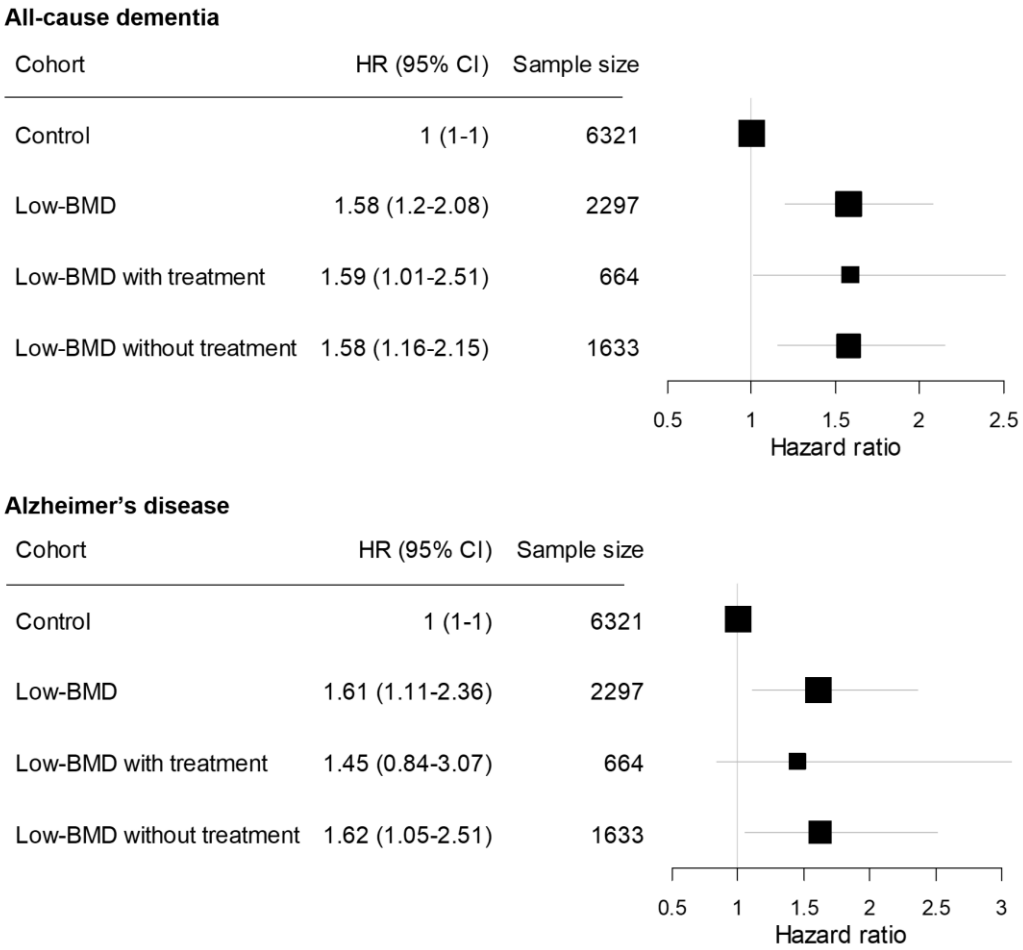

Figure 3. Adjusted hazard ratios for dementia: main and subgroup analyses

This figure presents the adjusted HRs with 95% CIs for all-cause dementia and AD in the study cohort and across different subgroups. The reference group for all comparisons was the control group (HR: 1.0). The top panel displays the results for all-cause dementia: the low-BMD group, particularly those without treatment, had significantly higher risks than the control group. The bottom panel displays the results for AD. The subgroup analyses compared the outcomes between low-BMD individuals with and without subsequent osteoporosis treatment within six months. "Treatment" refers to the use of the following osteoporosis medications: selective oestrogen receptor modulators, bisphosphonates, denosumab, teriparatide, and romosozumab.

Abbreviations: AD, Alzheimer's disease; BMD, bone mineral density; CI, confidence interval; HR, hazard ratio.

Table 1. Participant characteristics

	Overall	Low-BMD group	Control group	SMD (unadjusted)	SMD (adjusted)
n	**8618**	**2297**	**6321**		
Age, years (median [IQR])	73.0 [70.0, 78.0]	75.0 [71.0, 80.0]	73.0 [69.0, 77.0]	0.333	0.009
FY (%)					
2019	3204 (37.2)	1300 (56.6)	1904 (30.1)	0.554	0.011
2020	5414 (62.8)	997 (43.4)	4417 (69.9)		
Follow-up period, months (median [IQR])	30.0 [26.0, 38.0]	37.0 [29.0, 42.0]	29.0 [25.0, 34.0]	0.691	0.528
All-cause dementia (%)	267 (3.1)	135 (5.9)	132 (2.1)	0.195	0.118
AD in all-cause dementia (%)	155 (50.7)	66 (48.9)	89 (52.0)	0.063	0.035
LTC (%)					
Support Levels and Care Level 1	234 (2.7)	92 (4.0)	142 (2.2)	0.126	0.012
Care Levels 2 and 3	45 (0.5)	20 (0.9)	25 (0.4)		
Care Levels 4 and 5	4 (0.0)	3 (0.1)	1 (0.0)		
Stroke (%)	1416 (16.4)	384 (16.7)	1032 (16.3)	0.011	0.019
Parkinson's disease (%)	62 (0.7)	21 (0.9)	41 (0.6)	0.03	0.001
Depression (%)	439 (5.1)	117 (5.1)	322 (5.1)	<0.001	0.014
CHF (%)	785 (9.1)	254 (11.1)	531 (8.4)	0.09	0.006
Hypertension (%)	4467 (51.8)	1236 (53.8)	3231 (51.1)	0.054	0.001
PAD (%)	162 (1.9)	52 (2.3)	110 (1.7)	0.037	0.001
Diabetes mellitus (%)	1988 (23.1)	528 (23.0)	1460 (23.1)	0.003	0.009
Cancer (%)	665 (7.7)	178 (7.7)	487 (7.7)	0.002	0.007
Rheumatoid arthritis (%)	228 (2.6)	79 (3.4)	149 (2.4)	0.065	0.027
Thyroid disease (%)	733 (8.5)	177 (7.7)	556 (8.8)	0.04	0.004
Hypoparathyroidism	12 (0.1)	3 (0.1)	9 (0.1)	0.003	0.049
CKD (%)	179 (2.1)	61 (2.7)	118 (1.9)	0.053	0.011
COPD (%)	44 (0.5)	20 (0.9)	24 (0.4)	0.062	0.022
Sleep apnoea (%)	29 (0.3)	3 (0.1)	26 (0.4)	0.054	0.028
Antihypertensives (%)	3990 (46.3)	1130 (49.2)	2860 (45.2)	0.079	0.004
Lipid-lowering agents (%)	3977 (46.1)	1005 (43.8)	2972 (47.0)	0.066	0.018
Antidepressants (%)	128 (1.5)	46 (2.0)	82 (1.3)	0.055	0.009
PPIs (%)	1574 (18.3)	475 (20.7)	1099 (17.4)	0.084	0.004
Corticosteroids (%)	1689 (19.6)	444 (19.3)	1245 (19.7)	0.009	0.016
Benzodiazepines and related drugs (%)	1085 (12.6)	286 (12.5)	799 (12.6)	0.006	0.001
Vitamin D (%)	520 (6.0)	447 (19.5)	73 (1.2)	0.631	0.043

Abbreviations: AD, Alzheimer's disease; BMD, bone mineral density; CHF, congestive heart failure; CKD, chronic

kidney disease; COPD, chronic obstructive pulmonary disease; FY, fiscal year; IQR, interquartile range; LTC, long-term care; PAD, peripheral artery disease; PPI, proton-pump inhibitor; SMD, standardised mean difference.