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Authors: Zhenjie Gu, Yang Yuanyuan, Zhang Lingyu, Chen Cong

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Assessment of the risk of incident heart failure in osteoporosis patients: a systematic review and meta-analysis of eligible cohort studies

Zhenjie Gu¹*, Yang Yuanyuan², Zhang Lingyu¹, Chen Cong¹

1. The First Department of Cardiology, Maoming People’s Hospital
2. The Second Department of Respirology, Maoming People’s Hospital

*Corresponding author: Gu Zhenjie, Master, the First Department of Cardiology, Maoming People’s Hospital, No. 101, Weimin Road, Maoming, Guandong Province, China, 525000, +86-668-2922081, Email cubagu@163.com

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Conflict of interest statement: None.
What’s new?

The association between bone health and cardiovascular diseases has been raised in previous studies. However, whether osteoporosis is related to incident heart failure (HF) remains debatable. Data concerning the risk of incident heart failure in osteoporotic patients were systematically reviewed in the present study. We reported a significant increased overall hazard ratio (HR) of incident HF in patients with osteoporosis than in those without (pooled HR=1.17; 95% CI, 1.08-1.26, P<0.001).
**Introduction:** It has been increasingly reported that cardiovascular diseases are related to bone health. But the association between osteoporosis and incident heart failure (HF) is not determined.

**Objective:** We aimed to summarize available evidence to evaluate whether osteoporosis was associated with increased risk of incident HF.

**Patients and methods:** Major databases, including PubMed, Embase, the Cochrane library, Web of Science, and ClinicalTrials, were searched for cohort studies reporting the hazard ratio (HR) for incident HF in osteoporosis patients. The pooled HRs and 95% confidence interval (CI) were estimated by using a random-effects model. Heterogeneity was evaluated by $I^2$ statistics and chi-square test.

**Results:** Three studies consisting of 70,697 people were included, with a mean (SD) age of 62.9 (13.3) years. Osteoporosis was associated with an increased overall risk of incident HF (pooled HR=1.17; 95% CI, 1.08-1.26, $P<0.001$; heterogeneity $I^2=13.28\%$, $P=0.32$). The risk of incident HF was elevated in osteoporotic males (HR=1.30; 95% CI, 1.05-1.62, $P=0.02$; $I^2=71.57\%$, $P=0.03$); however, no significant association was found for females (HR=1.14; 95% CI, 0.94-1.37, $P=0.19$; $I^2=64.66\%$, $P=0.06$). The association between osteoporosis and incident HF risk was positive among individuals of Asian ethnicity (HR=1.18; 95% CI, 1.06-1.30, $P=0.002$; $I^2=52.61\%$, $P=0.15$).

**Conclusions:** Osteoporosis was associated with a modest but significantly increased risk of incident HF. Considering the limited number and quality of available studies, future high-quality data are required to further demonstrate the association between osteoporosis and incident HF.
Key words: Incident heart failure, osteoporosis, meta-analysis.

Introduction

Heart failure (HF) is a clinical syndrome caused by structural and/or functional cardiac abnormality, resulting in pulmonary and/or systemic congestion and insufficient organ perfusion. It usually manifests typical symptoms such as breathlessness, fatigue and lower limb swelling, which may be accompanied by signs such as pulmonary crackles, peripheral edema, jugular vein engorgement or even distension. The diagnosis of HF requires thorough assessment of symptoms, signs, clinical history, blood biomarkers (e.g., B-type natriuretic peptide (BNP), N-terminal pro-BNP (NT-proBNP)), and echocardiographic estimates (e.g., ejection fraction). Its incidence increases with age. It is reported to be the most common cardiovascular reason for hospitalization in people over 60 years of age and carries a poor prognosis. It not only greatly impairs an individual’s life quality and expectancy but also imposes a heavy burden on the health care system.

HF is a heterogeneous disorder in terms of etiology (e.g., coronary artery disease, hypertension, and diabetes). Substantial effort has been made to treat the underlying causes. However, more risk factors are being suggested with the deepening of research. Osteoporosis, characterized by low bone density and increased bone fragility, is also an age-dependent disease with high morbidity, affecting up to 200 million people worldwide. Low bone mass has been reported to be related to cardiovascular diseases. It has been found that osteoporosis and HF share common risk factors, such as advanced age, vitamin D deficiency, renal disease and other comorbidities. HF is a known risk factor for osteoporosis and vice versa. However, most of reported studies discussing the association between osteoporosis and HF are based on
cross-sectional design. That if osteoporosis is related to an increased risk of future HF remains to be answered, which requires longitudinal data. But clinical data to date regarding the relationship between osteoporosis and the risk of incident HF have been scarcely reported. Thus, the purpose of this study is to assess the risk of incident HF in osteoporosis patients through a systematic review of eligible cohort studies.

**Material and method**

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. (Supporting Table 1,2)

Search strategy

Two independent reviewers (CC and ZLY) performed database searches in PubMed, Embase, the Cochrane library, Web of Science, and ClinicalTrials by using the following items: (heart failure OR heart insufficiency OR cardiac insufficiency OR myocardial insufficiency OR myocardial failure OR cardia* failure OR heart decompensation OR cardiac decompensation OR myocardial decompensation) AND (osteoporosis OR osteoporos* OR osteopenia OR bone mineral density OR bone density OR bone densit* OR bone conten* OR bone loss*), with publishing dates to April 16, 2019. There was no language restriction in our searches. And we performed a limited updated search from April 16, 2019 to June 21, 2020. Detailed search strategies in each database are reported in Supporting Table 3 to 7.

Eligible criteria and study selection
Studies were eligible if they met the following criteria: (1) having a longitudinal design; (2) including people with osteoporosis or osteopenia (defined by bone mineral density (BMD) assessment using any validated tool according to a clear standard diagnostic criteria or any documented medical or insurance records); (3) including a control group (with normal BMD, or without osteoporosis); (4) the endpoints were incident HF (defined through diagnosis information from any medical or insurance records or self-report of a physician diagnosis of HF confirmed by standard diagnostic criteria using medical records documenting series of symptoms, physical signs and other supporting clinical findings); and (5) providing the hazard ratio (HR) for incident HF. The primary outcome of our analysis was the risk of incident HF in osteoporosis patients, assessed through HRs for incident HF.

Two authors (GZJ and YYY) developed the lists of studies independently during the selection process. And a third author (CC) was prepared to adjudicate the lists, and discussed with the above two authors to reach a consensus if discrepancies were found. If two studies were reported from the same cohort, the study with bigger sample size was included. The references of included articles were searched to identify additional potentially relevant publications. We also considered conference abstracts in our database searches. We contacted the corresponding authors to acquire the data to evaluate the eligibility of potentially relevant conference abstracts.

Data extraction and quality assessment

Two reviewers (CC and ZLY) independently extracted data from the included studies using a standard form. Disagreements between the two reviewers were solved by a formal discussion to reach a consensus. Data were extracted on: (1) basic characteristics of included studies (first author, publication year, country, race,
number of patients, mean age, percentage of female patients, follow-up period, adjusted covariates); (2) descriptions of exposure measurement (osteoporosis or osteopenia) and endpoint (incident HF); and (3) outcome data (hazard ratio). The quality of prognostic studies was assessed according to the recommendations by Hayden et al. using the following domains: study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and control, and analysis\textsuperscript{11}. Two reviewers (GZJ and YYY) performed the quality assessment of each of the included studies independently. Discrepancies were solved by discussion with a third reviewer (ZLY). The domains would be rated as yes, partly, unsure, or no for its appropriateness, respectively.

Statistical analysis

We performed random-effects meta-analysis using Comprehensive Meta-Analysis (CMA) 2.0 \textsuperscript{12}. In primary analysis, we calculated the pooled HR and 95% confidence interval (CI) from all included studies. We only included the HR adjusted for the highest number of covariates for each study. The same procedure was performed in the post-hoc subgroup analysis. Study heterogeneity was evaluated by using the $I^2$ statistics and chi-square test. A value of over 50\% for the former and a $P$ value $<$0.05 for the latter suggested significant moderate or higher heterogeneity\textsuperscript{13}. Sensitivity analyses were conducted by the two means as follows. First, a fixed-effect model was additionally used to estimate the pooled HR of all included studies in order to compare with random-effects model. Secondly, we estimated the respective HRs by random-effects model in the condition of excluding one study in a time. Publication bias was not performed for the limited number of included studies (less than 10) in the present review. A $P$ value $<$0.05 was considered to be significant.
Ethics statement

This study was approved by the Academic Administration Committee of Maoming People’s Hospital. And informed consent was not required in this study.

Results

Description of included studies

A total 5,451 articles were identified from the search. All the articles were derived from the abovementioned databases, and no other sources of studies or unpublished studies were used. Then, 5,428 articles were excluded after the screening of their titles and abstracts. Twenty-three articles (5 in PubMed, 9 in Web of Science, 9 in Embase) were reviewed. Thirteen duplicated articles were excluded. Of the 10 remaining full-text studies, 7 were further excluded with reasons (mainly because of overlapping patients, case series report and missing HR data for incident HF) (Supporting Table 8), and 3 studies were ultimately included 14-16 (Fig. 1). Among included studies, the cohort study conducted in the USA was prospectively designed 14, while the other two from Taiwan were retrospectively designed 15,16. The main features of the included studies are shown in Table 1.

All participants were recruited from patients with end-stage renal disease (ESRD) in the study of Yu et al 16.

The sample sizes ranged from 1,250 to 57,148, with 70,697 people analyzed in total. The mean (SD) age of all included people was 62.9 (13.3) years. Ninety-eight percent of the people were Asians, and the rest were mostly Caucasians. Only a small amount of black people were included in the study from Fohtung et al in this review. But no
black individuals were included in the final analysis in the study from Fohtung et al. since scant osteoporosis was diagnosed in black participants 14.

More females, accounting for 76.7% of all included people, were included than males. The follow-up period varied from 6.9 to 10.5 years, but one study did not provide relevant data. All studies listed detailed adjusted covariates, mainly consisting of age, sex, smoking, alcohol consumption, comorbidities, and medications. The mean number of adjusted covariates was fourteen.

Osteoporosis and HF were ascertained directly by documented information from health insurance databases in the two studies from Taiwan. In the study from the USA, osteoporosis was identified through measurements of individuals’ BMD according to the World Health Organization classification of osteoporosis using T-scores. And HF was confirmed by an expert panel based on standard diagnostic criteria through careful evaluation of medical records documenting series of symptoms, physical signs and other supporting clinical findings.

Quality assessment of included studies

According to the quality assessment criteria of prognosis studies in the systemic review (Table 2), the study participation was adequate in all 3 included studies. We were unsure about the study attrition in all 3 studies not reporting relevant data about loss to follow-up. We were also unsure about the appropriateness of ascertainment of osteoporosis and HF in the 2 studies from Taiwan since the criteria for diagnosis were not provided. Potential confounders were adequately accounted for in two studies, except for the study from Yu et al rated as partly for this domain. Appropriate statistical analysis was employed in all studies and sufficiently limited the potential for the presentation of invalid results. Taken together, one study was considered to be
of good quality, while the other two were considered to be of moderate quality. The major insufficiencies were derived from the measurements of exposure and outcome in the two retrospective cohorts. These two studies identified osteoporosis and incident HF through documented medical records, in which diagnostic information was missing and inconsistent diagnostic criteria might be used. It possibly resulted into inconsistencies in exposure and outcome measurements and caused heterogeneity among included studies.

Analysis of included studies

We first evaluated the estimated HRs for female and male patients and the entire cohort in the study from Fohtung et al since they only provided HRs based on bone sites and gender.

As reported in Fig. 2, osteoporosis patients had an increased overall risk of incident HF using a random-effects model (pooled HR=1.17; 95% CI, 1.08-1.26, \( P<0.001 \)), as was the case with the fixed-effect model (pooled HR=1.16; 95% CI, 1.09-1.23, \( P<0.001 \)). There was modest heterogeneity among included studies (\( I^2=13.28\% \), \( P=0.32 \)). Due to the relative low number of included studies (less than 10), the evaluations of publication bias were not performed. Sensitivity analyses were conducted to test the influence of each included study on the overall effect estimate by excluding one study at a time. There were consistent HRs observed favoring osteoporosis in increasing the risk of incident HF in sensitivity analyses (see Supporting Table 9).

Post-hoc subgroup analyses
Gender and race have been demonstrated to be important factors in HF development, meaning that they could be clinically-associated effect modifiers in this condition. Subgroup analysis regarding gender, as shown in Fig. 3, indicated that osteoporosis was positively associated with increased risk of incident HF for males (HR=1.30; 95% CI, 1.05-1.62, P=0.02; I²=71.57%, P=0.03). There was elevated risk of incident HF observed in osteoporotic females, though such association was without statistical significance (HR=1.14; 95% CI, 0.94-1.37, P=0.19; I²=64.66%, P=0.06).

Since the large majority of included people were Asians, we performed subgroup analysis by race. It was found that Asian patients with osteoporosis were at increased risk of incident HF (2 studies, HR=1.18; 95% CI, 1.06-1.30, P=0.002; I²=52.61%, P=0.15) (Fig. 4). However, we failed to assess the risk for non-Asian patients (mostly Caucasians) because only one study was available in the present analysis.

Discussion

In the present meta-analysis, including 3 cohort studies with a total of 70,697 participants, we observed a 17% increase in the overall risk of incident HF in people (mean (SD) age of 62.9 (13.3) years) with osteoporosis compared with those without. In post-hoc analyses by gender, the risk of incident HF increased by 30% in osteoporotic males. A slightly raised risk of incident HF was also seen in osteoporotic females (HR =1.14); however, it lacked statistical significance. Although the outstanding previous study by Veronese, N. et al had raised the association between low BMD and future cardiovascular diseases, but they did not account for HF patients.
in their analysis. Our study specifically synthesized available data to date to demonstrate that osteoporosis could be a risk factor for incident HF, which summarized the current knowledge in this field. However, this observation should be interpreted cautiously, since people at the age of 62.9 (13.3) years mostly have other comorbidities including a variety of causes and risk factors of HF (e.g. coronary artery disease (CAD), hypertension, valvular heart disease, cardiomyopathy, diabetes mellitus, obesity and so on). These covariates could be confounders for the estimation of the association between osteoporosis and incident HF. In the present review, there were some important covariates not considered in adjustment among included studies. For example, CAD, an established cause for HF development, was not included in covariates adjustment in the study from Yu et al. Adequate adjustment for causes and risk factors of HF should be emphasized in the future studies. On the other hand, low BMD itself is found to be related to other comorbidities like cardiovascular calcification, chronic obstructive pulmonary disease, which raises a potential that people with osteoporosis themselves may have more pathological conditions, thus predispose to HF development.

We suggested that osteoporosis was independently associated with an increased risk of incident HF. However, the underlying mechanisms still remain unclear. One potential explanation could be the activation of renin-angiotensin-aldosterone (RAAS) in these two conditions. Accumulating data have suggested that RAAS might contribute to osteoporosis development and progression. For instance, in vitro studies found that angiotensin II could activate osteoclasts, a key mediator in osteoporosis. Animal studies using mice or rats showed that renin and angiotensin accelerated BMD decrease and that blockage of them could improve bone quality. Furthermore, a significant increase of serum angiotensin-converting enzyme (ACE)
activity had been revealed in osteoporotic women. Long-term intervention with RAAS inhibitors reduced osteoporotic fracture in postmenopausal women and protected against bone loss in hypertensive black men. A cohort from Taiwan also demonstrated that the long-term usage of RAAS inhibitors lowered the risk of osteoporotic fracture in a hypertensive population. All these data consistently indicated that the RAAS might be involved in osteoporosis. RAAS activation had been well demonstrated to play an important part in various conditions, such as hypertension, endothelial dysfunction, myocardial remodeling, atherosclerosis, and inflammation, which lead to HF development. Whether osteoporosis could contribute to HF development via RAAS activation warrants further future investigations. Another potential mediator could be osteoprotegerin (OPG). OPG was initially revealed to be a key regulatory protein in bone metabolism and was then found to be expressed in heart and vasculature. Its expression was shown to be increased with age. In animal studies, the OPG-knockout mice not only developed osteoporosis at an early age but also manifested increased apoptotic myocardial cells, cardiac eccentric hypertrophy, attenuated contractile function and artery calcification. In clinical studies, serum OPG was demonstrated to be positively associated with BMD, and its expression was reported to be increased in HF patients. Thus, OPG seemed to be a protective protein to HF and osteoporosis. The dysregulation of OPG might be involved in osteoporosis-associated incident HF. However, the data were not consistent to date with regard to the expression of serum OPG in osteoporotic patients, especially for females, for serum OPG expression might be influenced by estrogen, diabetes mellitus, chronic renal disease or other metabolic disorders. Future research with large sample sizes will be necessary to elucidate the mechanism underlying the regulation of OPG expression in these two conditions.
Gender differences in HF development are well demonstrated previously. It appeared that osteoporotic males might have a higher risk of incident HF compared with females in our analysis, although we failed to prove it with statistical approach. The discrepancy might be affected by the gender difference in overall lifetime risk of HF, which was shown to be greater in males and probably related to heavier burden and earlier onset of CAD in males versus females. In addition, risk factors such as smoking, alcohol consumption, inappropriate lifestyle, are more common in males. Another explanation might be that osteoporosis in men was often secondary and associated with poor health status or with a greater number of risk factors, which might also have a negative impact on the cardiovascular system. However, that if males with osteoporosis carry a higher risk of incident HF than females still remains further discussed with more well-designed studies.

Our analysis had several limitations. First, the number of included studies was relatively small, and the overall quality of included studies was moderate. Second, the sample sizes of included studies differed tremendously, and the pooled HR was mainly driven by 2 retrospective cohorts from Taiwan. Third, a large majority of included people were Asians in our analysis, making the observation in our analysis possibly not fit for other races. Fourth, our present analysis was unable to further discuss the impact of covariates such as age, comorbidity, and medication on the relationship between osteoporosis and incident HF, which seemed to be helpful in further understanding the underlying interactions between them. Accordingly, the results presented in our analysis should be interpreted with caution.

**Conclusion**
In conclusion, the present meta-analysis showed that osteoporosis was associated with a modestly higher risk of incident HF. Given the limited quantity and quality of current available data, more future studies with good quality are required to further demonstrate the association between osteoporosis or low BMD and the risk of incident HF, to evaluate whether proper management of osteoporosis could reduce HF incidence, and to elucidate the underlying mechanism of the interaction between these two disorders.

**Contribution statement**

Gu ZJ conceived the concept of the study. Gu ZJ and Yang YY contributed to the design of the research. All authors were involved in data collection. Gu ZJ and Yang YY analyzed the data. All authors edited and approved the final version of the manuscript.

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**Disclosure**

Gu Zhenjie, Yang Yuanyuan, Zhang Lingyu and Chen Cong declare that they have no conflicts of interest.

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5451 records identified from search strategy (Pubmed=568; Web of Science=1465; Embase=3107; Cochrane=302; ClinicalTrials=9)

Records from each database were screened individually (title and abstract)

23 records reviewed (Pubmed=5; Web of Science=9; Embase=9; Cochrane=0; ClinicalTrials=0)

Records excluded due to:
1. Non-cohort study
2. Review
3. Editorial or letters
4. Other diseases
5. Other aspects

13 duplicate articles excluded

10 full articles reviewed

Articles excluded due to:
1. Overlapping patients (2)
2. Case series report (1)
3. Hazard ratio or event statistic for heart failure not provided (1)
4. No data concerning heart failure (1)
5. BMD as the only exposure without further classification into osteoporosis or osteopenia (1)
6. Fragility fracture as the exposure (1)

3 articles included

Additional records identified through other sources (n=0)

Fig. 1. PRISMA Flow chart for study selection.
Fig. 2. Forest plot of the overall risk of incident heart failure with osteoporosis. Control defined as normal bone mineral density, or without osteoporosis.

| Study name  | Hazard ratio | Lower limit | Upper limit | Z-Value | p-Value |
|-------------|--------------|-------------|-------------|---------|---------|
| Chia 2017   | 1.13         | 1.06        | 1.21        | 3.62    | <0.001  |
| Yu 2014     | 1.26         | 1.11        | 1.44        | 3.45    | <0.001  |
| Fohuang 2017| 1.41         | 0.59        | 3.38        | 0.77    | 0.44    |
|             | 1.17         | 1.08        | 1.26        | 4.04    | <0.001  |

Control  
Osteoporosis

Fig. 3. Forest plot of the gender-specific risk of incident heart failure with osteoporosis. Control defined as normal bone mineral density, or without osteoporosis.

| Group by   | Study name | Subgroup within study | Hazard ratio | Lower limit | Upper limit | Z-Value | p-Value |
|------------|------------|-----------------------|--------------|-------------|-------------|---------|---------|
| Female     | Chia 2017  | Female                | 1.11         | 1.03        | 1.20        | 2.40    | 0.017   |
| Female     | Yu 2014    | Female                | 1.31         | 1.33        | 1.32        | 3.57    | <0.001  |
| Female     | Fohuang 2017| Female              | 1.33         | 1.33        | 1.32        | 3.57    | <0.001  |
| Male       | Fohuang 2017| Males                | 2.24         | 1.43        | 3.04        | 2.31    | <0.001  |
| Male       | Chia 2017  | Males                | 1.21         | 1.08        | 1.40        | 2.40    | 0.039   |
| Male       | Yu 2014    | Males                | 1.31         | 1.35        | 1.34        | 3.57    | <0.001  |
| Male       | Fohuang 2017| Males              | 1.33         | 1.34        | 1.33        | 3.57    | <0.001  |

Control  
Osteoporosis
Fig. 4. Forest plot of the risk of incident heart failure with osteoporosis in Asians. Control defined as normal bone mineral density, or without osteoporosis.
Table 1. Characteristics of the included studies

| Source (Country of study) | Setting | Number of participants | Race (%) | Female (%) | Follow-up (years) | Mean age (years) | Number of adjusted covariates | Match | Exposure measure | HF ascertainment |
|---------------------------|---------|------------------------|----------|------------|------------------|-----------------|-----------------------------|-------|-----------------|-----------------|
| Fohtung et al. 2017 (USA) | Community | 1,250; 1,014 (Nonblack) | Nonblack (81), black (19) | 59; 58.1 (among nonblack) | 10.5 | 76.7 (5) | 16* | No | BMD (DXA at total hip or femoral neck), classified into osteoporosis, osteopenia and normal BMD | Medical record (adjudication by expert panel) |
| Chiu et al. 2017 (Taiwan) | Nationwide population | 57,148 | Asian (100) | 78.3 | Osteoporosis: 7.07 (3.49); Control: 6.90 (3.50) | Osteoporosis: 63.9 (12.8); Control: 63.1 (13.1) | 19** | Yes | Osteoporosis (Health information from the National Health Insurance Research Database) | Health information from the National Health Insurance Research Database |
| Yu et al. 2014 (Taiwan) | Nationwide population | 12,535 | Asian (100) | 71.0 | NA | Osteoporosis: 59.8 (13.5); Control: 58.5 (14.2) | 8*** | Yes | Osteoporosis (Health information from the National Health Insurance Research Database) | Health information from the National Health Insurance Research Database |

*Age, body mass index, systolic blood pressure, antihypertensive medication, diabetes mellitus, smoking, alcohol consumption, physical activity, estrogen replacement (women), prevalent coronary heart disease, prevalent stroke or transient ischemic attack, prevalent peripheral arterial disease, prevalent atrial fibrillation, estimated glomerular filtration rate, forced expiratory volume in 1 second, and C-reactive protein.

**Age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, CKD, stroke, COPD, asthma, alcohol-related illness, CAD, and liver diseases, and medications including prednisolone, estrogen, statin, ACEI, ARB, spironolactone, and thiazides.

***Age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, mental disorders, hepatitis B infection, and hepatitis C infection.

Abbreviations: NA, not available; RA, rheumatoid arthritis; BMD, bone mineral density; DXA, Dual-energy X-ray absorptiometry; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker.
Table 2. Quality assessment of included studies

| Study             | Study participation* | Study attrition** | Osteoporosis or osteopenia ascertainment *** | Outcome defined and described appropriately# | Control of confounding ## | Analysis described appropriately ### |
|-------------------|----------------------|-------------------|---------------------------------------------|---------------------------------------------|---------------------------|-----------------------------------|
| Chiu et al. 2017  | Yes                  | Unsure            | Unsure                                      | Yes                                        | Yes                       | Yes                               |
| Fohtung et al. 2017 | Yes                 | Unsure            | Yes                                         | Yes                                        | Yes                       | Yes                               |
| Yu et al. 2014    | Yes                  | Unsure            | Unsure                                      | Partly                                      | Yes                       | Yes                               |

*The study sample represents the population of interest on key characteristics to sufficiently limit the potential bias.

**Loss to follow-up (from sample to study population) is not associated with key characteristics (the study data adequately represent the sample), sufficiently limiting potential bias.

***The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias.

#The outcome of interest is adequately measured in study participants to sufficiently limit potential bias.

##Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest.

###The statistical analysis is appropriate for the design of the study, limiting potential for presentation of valid results.

Each of the bias can be judged as yes, partly, no, and unsure.