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Review Article

Association between Osteoporosis, Bone Mineral Density Levels and Alzheimer's Disease: A Systematic Review and Meta-analysis

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SUMMARY

We aimed to perform a systematic literature research and meta-analysis to explore the association between osteoporosis/bone mineral density (BMD) and Alzheimer's disease (AD). PubMed, Embase, and Web of Science were searched up to 31 December 2016, and the reference lists of relevant articles were also checked. Association between osteoporosis and AD was qualitatively analyzed, and BMD with AD was analyzed using a meta-analysis. Pooled standardized mean difference (SMD) or hazard ratio (HR) and 95% confidence intervals (CIs) were calculated. The Q statistic and I^2 methods were used to test for heterogeneity. We used subgroup analysis to explore possible sources of heterogeneity. Eight studies were included. Three provided data on osteoporosis and AD, and five reported BMD levels with AD. We performed two meta-analyses. The combined results indicated that AD patients had lower BMD compared with controls (SMD -1.23, 95% CI -1.93–0.54), and lower femoral neck BMD were associated with increased risk of AD after adjusting for confounding variables (HR 2.19, 95% CI 1.67–2.88), respectively. Our study suggested that AD patients are at higher risk for osteoporosis and have lower BMD than controls, while osteoporosis and lower femoral neck BMD are also associated with a higher risk of AD.

1. Introduction

Osteoporosis is a common disorder in the elderly, with a consequent increase in fracture susceptibility.[1] And fractures especially in hip usually increase the morbidity, mortality and medical costs. Measuring bone mineral density (BMD) has been suggested as a method of identifying individuals at high risk of osteoporosis and fracture.[2] Alzheimer's disease (AD) is a common neurodegenerative disorder characterized by progressive loss of memory and cognitive function. With the accelerating population aging process, the prevalence of AD is estimated to rise steadily.[3] Meanwhile the economic and social burden of AD is also expected to increase.

Accumulating studies indicated that osteoporosis and AD often coexist in elderly population.[4,5] However, osteoporosis was often unrecognized in AD patients until a fracture occurs. The associations between osteoporosis/BMD and AD had drawn increasing interests.[5–10] But the results were inconsistent. Some studies suggested that AD patients had lower BMD than controls,[11–13] while others showed no significant differences.[14] Some studies showed that AD patients were at high risk for osteoporosis,[15,16] while others showed the higher prevalence of AD in osteoporosis patients.[17,18] Therefore, our aim was to systematically review the current evidence on this association to summarize previous findings.

2. Methods

2.1. Literature search strategy

PubMed, Embase, and Web of Science were searched up to 31 December 2016. The search terms included Alzheimer's disease, Alzheimer disease, osteoporosis, osteopenia, bone density, bone mineral density and bone mass. In addition, the references lists of retrieved articles were also manually reviewed to identify relevant studies missed by the search strategy.

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2.2. Inclusion and exclusion criteria

The inclusion criteria: (1) With a comparative group and results were presented by mean and standard deviation, relative risk (RR) or hazard ratio (HR); (2) BMD must have been measured by absorptiometry (single or dual energy, photon or x ray), quantitative computed tomography, or quantitative magnetic resonance imaging. Osteoporosis was diagnosed as a BMD value 2.5 or more standard deviations below the mean value of healthy adults of the same gender and race based on the WHO criteria[19]; (3) Studies those adopted internationally recognized diagnostic criteria of AD, such as the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) or the Diagnostic and Statistical Manual of Mental Disorders (DSM-III, III-R, or IV); (4) In general, there was more than one publication for each research population. Studies with the longest follow up time or the most completed data were included; (5) Articles in English.

The exclusion criteria: (1) the control group was not cognitively normal person; (2) Abstracts, case reports, letters, reviews, or animal experiments were not considered.

2.3. Quality assessment

The Newcastle-Ottawa Scale (NOS)[20] was used to assess the quality of the included studies. The total score was 9. Studies that scored $\geq$7 were considered as high quality, 4–6 as fair quality, and $\leq$3 as low quality.

All included studies would be assessed by two researchers (Jing Zhang and Zhou-Xin Yang) independently and discrepancies, if any, would be resolved by consensus.

2.4. Data extraction

The following information was extracted: name of the first author, year of publication, study design, time of follow-up, study location, age, total cases, total population, ratio of females, measurement of osteoporosis and BMD, diagnosis of AD and adjustment.

When information was reported for more than one subpopulation (for example, male or female) in one study, each subpopulation was treated as a separate comparison.

2.5. Statistical analysis

Pooled standardized mean difference (SMD) or HR, and 95% confidence intervals (CIs) were used to assess the association between BMD and AD. Statistical heterogeneity among studies was estimated by Q statistic ($P < 0.10$ as significant) and I^2 statistic (I^2 <25%, no heterogeneity; I^2 25–50%, moderate heterogeneity; I^2 >50%, large or extreme heterogeneity). We used subgroup analysis to explore possible sources of heterogeneity. A sensitivity analysis was carried out to illustrate the accuracy and stability of the analytic results using different models (fixed or random effects model). Begg's and Egger's test were used to test publication bias. Stata 12.0 (StataCrop, College station, Tex) was used to perform data analysis. A two-sided $P < 0.05$ was considered statistically significant.

3. Results

A flow diagram of the study selection process was shown in Fig. 1. Eight studies were finally included (Table 1). Of which, three

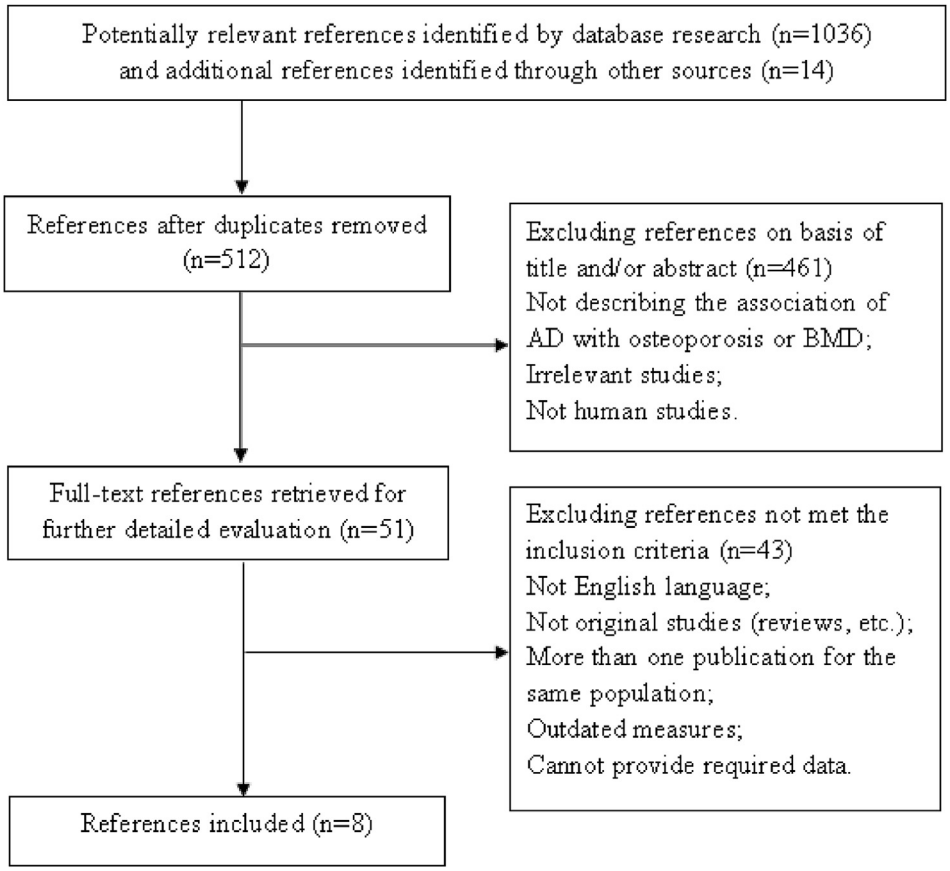

Fig. 1. The flow diagram for study selection.

Table 1
Characteristics of articles included in this study.

Studies	Study design	Follow-up	Study location	Age (mean ± SD/year)	Cases/Total population	Gender (Female%[a])	Measurement of Osteoporosis and BMD	Diagnosis of AD	Adjustment	NOS scores
Li F,[21] 2016	retrospective case-control study		Liaoning, mainland China	AD group, 78.9 ± 6.1 Control group, 78.9 ± 6.1	345/1725	49.91%	Osteoporosis, BMD 2.5 standard deviations (SDs) below the mean for sex-specific young adult	NINCDS-ADRDA criteria		8
Liu D,[15] 2016	Prospective cohort study	6 years	Chong qing, mainland China	Osteoporosis group, 68.9 ± 4.4 No osteoporosis group, 65.1 ± 4.7	478/1802	47.11%	DXA, GE Medical Systems, Madison, WI; Osteoporosis, BMD 2.5 SDs below the mean for healthy women aged 20−29 years	NINCDS-ADRDA criteria	age, female, AD, 25-hydroxyvitamine D (25(OH)D), smoking, drinking and stroke	7
Kuang-Hsi Chang,[17] 2014	Retrospective cohort study	10 years	Taiwan	≥50	23,941/71,520	77.96%	Osteoporosis, ICD-9-CM code 733.0	ICD-9-CM code 331.0	age, sex, income, occupation, stroke, head injury, depression and estrogen supplement	8
Ayhan F,[11] 2007	Case-control study		Turkey	AD group, 70.6 ± 5.7 Control group, 69.1 ± 4.3	75/131	88.55%	Lunar DEXA IQ (Madison, Wisconsin, USA) bone mineral densitometry system, T-score	DSM-IV-R criteria and NINCDS-ADRDA criteria		5
Loskutova N,[12] 2009	Cross-sectional study		USA	Early AD group, 74.9 ± 6.6 Control group, 73.3 ± 6.9	71/140	57.86%	DXA, Prodigy fan-beam densitometer, Lunar Corp., GE Medical Systems, Madison, WI g/cm^2	NINCDS-ADRDA; CDR 0.5 and 1		6
Suzuki A,[13] 2007	Prospective cohort study	2 years	Japan	AD group, 82 ± 8 Control group, 78 ± 8	32/43	100.00%	QCT, CT9000 (Yokogawa, Tokyo, Japan) with a $CaCO_3$ phantom (Chugai Pharmaceutical, Tokyo, Japan), g/cm^3	DSM-IV-R criteria		7
Zhou R,[9] 2011	Prospective cohort study	5 years	Chong qing, mainland China	AD group, 75.3 ± 4.3 Control group, 72.0 ± 4.5	132/2019	42.69%	DXA, Prodigy fan beam densitometer, Lunar Corp, GE Medical System, Madison, WI g/cm^2	NINCDS-ADRDA criteria	age, gender, and education	9
Tan ZS,[10] 2005	Prospective cohort study	8 years	USA	Women, 76.1 ± 5.0 Men, 75.5 ± 4.9	75/987	61.80%	DP3, Lunar Corp, Madison, Wis; SP2, Lunar Corp.	NINCDS-ADRDA criteria	age, sex, apolipoprotein E ε4, baseline homocysteine level, education, estrogen use, smoking, and stroke	9

Note: Female% [a], the proportion of female; BMD, Bone Mineral Density; AD, Alzheimer's disease; DXA/DEXA, Dual energy X-ray absorptiometry; DSM-IV-R, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Revised; NINCDS-ADRDA, National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association; CDR, Clinical Dementia Rating; WHO, World Health Organization; DP, Dual-photon absorptiometry; SP, Single-photon absorptiometry; QCT, Quantitative CT; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; ICD-9-CM, International Classification of Disease, Ninth Revision, Clinical Modification; NOS, Newcastle-Ottawa Scale.

provided data on osteoporosis and AD[15,17,21] and five[9–13] reported BMD with AD. Quality assessment (Table 1) showed that all of the studies scored ≥7 points on the NOS scale, except for one study which scored 5 points and one scored 6 points,[11,12] which indicated the relatively high qualities.

3.1. Osteoporosis and AD

Two studies reported on the risk of osteoporosis in AD patients, and another one reported the risk of developing AD in osteoporosis patients.

A retrospective case-control study conducted by Li F[21] with 345 hospitalized patients and 1380 controls showed that the proportion of patients with osteoporosis was significantly higher in the AD group ($P < 0.01$). A prospective cohort study conducted by Liu D et al.[15] with 6 years of follow-up in 1802 patients randomly selected from 8 communities showed that AD (HR 2.48, 95%CI 1.66–2.94) was associated with an increased risk of osteoporosis.

While a retrospective cohort study conducted by Chang KH et al.[17] with 10 years of follow-up examined 23,941 patients with osteoporosis and 47,579 controls. The osteoporosis patients showed 1.39-fold (95%CI 0.95–2.02) higher risk of AD compared with controls.

3.2. BMD levels and AD

Four studies[9,11–13] reported mean and standard deviation on BMD and two cohort studies[9,10] reported HR and 95% CI.

Combining data from the four studies, a negative significant correlation was observed between BMD and AD (SMD -1.23, 95% CI -1.93–0.54) (Fig. 2). Subgroup analyses based on gender and measuring sites were performed (Table 2, Fig. 3 and Fig. 4). Subgroup analysis revealed no alteration in the findings across subgroups except for all genders and lumbar spine. For all genders and lumbar spine which showed no statistically significance in a random effects model, the sensitivity analysis changed the pattern of the results (Table 2). No publication bias was found (Fig. 5).

In the two cohort studies, quartiles of BMD were used to investigate the relationship between femoral neck BMD and AD. Combining data from these two studies, we found that lower femoral neck BMD was associated with increased risk of AD after adjusting for confounding variables (HR 2.19, 95% CI 1.67–2.88). The results were consistent with all genders and female. However, a similar but statistically non-significant relationship was observed in male. Details were showed in Table 3 and Fig. 6. The funnel plot showed no publication bias (Fig. 7).

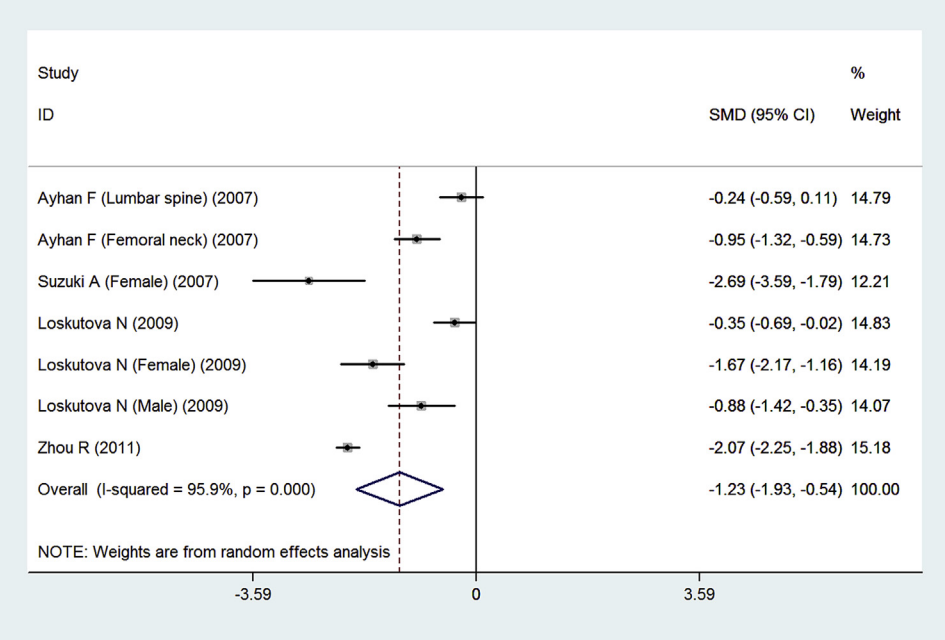

Fig. 2. Pooled estimate of SMD and 95% CI of the association between BMD and AD. SMD, Standardized Mean Difference; CI, Confidence Interval.

Table 2
Results of subgroup and sensitivity analysis for the association between BMD and AD.

	Involved studies	Fixed effect SMD 95%CI	Random effect SMD 95%CI	Heterogeneity			Significant	
				χ^2	P	I^2 (%)	Z	P
Total	4	−1.36 (−1.49,−1.23)	−1.23 (−1.93,−0.54)	147.09	<0.01	95.90	3.47	<0.01
Sex								
All genders	3	−1.34 (−1.47,−1.20)	−0.91 (−1.90,0.08)	134.05	<0.01	97.80	1.79	0.07
Female	2	−1.91 (−2.36,−1.47)	−2.11 (−3.11,−1.11)	3.80	>0.05	73.70	4.15	<0.01
Male	1	−0.88 (−1.42,−0.35)		–	–	–	3.23	<0.01
Measuring sites								
Lumbar spine	2	−0.56 (−0.88,−0.23)	−1.43 (−3.84,0.97)	24.89	<0.01	96.00	1.17	0.24
Femoral neck	2	−1.83 (−2.00,−1.67)	−1.52 (−2.61,−0.43)	28.21	<0.01	96.50	2.74	<0.01
Whole body	1	−0.78 (−1.03,−0.53)	−0.95 (−1.74,−0.16)	18.20	<0.01	89.00	2.36	0.02

Note: SMD, Standardized Mean Difference; CI, Confidence Interval.

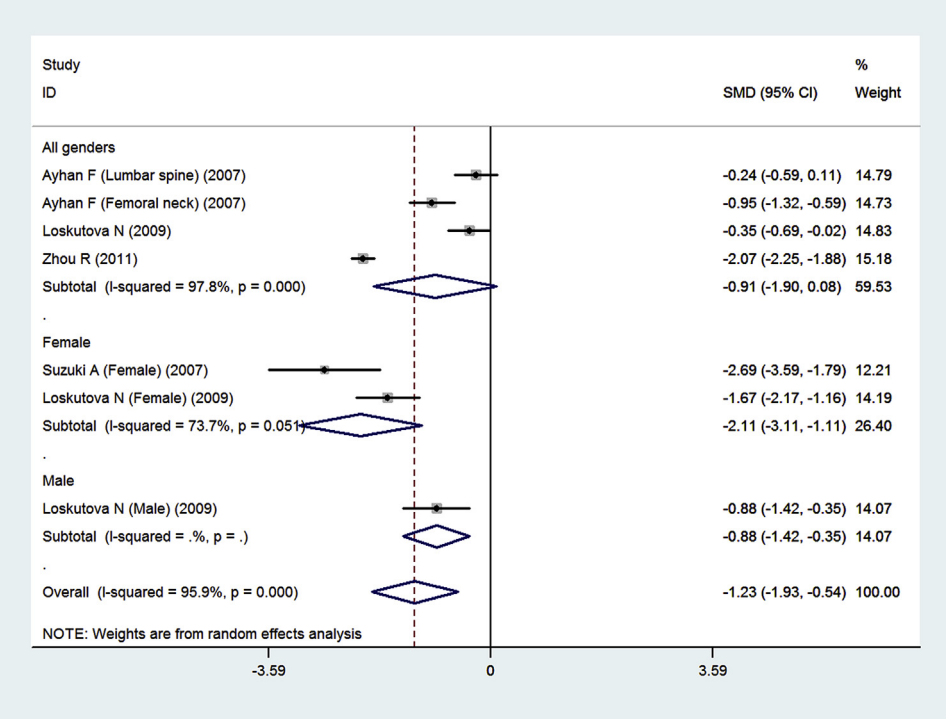

Fig. 3. Pooled estimate of SMD and 95% CI of BMD and AD stratified by sex (All genders, Female and Male).

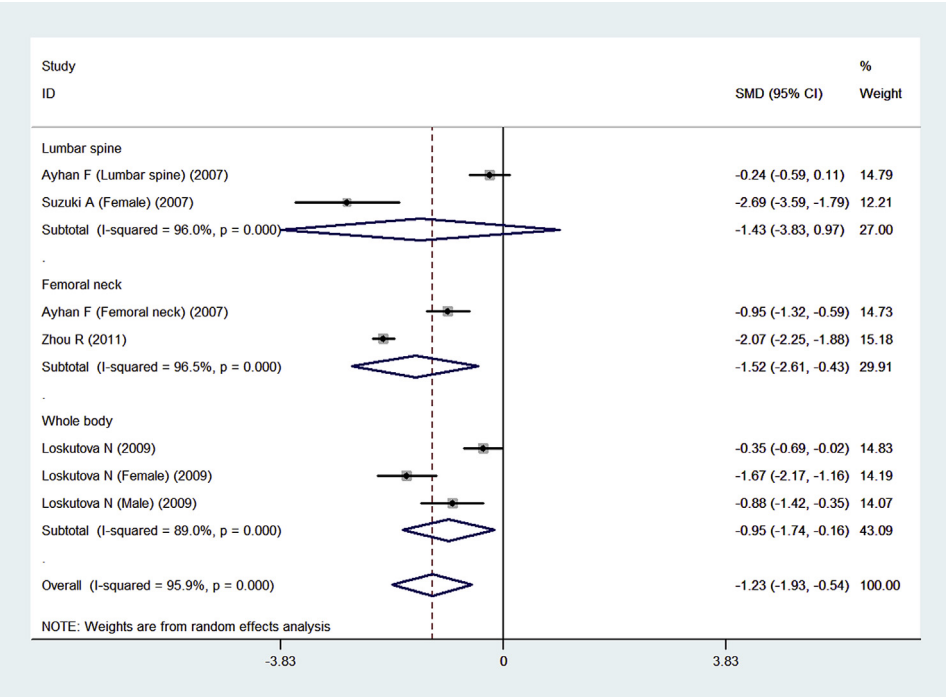

Fig. 4. Pooled estimate of SMD and 95% CI of BMD and AD stratified by measuring sites (lumbar spine, femoral neck and whole body).

4. Discussion

In most studies, the relationships between osteoporosis/BMD and AD were assessed by comparing incidence of osteoporosis or mean BMD between AD patients and controls. While there were a few articles assessed the relationship by comparing the risk of AD between osteoporosis patients or low BMD (cutpoint or percentile) and controls.

For the relationships between osteoporosis and AD, two articles in our study reported the risk of osteoporosis in AD patients, while one article assessed the incidence of AD in osteoporosis patients. In addition, there was evidence of an increased risk of dementia in Asian

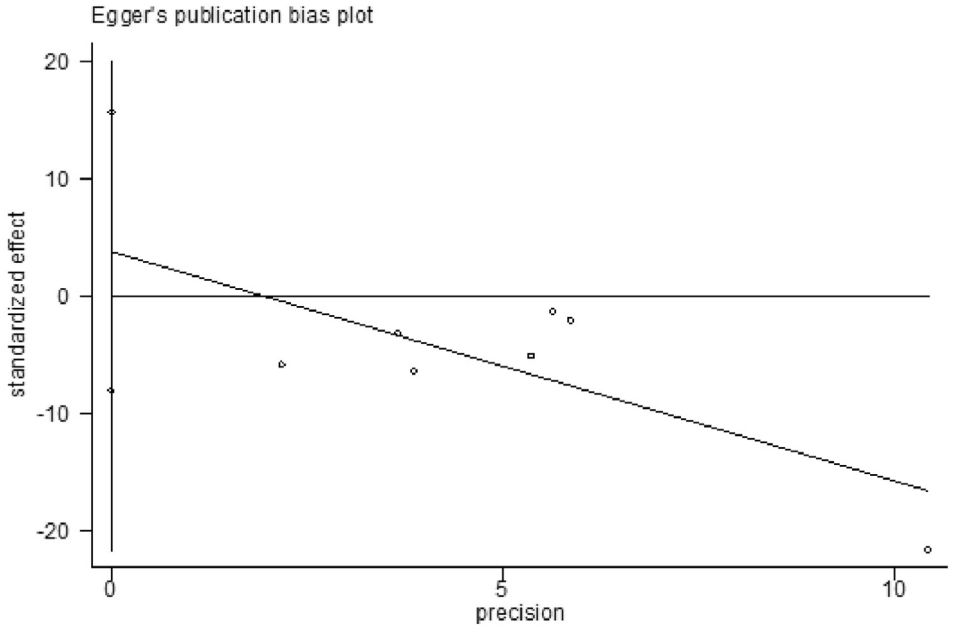

Fig. 5. The Egger's publication bias plot of four studies reporting mean and standard deviation of BMD between AD patients and controls. s.e., standard error.

Table 3
Combined results for the association between femoral neck BMD and AD.

	Involved articles	Fixed effect HR 95%CI	Heterogeneity			Significant	
			χ^2	P	I^2 (%)	Z	P
Total	2	2.19 (1.67, 2.88)	2.63	0.76	0.00	5.66	<0.01
Sex							
All genders	2	2.18 (1.49, 3.20)	0.95	0.33	0.00	4.00	<0.01
Female	2	2.39 (1.48, 3.86)	0.69	0.41	0.00	3.55	<0.01
Male	2	1.90 (0.99, 3.61)	0.67	0.41	0.00	1.94	>0.05

Note: HR, Hazard Ratio.

osteoporosis populations.[17] Zhou R et al.[22] analyzed the association of low BMD with conversion from MCI to AD in a Chinese cohort suggesting that osteoporosis was related to an increased risk of incident AD. And for the associations between BMD and AD, we executed two meta-analyses. The combined results indicated that AD patients had lower BMD compared with controls, and lower femoral neck BMD was associated with increased risk of AD, respectively. The health of bones was therefore important for disability and mortality in AD patients since BMD strongly predicted fracture.

Gender was an important factor. Although only about 20% of osteoporosis patients were males, males maintain 30%–40% of osteoporotic fractures.[23] Moreover, the incidence of AD was different between females and males.[24] The first subgroup analysis showed that AD was associated with low BMD both in female and male. While the second indicated that lower femoral neck BMD was associated with increased risk of AD in female but not in male. For measuring sites, AD was associated with low BMD in femoral neck and whole body except for lumbar spine. Between two studies reporting BMD of lumbar spine, Ayhan F, 2007[11] sampling in Turkish females showed the consistent results with our study, and the other one from Suzuki A, 2007[13] sampling in Japanese females showed the inconsistent results. The most common sites of osteoporotic fracture were the hip, humerus, wrist, and spine. Among these fractures, hip fracture was life-threatening.[25]

To increase the comparability of applied technologies we excluded articles using metacarpal measurements which were discussed before by Tysiewicz-Dudek M et al.[5] Articles of Sato et al.[26–28] revealed a low BMD of the second metacarpal bone measured by an X-ray based densitometric technique (computer-linked X-ray densitometer-CXD, Tokyo, Japan) in AD patients.

Previous studies suggested that osteoporosis and AD shared some common risk factors, such as old age, gender, smoking, excessive drinking, estrogen levels, leptin levels, 25 (OH)D and vitamin D3 levels, and the ApoE genotype.[9,17,29,30] Oxidative stress was thought to play an important role in the development of osteoporosis, and that sex steroids were important in protecting against this.[31] Calcium was a major constituent of the bone and vitamin D helped maintain calcium homeostasis. Calcium and vitamin D supplements had long been recognized as the cornerstones for prevention and treatment of osteoporosis and fractures.[32] The sunlight deprivation in immobilized AD patients might also lead to vitamin D deficiency. APPswe, an AD risk gene, was shown as an unfavorable factor for AD-associated osteoporosis and might have potential clinical value in the treatment of osteoporosis.[33] Dickkopf-related protein 1 (Dkk1) as an important antagonist of Wnt signaling was considered as a common potential risk factor for osteoporosis and AD.[34] Dkk1 might possessed a fundamental role in balancing the function of osteoblast and osteoclast, which determined the osteoporosis susceptibility.[34] Meanwhile, high level of Dkk1 in the brain also increased the risk of AD. The ApoE4 allele as a major cholesterol carrier was a well-established genetic risk factor for AD via its binding to Amyloid beta peptide.[27] Possible alternate explanations of ApoE for osteoporosis included an effect on vitamin K, bone turnover, or weight loss.[35]

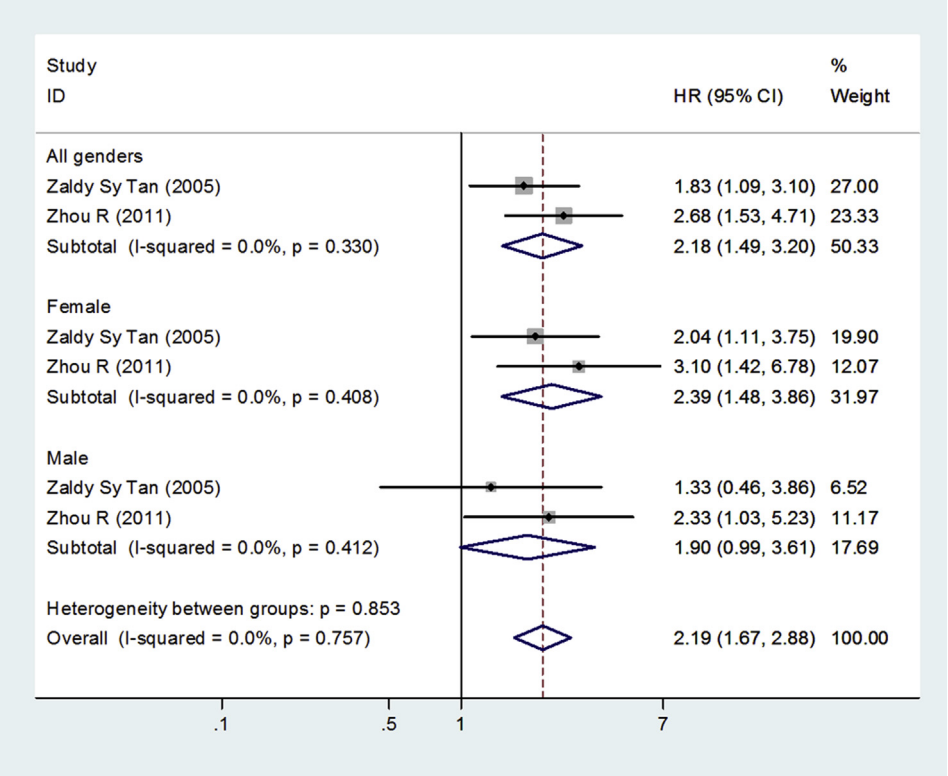

Fig. 6. Pooled estimate of HR and 95% CI of femoral neck BMD and AD stratified by sex (All genders, Female and Male). HR, Hazard Ratio.

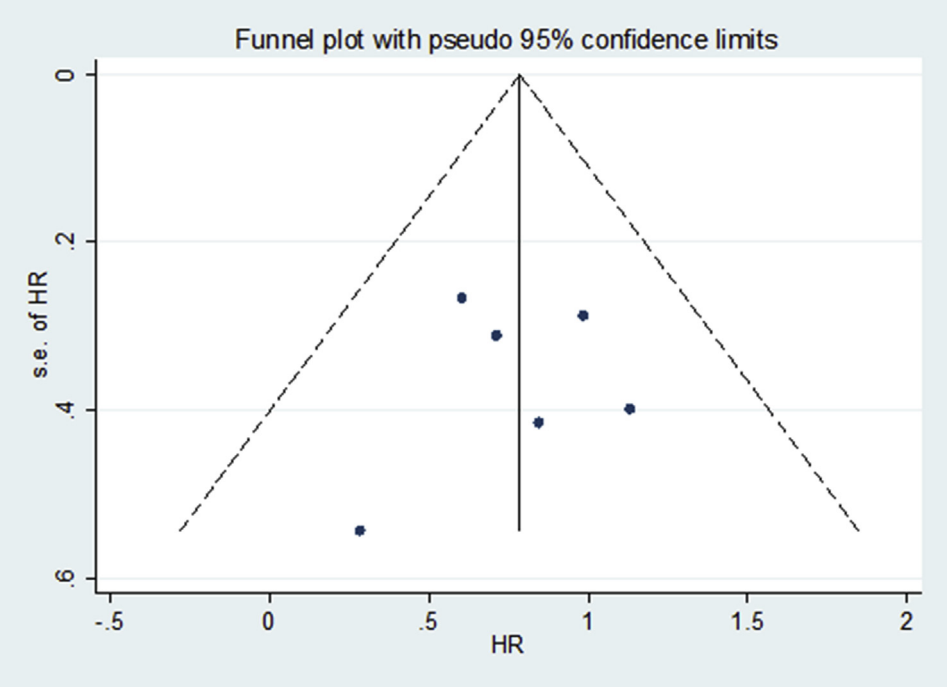

Fig. 7. The funnel plot of two cohort studies for femoral neck BMD with AD.

BMD was regulated through the brain,[36,37] suggesting that AD-related brain changes might affect bone remodeling or that bone loss and AD might share common biological mechanisms. And this might partially explain the underlying relationship.

It had some limitations that should be considered. Firstly, measurement or diagnosis of BMD and AD was not fully unified. Secondly, statistical quality of observational study was regarded as lower than that of randomized trial because of potential biases

related to adjustments for confounding variables. Thirdly, different inclusion of potential confounders was another critical point. Finally, many factors that might have exerted an influence on disease progression could not be considered. Such as fall rate, supplement of anti-osteoporosis and anti-AD drugs, exposure to sunlight and so on. Despite of these limitations, our research provided a comprehensive conclusion on the association between osteoporosis/BMD and AD.

5. Conclusion

We conclude that there is an association between osteoporosis/BMD and AD. AD patients are at higher risk for osteoporosis and have lower BMD than controls, while osteoporosis and lower femoral neck BMD are also associated with a higher risk of AD. The risk of AD in osteoporosis patients and the risk of osteoporosis/BMD in AD patients are two different aspects to explore the connections between these two disorders. It is therefore impossible to rule out causality as an alternative explanation. A result of disease development may be the answer rather than being causal. More research with better design were needed to address this issue.

Conflict of interest

All authors declare to disclose any conflict of interest.

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