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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.
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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

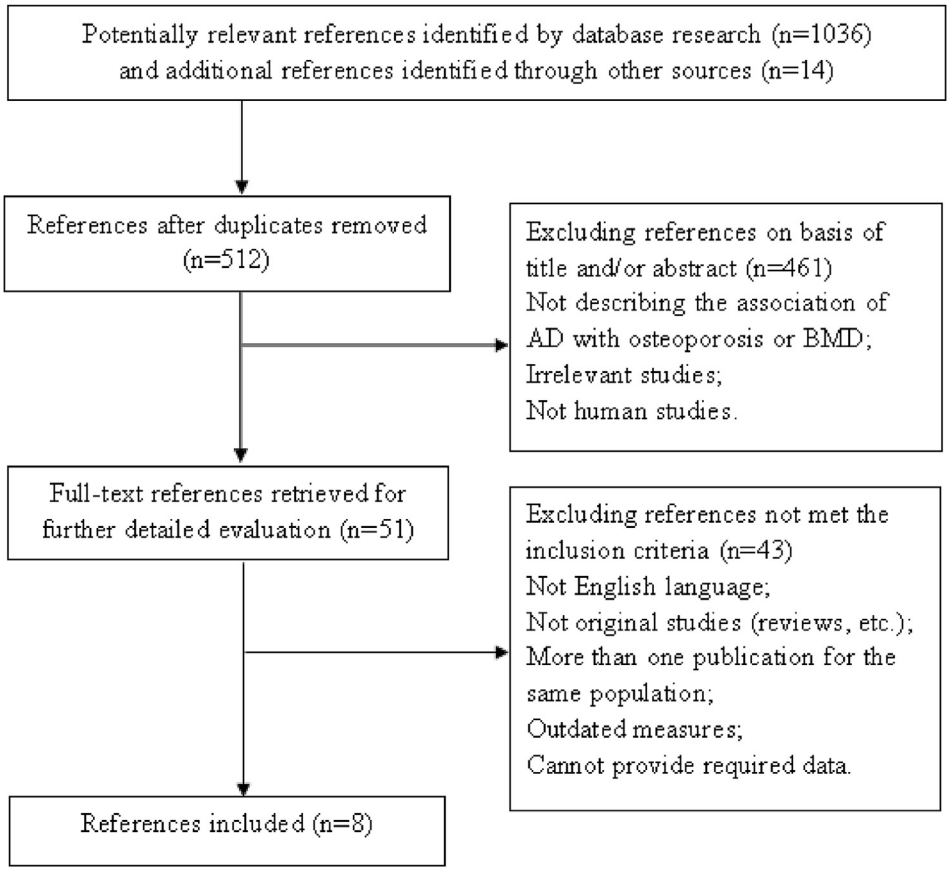

Fig. 1. The flow diagram for study selection.

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