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Association between Bone Mineral Density and the Risk of Alzheimer's Disease

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Abstract. Alzheimer's disease (AD) and osteoporosis are common chronic degenerative disorders which are strongly associated with advanced age. Some studies suggest that low bone mineral density (BMD) is related to the increased risk of AD. We conducted a 5-year prospective study to exam the association between BMD and the risk of AD in a cohort of Chinese elderly people. Of 3263 community residents aged 65 years and over, 2019 were enrolled into the study and followed up annually for 5 years. At baseline demographic data, smoking and drinking status, medical history, cognitive status, and blood samples were collected. BMD was measured by dual energy X-ray absorptiometry (DEXA) scanning at baseline and during follow-up. Cox proportional hazards analysis was used to evaluate the association with BMD and incidence of AD. Over the follow-up of 5 years, AD developed in 132 subjects. Baseline BMD, bone loss rate, current smoking, and daily drinking were associated with increased risk of AD, while higher baseline plasma leptin level was associated with decreased risk of AD, in both women and men. Low BMD and increased loss rate of BMD were associated with higher risk of AD. Cigarette smoking, alcohol drinking, and lower leptin level are risk factors for AD. Uncovering the relation linking osteoporosis and AD is important for understanding the pathogenesis and developing therapeutic strategies for these two common disorders afflicting elderly people.

Keywords: Alzheimer's disease, bone loss, bone mineral density, leptin

INTRODUCTION

Alzheimer's disease (AD) and osteoporosis are common chronic degenerative disorders which are strongly associated with advanced age. As the world population is aging, the prevalence of AD and osteoporosis is rising dramatically and becoming the major health problems. China has the largest elderly population of 160 million in the world [1], with high incidence of AD and osteoporosis [2, 3]. AD is the most common form of dementia. The prevalence of AD in Chinese elderly aged 65 years old and over is 3.5%, which is comparable with that in western populations [4]. Currently, there are 5 million patients living with AD in China [2]. It is projected that the prevalence of AD will be four times of that in the middle of this century [5]. Osteoporosis is a common systemic skeletal disease affecting the elderly, characterized with low bone mass and micro-architectural deterioration, with a consequent increase in bone fragility and fracture susceptibility. There are 90 million people with osteoporosis in China at the present time [6, 7]. The number of osteoporosis fracture exceeds the amount of myocardial infarction, stroke, and cancer [8].

The relation between these two common disorders remains unclear. Previous studies suggest that they share some common risk factors such as old age, being

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female, smoking, excessive drinking, low estrogen, and vitamin D3 levels [9]. It remains unclear whether low bone mineral density (BMD) is related to the risk of AD [10, 11]. Given the differences in race, economic level, and lifestyles between China and western countries, the relationship between BMD and AD in China may differ from that in western countries. Thus we conducted a 5-year prospective study to exam the association of BMD with risk of AD in a cohort of Chinese elderly people.

METHODS

Study subjects

Chongqing, the largest municipality in western China, has a population of 35 million, of which ten million live in urban areas. The city of Chongqing is located in the middle of Chongqing, with a total population of three million. Subjects were sampled from three randomly selected communities in the city of Chongqing. This study was approved by the Institutional Review Board of the Daping Hospital, and all subjects provided informed consent.

Baseline screening

The baseline screening of the present study was performed between January 1, 2003 and June 30, 2003. In the selected communities, there was a total of 3263 people aged 65 and above. The subjects were interviewed by holding meetings in community centers. For people who were absent at the meeting time, or who were not able to attend due to physical disabilities, our staff went to their home to perform the interview. 2451 individuals were screened at baseline, while 812 subjects, who were not available at the time of screening ($n = 445$) or declined to participate ($n = 367$), were excluded from the present study. A total of 165 cases with dementia was diagnosed and excluded from the study. 2286 without dementia were enrolled at baseline (Fig. 1).

The following data were collected: demographic data, bone density, smoking and drinking status, medical history, clinical assessment, functional and cognitive status, and depressive symptomatology. These procedures were administered by trained interviewers composed of experienced neurologists, psychiatrists, and senior nurses. The Cohen's K statistic was used to measure the reliability across interviewers. The agreement on data collection was found to be excellent based on the same sample of subjects, with a kappa of 0.93.

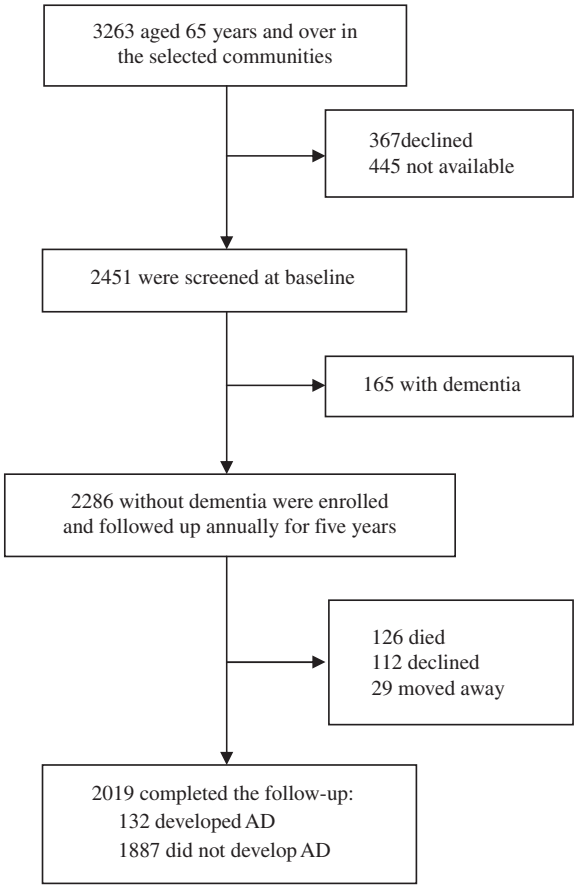

Fig. 1. Flowchart of analysis sample selection. AD = Alzheimer's disease.

(1) Demographic data: These data included age, gender, educational level [lower educational level (illiteracy or primary school), and higher educational level (above secondary school)].
(2) BMD: Dual energy X-ray absorptiometry (DXA, Prodigy fan beam densitometer, Lunar Corp, GE Medical System, Madison, WI) was used to determine BMD. BMD of femoral neck bone was used as a measure of global bone health. BMD was measured at baseline and three years after enrollment. Annual percentage change [$100 \times$ (BMD1-BMD2)/BMD1 $\times$ length of follow-up in years] and absolute annual change in bone density during the three years' follow-up period were calculated. Baseline BMD and the percentage change were categorized into quartiles based on the sample distribution.
(3) Smoking and drinking status: The smoking status was classified as past smokers who had quit

smoking for at least 6 months, current smokers, or those who never smoked. Drinking status was classified as daily drinking, weekly drinking, monthly drinking, or occasional drinking as defined previously [12, 13].

(4) Clinical assessment: The medical history was collected from self report, available medical records or medication. The data included prior head trauma and surgery, prior gas poisoning, schizophrenia, hypothyroidism, coronary heart diseases, atrial fibrillation, chronic obstructive pulmonary disease, chronic hepatitis, chronic renal insufficiency, hypertension, diabetes mellitus, hypercholesterolemia and Parkinson's disease.

Blood pressure measurement and electrocardiogram were performed on-site, and fasting blood samples were collected to measure glucose, total cholesterol, calcium, APOE4, 25-(OH)D3, adiponectin, leptin and estradiol. Body mass index (BMI) was measured. Subjects with abnormalities, implying potential diseases that were not previously diagnosed, were introduced to Daping hospital for further investigation. Diagnosis of diseases including anemia, hypothyroidism, hypertension, diabetes mellitus, hypercholesterolemia, obesity, coronary heart diseases, atrial fibrillation, chronic renal insufficiency, and chronic hepatitis were based on the International Classification of Diseases, 9th revision (ICD-9).

(5) Neuropsychological evaluation: Cognitive status was assessed using the Chinese version of the Mini-Mental Status Examination (MMSE), which was validated previously in the Chinese elderly [14, 15]. Additive scores of MMSE ranged from 0 to 30. The boundary score of MMSE was defined as 17 (illiteracy), 20 ($\leq$6 years of education), and 24 (>6 years of education). The subjects with cognitive decline after MMSE screen were further administered a battery of neuropsychological tests developed for epidemiological studies in Chinese people [14], including Fuld Object Memory Evaluation for detecting extensive cognitive dysfunction mainly composed of memory [16], Rapid Verbal Retrieve for detecting the function of semantic memory [17], Wechsler Adult Intelligence Scale for evaluating immediate memory and function of graphical recognition [18], Pfeiffer Outpatient Disability Questionnaire for assessing ability of social activities [19], and Hamilton Depression Rating Scale for measuring emotional status [20]. The functional ability in basic and instrumental activities was evaluated using modified Activities of Daily Living (ADL) [21], which consists of 20 basic and instrumental activities of daily living. Each activity was rated on a 4-point scale, with 1 point indicating "no limitation", 2 points indicating "does activity by oneself with some difficulties", 3 points indicating "needs help with activity", and 4 points indicating "unable to do activity". Additive score of ADL ranged from 20 to 80, an ADL score >60 indicated that the subject had no self-care ability.

(6) Diagnosis of dementia: The clinical diagnosis of dementia was made by a group of senior neurologists and psychiatrists following the protocol described in our previous studies [14, 22]. In brief, dementia was diagnosed based on criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) [23]. Patients with dementia were further subjected to brain computed tomography (CT) or magnetic resonance image (MRI). A diagnosis of AD was made according to the criteria of National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [24], while diagnosis of vascular dementia was based on the criteria of National Institute of Neurological Disorders and Stroke/Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) [25].

Follow-up

Subjects were followed up annually for five years from July, 2003 to June, 2008. Cognitive status was assessed using the same procedure as baseline screening.

Statistical analysis

In univariate analyses, baseline variables between subjects who developed AD and those who did not were compared using Pearson Chi square test, Fisher exact test, a t test, or the Mann-Whitney U test as deemed appropriate. The Cox proportional hazards models were used to assess the associations between BMD or bone loss rate and the risk of AD in three steps. Firstly, the associations were analyzed without

adjustment for other covariates. Secondly, the associations were analyzed with adjustment for potential confounders, including age, gender, and education. Thirdly, as gender has important impact on both BMD and AD, the associations were analyzed in subgroups of men or women with or without adjustment for age and education. The statistical analyses were performed using SPSS 15.0 for Windows.

RESULTS

2286 subjects without dementia were enrolled into the present study at baseline. Five years later, 132 developed AD, 126 (5.5%) died, 112 (4.9%) declined, and 29 (1.3%) moved away during the follow-up, 2019 (88.3%) people completed the follow-up (Fig. 1).

Baseline characteristics in subjects who did and did not develop AD

The demographic and clinical characteristics of the subjects who developed AD and who did not were shown in Table 1. For subjects who completed the follow-up, the average age was 72.2 ± 4.5 years. Compared with subjects who did not develop AD, those who did were older (75.3 ± 4.3 vs 72.0 ± 4.5, $p < 0.001$), more frequent in female (59.1% vs 41.5%, $p < 0.001$), current smokers (36.4% vs 19.9%, $p < 0.001$), and daily drinking (28.8% vs 19.1%, $p = 0.023$), had lower BMD (0.61 ± 0.11 g/cm^2 vs 0.78 ± 0.08 g/cm^2, $p < 0.001$) and plasma leptin level (20.2 ± 11.4 ng/ml vs 26.6 ± 10.7 ng/ml, $p < 0.001$).

Association between BMD and the risk of AD

Table 2 shows the associations between BMD, leptin, adiponectin, cigarette smoking or drinking, and the risk of AD. The unadjusted hazard risk (HR) of AD for each component were as follows: BMD (HR 3.48, 95% CI 1.99–6.08, Q1 : Q4), current smoker (HR 2.35, 95% CI 1.28–4.30), daily drinking (HR 1.79, 95% CI 1.12–2.87), and leptin (HR 0.92, 95% CI 0.90–0.94). These associations remain essentially unchanged after adjustment with age, gender, and education, suggesting that lower BMD, current smoking and daily drinking are associated with increased risk of AD, while higher leptin level is associated with decreased risk of AD.

Table 1
Baseline characteristics in subjects who did and did not develop AD

	Did not develop AD ($n = 1887$)	Developed AD ($n = 132$)	p-value
Physical characteristics			
Age (y), ±SD	72.0 ± 4.5	75.3 ± 4.3	<0.001
Female, n (%)	784 (41.5)	78 (59.1)	<0.001
Lower education level (≤6 years), *n* (%)	503 (26.7)	56 (42.2)	<0.001
BMD (g/cm^2), ±SD	0.78 ± 0.08	0.61 ± 0.11	<0.001
BMI (kg/m^2), ±SD	24.2 ± 3.7	23.8 ± 2.6	0.115
Biochemical markers			
ApoE4, *n* (%)	427 (22.6)	38 (28.8)	0.101
25-(OH)D3 (nmol/L), ±SD	54.9 ± 11.9	53.4 ± 13.7	0.175
Estradiol (pg/ml), ±SD	100.3 ± 34.0	95.5 ± 26.2	0.109
Leptin (ng/ml), ±SD	26.6 ± 10.7	20.2 ± 11.4	<0.001
Adiponectin (μg/ml), ±SD	17.6 ± 6.6	16.6 ± 8.9	0.118
Smoking status			
Never smokers, *n* (%)	759 (40.2)	41 (31.1)	
Past smokers, *n* (%)	752 (39.9)	43 (32.6)	
Current smokers, *n* (%)	376 (19.9)	48 (36.4)	<0.001
Drinking status			
Occasional drinking, *n* (%)	555 (29.4)	32 (24.2)	
Daily drinking, *n* (%)	361 (19.1)	38 (28.8)	0.023
Weekly drinking, *n* (%)	376 (19.9)	30 (22.7)	
Monthly drinking, *n* (%)	595 (31.5)	32 (24.2)	
Vascular risk factors			
Hypertention, *n* (%)	614 (32.7)	38 (36.4)	0.389
Diabetes mellitus, *n* (%)	450 (23.8)	39 (29.5)	0.142
Hypercholesterolemia, *n* (%)	402 (21.3)	29 (22.1)	0.881
MMSE, ±SD	27.2 ± 2.3	17.5 ± 2.1	<0.001
ADL, ±SD	20.6 ± 3.5	26.2 ± 5.1	<0.001

Table 2
The relation between bone density and the risk of developing AD

Variable	Hazard ratio for AD Unadjusted	Hazard ratio for AD Adjusted*
BMD		
Q1	3.48 (1.99–6.08)	2.68 (1.53–4.71)
Q2	2.25 (1.25–4.05)	2.11 (1.17–3.80)
Q3	1.61 (0.86–3.00)	1.67 (0.90–3.12)
Q4	1	1
Leptin	0.92 (0.90–0.94)	0.93 (0.91–0.95)
Adiponectin	0.98 (0.95–1.01)	0.98 (0.96–1.01)
Smoking Status		
Never smokers	1	1
Past smokers	1.05 (0.69–1.62)	1.01 (0.66–1.55)
Current smokers	2.24 (1.47–3.39)	2.03 (1.34–3.09)
Drinking		
Occasional drinking	1	1
Daily drinking	1.79 (1.12–2.87)	1.72 (1.07–2.75)
Weekly drinking	1.36 (0.83–2.24)	1.40 (0.85–2.30)
Monthly drinking	0.94 (0.57–1.53)	0.82 (0.50–1.33)

BMD: Q1: <0.641, Q2: 0.642–0.765, Q3: 0.766–0.882, Q4: >0.883.
*Adjusted for age, gender, and education.

Association between BMD and the risk of AD in women and men

As gender is associated with the risk of both BMD and AD in the elderly, we further examined the association between BMD and AD in either women or men. Table 3 shows the association between BMD and the risk of AD in women and men. Compared with BMD in the highest quartile (Q4), women with BMD values in the lowest quartile (Q1) had a HR of 3.87 (95% CI 1.78–8.40). The association remained statistically significant after adjustment with age, gender, and education (HR 3.10, 95% CI 1.42–6.78). Similarly, men with BMD values in the lowest quartile (Q1) had an unadjusted HR of 2.98 (95% CI 1.33–6.69) and adjusted HR of 2.33 (95% CI 1.03–5.23) relative to men with BMD values in the highest quartile (Q4). These results suggest that the lower BMD is associated with increased risk of AD in both women and men.

The association between rate of bone loss and the risk of AD

Table 4 shows the association between rate of bone loss and the risk of AD. Compared with subjects whose bone loss rates were in the lowest quartile (Q1), subjects whose bone loss rates were in the highest quartile (Q4) had a HR of 2.35 (95% CI 1.39–3.96). The association remained statistically significant after adjustment for age, gender, and education (HR 2.67, 95% CI 1.58–4.52). In further analyses for both women and men, these associations remained essentially the same, with higher HR values in women than in men. These results suggest that bone loss rate is also associated with increased risk of AD.

DISCUSSION

In the present study, we examined, for the first time, the association between BMD and the risk of AD in

Table 3
Association between BMD and risk of AD in women and men

BMD	Women		Men	
Quartile	Hazard ratio Unadjusted	Hazard ratio Adjusted*	Hazard ratio Unadjusted	Hazard ratio Adjusted*
Q1	3.87 (1.78–8.40)	3.10 (1.42–6.78)	2.98 (1.33–6.69)	2.33 (1.03–5.23)
Q2	2.85 (1.27–6.41)	2.58 (1.15–5.80)	1.70 (0.71–4.05)	1.67 (0.70–3.99)
Q3	2.07 (0.89–4.89)	2.08 (0.89–4.86)	1.20 (0.47–3.03)	1.26 (0.50–3.19)
Q4	1	1	1	1

BMD: Q1: <0.641, Q2: 0.642–0.765, Q3: 0.766–0.882, Q4: >0.883.
*Adjusted with age and education.

Table 4
The association between rate of bone loss and the risk of AD

Quartile of change in BMD	Women and men		Women		Men	
	Hazard ratio Unadjusted	Hazard ratio Adjusted#	Hazard ratio Unadjusted	Hazard ratio Adjusted*	Hazard ratio Unadjusted	Hazard ratio Adjusted*
Q1	1	1	1	1	1	1
Q2	1.59 (0.91–2.77)	1.83 (1.04–3.20)	2.08 (0.98–4.45)	2.29 (1.07–4.89)	1.15 (0.50–2.66)	1.37 (0.59–3.17)
Q3	1.66 (0.95–2.89)	1.96 (1.12–3.42)	2.17 (1.03–4.59)	2.55 (1.21–5.39)	1.12 (0.48–2.63)	1.33 (0.56–3.14)
Q4	2.35 (1.39–3.96)	2.67 (1.58–4.51)	2.48 (1.19–5.13)	2.90 (1.39–6.02)	2.17 (1.02–4.61)	2.50 (1.17–5.30)

#: Adjusted with age, gender, and education.
*: Adjusted with age and education. Quartile of change in BMD: Q1: <−0.27, Q2: 0.27–0.35, Q3: −0.35–1.05, Q4: >1.05.

Chinese elderly people. After five years' follow up, we found that lower baseline BMD, higher bone loss rate, current smoking, and daily drinking were associated with increased risk of AD, while higher baseline plasma leptin level was associated with decreased risk of AD, in both women and men.

The association between BMD and AD is less studied. To our knowledge, there are three studies which investigated the relationship between BMD and AD [10, 11, 26], and which found that lower bone density is associated with the higher risk of AD in western population [11]. Consistently, the lower BMD was also associated with increased risk of AD in our Chinese cohort. This is further confirmed by the association between bone loss rate and risk of AD. In a study of western people, the association between BMD and AD is significant only in women [11]. It is proposed that decreased estrogen level in the older women is related to both osteoporosis and AD [11, 27]. However, in the present study this association remained significant in both women and men. This may reflect that AD and osteoporosis share the common risk factors such as smoking and drinking, of which the prevalence is higher in Chinese men relative to western populations [28–30].

A link between osteoporosis and AD is that they share some common risk factors, such as current smoking, daily drinking, and low leptin levels. This may explain, at least in part, the association between BMD and risk of AD.

Smoking is suggested to be associated with increased risk of AD in both western populations and in our Chinese cohort [31]. The mechanism by which smoking increases the risk of AD remains unclear. Nicotine administration increases *tau* phosphorylation and related pathologies in animal models of AD in our previous studies and others [32, 33]. Additionally, increased oxidative stress that resulted from smoking is evident in AD and may cause neuronal degeneration. Smoking is also a risk factor of osteoporosis. It has been found that current smokers have decreased BMD than non-smokers. The impact of smoking on bone status is associated with the smoking year and amount [34]. BMD is reduced in smokers due to increased bone resorption and bone formation inhibition by cigarette smoking [35]. Nicotine increases alkaline phosphatase activity and weakens the biological properties of bone, thus disturbs the balance between bone resorption and formation.

Studies examining the effects of alcohol consumption on dementia have produced conflicting results. Some studies have found no association between alcohol drinking and AD, whereas others have found an association between excessive drinking and increased risk of dementia [13, 36]. Our present and previous studies suggest that daily drinking is related to higher risk of AD [30]. Excessive drinking also increases the risk of osteoporosis, interferes with bone metabolism, accelerates bone loss, and reduces bone mineral density [37].

Leptin is mainly synthesized by white adipose tissue and its plasma level is associated with body mass index (BMI) and fat mass. The relation between leptin and AD was less investigated before. Consistent with a recent prospective study [38], we found that higher leptin level is associated with lower risk of AD. Recent studies suggest that leptin receptors are expressed in many extra-hypothalamic brain regions, in particular the CA1 region of the hippocampus [39]. Activation of leptin receptors facilitates long-term potentiation and synaptic plasticity in the hippocampus [40]. Leptin promotes amyloid β clearance, reduces *tau* phosphorylation, and improves memory function in animal models of AD [41]. Leptin is also found to be negatively associated with BMD in both men and women [42]. Leptin regulates bone remodeling via hypothalamus relay [43]. Leptin may cause bone loss and is significantly related to high-turnover serum bone markers [44]. One mediator linking leptin signaling in the brain to bone remodeling is the sympathetic tone which inhibits bone formation and favors bone resorption through the β2 adrenergic receptor expressed in osteoblasts [42].

The relations between adiponectin, vitamin D3 and AD were less reported. In the present study, both adiponectin and vitamin D3 were not associated with risk of AD. However, some other studies suggest that lower levels of adiponectin and vitamin D3 are risk factors of AD [45, 46]. It is proposed that adiponectin can reduce atherosclerosis and increase the insulin sensitizing effect, thus reduce the risk of AD [46]. As a key component affecting bone mineral density [47], vitamin D3 also promotes production of neurotrophic factors and enhances the cognitive function [45].

The mechanism linking AD and osteoporosis remains unclear. Increasing evidence that neurons and neurotransmitters are involved in bone remodeling has shed light on a novel regulatory mechanism for bone homeostasis. Recent studies suggest that the central nervous system regulates bone remodeling through hypothalamus by two pathways, namely, the neurohumoral arm and neural arm [10, 26]. Hypothalamus is also involved in memory through connections

with the hippocampal formation [10]. Recent studies observed the degeneration and volume loss of hypothalamus in AD [26]. In addition, abnormal calcium and phosphorus metabolism in osteoporosis can induce excessive influx of calcium and death of the neuron cells, which may exacerbate the formation of senile plaques and neurofibrillary tangles in AD [48–50]. This evidence implies the close relation between osteoporosis and AD, which need further investigation in the future.

Conclusively, the present study found that lower BMD and higher rate of bone loss were related to the higher risk of AD, suggesting that there is an intrinsic close relation between the osteoporosis and AD. Uncovering the relation linking osteoporosis and AD is important for understanding the pathogenesis and developing therapeutic strategies for these two common disorders afflicting the elder people.

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