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Bone mineral density and all-cause, cardiovascular and stroke mortality: A meta-analysis of prospective cohort studies

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ABSTRACT

Background: Low bone mineral density (BMD) has been associated with increased mortality in prospective cohort studies of the elderly, but the real relationship is still controversial. We undertook a meta-analysis to evaluate the association of BMD with risk of all-cause, cardiovascular and stroke mortality. *Methods:* We performed systematic searches on MEDLINE, EMBASE, OVID, CINAHL, and the Cochrane Library. Data extraction was performed independently by two reviewers. For each study, hazard ratios (HRs) and 95% confidence intervals (CI) per standard deviation (SD) decrease in BMD were extracted. Heterogeneity, publication bias, subgroup, and meta-regression analysis were performed. *Results:* The analysis included 46,182 participants from 10 studies with 3991 all-cause deaths, 1479 cardiovascular deaths and 403 stroke deaths during a median of 7 years follow-up (range 2.8–18.7 years). Lower BMD had a significant inverse relationship with all-cause and cardiovascular mortality, a per SD decrease in BMD at all sites being associated with a 1.17-fold (95% CI: 1.13–1.22) increase in total mortality and a 1.13-fold increase in cardiovascular mortality (95% CI: 1.06–1.20). Lower total hip/femoral neck BMD was also related to all-cause mortality (HR 1.20; 95% CI: 1.09–1.31) and cardiovascular mortality (HR 1.20; 95% CI: 1.04–1.35). BMD was not associated with the risk of stroke mortality (HR 1.08, 95% CI; 0.89–1.28). *Conclusions:* Lower BMD is associated with significantly increased risk of all-cause and cardiovascular mortality. There is no significant association between lower BMD and the risk of stroke mortality. The relationship between lower BMD and individual mortality should be investigated further in randomized trials.

1. Introduction

Osteoporosis is a major public health concern because of associated fractures, and related disability, decreased quality of life and increased mortality [1,2]. Epidemiological studies have indicated an inverse association between osteoporosis and the incidence of all-cause, cardiovascular or stroke mortality in asymptomatic osteoporosis patients [1–3]. An increased risk of death after osteoporotic fracture, especially hip fracture, is well established in both women and men [4]. Moreover, a recent meta-analysis of eight randomized placebo-controlled trials assessed whether osteoporosis treatment was associated with mortality risk [5]. It indicated that osteoporosis treatments, with established efficacy in vertebral and nonvertebral fractures, reduced mortality in older, frailer individuals with osteoporosis who were at high risk of fracture.

Bone mineral density (BMD) is an essential component in the assessment of osteoporosis. It is used to assess the risk of osteoporotic fracture and to monitor the natural progression of the treated or untreated patient [6]. Recent prospective and cross-sectional studies suggested independent associations between BMD and vascular calcification, which is an established surrogate marker for vascular events and mortality [7,8]. Several prospective cohort studies have investigated lower BMD in relation to risk of mortality, but the findings have been inconsistent [9–18]. In addition, the relationship of BMD to particular causes of mortality such as cardiovascular and stroke events, and whether this is independent of established cardiovascular or stroke risk factors, or other lifestyle factors, was unclear [19]. Therefore, we performed a systematic review and meta-analysis of the prospective studies to assess the relationship between BMD and risk of all-cause, cardiovascular and stroke mortality using strictly prearranged criteria for inclusion or exclusion.

2. Methods

We performed a systematic review of the existing literature, following the meta-analysis of prospective cohort studies in the MOOSE guidelines and the PRISMA statement [20,21].

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2.1. Search strategy

We performed a systematic literature search of MEDLINE (1966 to May 31, 2011), EMBASE (1980 to May 31, 2011), OVID (1950 to May 31, 2011), CINAHL (1982 to May 31, 2011), and the Cochrane Library for prospective cohort studies. All searches were performed using medical subject heading (MeSH) or free text words. We combined search terms for the outcomes (stroke, cerebral infarction, intracerebral hemorrhage, subarachnoid hemorrhage, cerebrovascular accident, myocardial infarction, heart attack, cardiovascular, ischemic heart disease, coronary artery disease, mortality, mortalities, death, fatality, fatal, survival, survival rate, and survivorship); the influencing factor (bone mineral density, bone density, bone strength, bone loss, and BMD); and risk estimates (risk ratio, relative risk, and hazard ratio). In addition, we searched the reference lists and unpublished studies of all identified relevant publications.

2.2. Selection criteria

Two reviewers (Q.XH. and H.XL.) independently evaluated studies for inclusion. Discrepancies about inclusion of studies and interpretation of data were resolved by arbitration (D.KR.), and consensus was reached after discussion. In the case of missing data for potentially suitable studies, the authors were contacted and asked to provide the necessary information. Studies were included in the meta-analysis if they met the following criteria: (1) prospective design; (2) adult population; (3) the influencing factor of interest was BMD; (4) the outcome of interest was all-cause, cardiovascular and stroke mortality; (5) risk estimates (relative risk or hazard ratio) with 95% confidence interval (CI) for BMD as a continuous variable (per standard deviation (SD) decrease) and/or for each category of baseline BMD were reported; and (6) follow-up of at least 2 years (mean or median). Studies that did not meet the inclusion criteria were discarded during the initial review.

2.3. Data extraction and quality assessment

All data were independently extracted by two reviewers (Q.XH. and H.XL.) using a standardized data collection form. Discrepancies were resolved through discussion with other investigators (D.KR. and T.TT.) and with reference to the original articles. The following data were extracted from each study: the first author's last name, publication year, country where the study was performed, study period, the data of BMD per SD decrease (g/cm^2), participant sex and age, sample size, number of cases, outcome reported, method of outcome assessment and BMD assessment, BMD measurement site, variables adjusted in the analysis, and risk estimates with corresponding confidence intervals (CIs for BMD as a continuous variable (per SD decrease) and/or for each category of baseline BMD). SDs mean differences between patient's BMD and that of the healthy young people norm are measured in units. Our primary outcomes were: (1) all-cause mortality, (2) cardiovascular mortality, and (3) stroke mortality. Quality was assessed using elements of the STROBE checklist for cohort studies considered important in these studies [22]. Any disagreement in abstracted data was resolved by a third reviewer (D.KR.).

2.4. Statistical analysis

The hazard ratio (HR) was used as the common measure of association across studies, and the relative risk (RR) was considered directly as the HR [23]. To summarize BMD association with the risk of all-cause, cardiovascular and stroke mortality, the effect measures were pooled for the continuous variable (per SD decrease). If the included studies were used categories, we estimated the HR as a continuous variable for a SD decrease in BMD according to the method described by Greenland and Longnecker, which takes into account that the level-specific HRs are correlated [24,25]. HRs or RRs per SD decrease in BMD were extracted from the selected studies, and their standard errors (SEs) were calculated from the respective relative CIs. For meta-analysis, both a fixed-effects model (weighted with inverse variance) and a random-effects model were considered [26]. Heterogeneity between studies was assessed using Cochran Q statistics and I^2 statistics [27]. As suggested by Higgins et al., I^2 values of 25%, 50%, and 75% were considered low, moderate, and high, respectively [28]. For $P<0.10$ values of the Cochran Q statistic, the assumption of homogeneity was deemed invalid and a random-effects model was reported. Funnel plot asymmetry was used to detect publication bias, and the Egger regression test was applied to measure funnel plot asymmetry. We also performed the "trim and fill" procedure to further assess the possible effect of publication bias in our meta-analysis. This method considers the possibility of hypothetical "missing" studies that might exist, imputes their HRs, and recalculates a pooled HR that incorporates the hypothetical missing studies as though they actually existed [29,30].

Subgroup analyses and meta-regression analyses were used to identify associations between risk of all-cause, cardiovascular and stroke mortality and relevant study characteristics (gender, mean age, length of follow-up, quality score, recruitment time, location of cohort, method of BMD assessment, and BMD measurement site) as possible sources of heterogeneity. All analyses were conducted using Stata 10 (StataCorp, College Station, Texas).

3. Results

The detailed steps of our literature search are shown in Fig. 1. We identified 29 articles after the initial title and abstract evaluation. Several articles lacked data for mortality, therefore could not be included. Another study was excluded as data were only provided for HRs and 95% CI per SD increase in BMD (Appendix Table 1). We finally included 10 studies in the meta-analysis [9–18]. Agreement between reviewers for studies to be included was good (Cohen's unweighted $\kappa = 0.89$).

3.1. Characteristics and quality of the study cohorts

The characteristics of the included prospective cohort studies are summarized in Table 1. The analysis included 46,182 participants from 10 studies with 3991 all-cause deaths, 1479 cardiovascular deaths and 403 stroke deaths. The cohorts were from five different countries (five studies from the United States, two from Sweden, and one each from Brazil, Australia and Finland). Five studies recruited both male and female participants, whereas five studies recruited only women. The age of participants ranged from 45 to 79 years. Study length ranged from 2.8 years to 18.7 years (median 7 years). Seven studies measured BMD values of the total hip or femoral neck by dual-energy X-ray absorptiometry (DXA), two studies measured left hand BMD by radiographic absorptiometry (RA), and one study measured radius and calcaneus BMD using single photon absorptiometry. Four studies reported only all-cause mortality, one only stroke mortality, and five reported combined outcomes. Thus, overall there were eight cohorts available to study the relationship between BMD and all-cause mortality, five cohorts available to study the relationship between BMD and cardiovascular mortality, and four cohorts to study the relationship between BMD and stroke mortality. All the included studies reported the HR or RR with corresponding CIs per SD decrease in BMD. Eight cohorts ascertained all-cause cardiovascular and stroke mortality according to the International Classification of Diseases (ICD) 9 or 10. The overall study quality, evaluated by the STROBE score, averaged 14.2 (range 11–17) on a scale up to 21.

3.2. BMD and risk of all-cause mortality

Detailed information on measurement site, all-cause death events, and HRs and 95% CI per SD decrease in BMD of the eight cohorts included in the meta-analysis are presented in Table 2 (28,516 participants and 3991 events), and the results of the pooled analysis are shown in Fig. 2. In the pooled analysis, lower BMD at all sites was

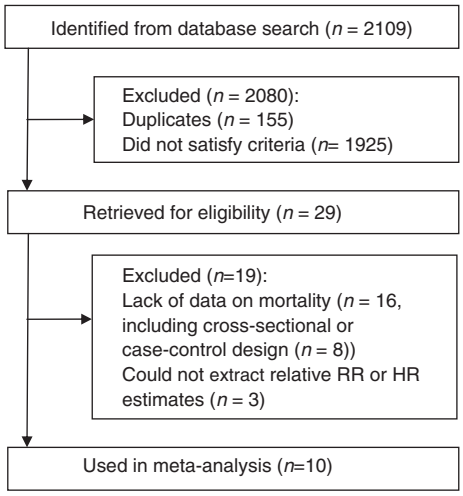

Fig. 1. Flowchart for study selection.