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Metabolic syndrome and the risk of bone fractures: A Meta-analysis of prospective cohort studies

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ABSTRACT

Increasing evidence has suggested an association between metabolic syndrome (MetS) and bone fractures. However, because of controversial results it is still not clear whether this effect is protective or detrimental. Therefore, we conducted a meta-analysis of prospective studies to assess the association between them. Pertinent studies were identified by searching PubMed and EMBASE databases until the end of July 2015. Summary relative risks (RRs) and 95% confidence intervals (CIs) for associations between MetS and fracture risk were estimated with random effects models. Our meta-analysis included five prospective studies. The summarized RRs of any type of fractures for MetS were 0.76 (95%CI: 0.59–0.97, $P = 0.026$) with moderate heterogeneity ($I^2 = 63.80\%$, $P = 0.064$). Notably, subgroup analyses by gender showed that significant inverse associations were observed only in men (summarized RR = 0.66; 95%CI = 0.51–0.86, $P = 0.002$; $I^2 = 27.90\%$, $P = 0.235$; n = 5) but not in women (summarized RR = 0.96, 95%CI: 0.60–1.54, $P = 0.866$; $I^2 = 83.40\%$, $P = 0.002$; n = 3). However, the difference of the pooled RRs from the two subgroups did not reach statistical significance with a test of interaction ($p = 0.179$ for the interaction test). When pooling the RRs of non-vertebral fractures, significant inverse associations were similarly observed in men (RR = 0.72, 95%CI: 0.52–0.99, $P = 0.048$) but not in women (RR = 0.99, 95%CI: 0.60–1.64, $P = 0.969$). There was no evidence of publication bias. Our findings demonstrated that MetS was significantly associated with a lower fracture risk. There might be gender differences in the relationship of MetS with fractures, but further confirmation is needed.

1. Introduction

Metabolic syndrome (MetS) is characterized by the presence of a variety of pathophysiological disorders including central obesity, insulin resistance, high blood pressure and dyslipidemia [1]. With industrialization and aging,MetS has become an epidemic worldwide, which is estimated to affect 20–30% of adults in the United States and European countries [2]. The association between MetS and increased cardiovascular morbidity and mortality has been extensively documented [3]. Data from epidemiologic studies have demonstrated that MetS and osteoporosis often coexisted among aging population [4], which promoted the exploration of the relationship between them and underlying mechanisms.

The individual components of MetS have been shown to have opposite effects on bone mineral density (BMD) and the risk of osteoporotic fractures. Obesity may exert a protective effect on bone due to higher 17β-estradiol levels and higher mechanical load [5–6]. Type 2 diabetes could lead to a higher BMD [7] but an increased risk of fractures [8]. High triglycerides and low high-density lipoprotein (HDL) were shown to be positively associated with BMD and risk of fractures in some but not all studies [4,9–11]. In terms of MetS as a whole, its association with osteoporotic fractures was not definitely documented. Two meta-analyses on this topic have been published but the results were inconsistent. The analysis by Sun. K et al. [12]did not find a statistically significant association between MetS and fracture risk while the analysis by Esposito K et al. [13]showed an association of borderline significance (RR:0.85, 95%CI:0.71–1.01, $P = 0.056$). Most of the studies included in these two meta-analyses were cross- sectional,which may result in high potentiality of inaccurate measurement of outcome and reverse causation and thus increase the likelihood of wrongly estimating the associations. The subgroup analyses of the two studies by pooling the results of cohort studies similarly yielded negative results (for Sun. K et al., RR: 0.88, 95%CI:0.37–2.12; for Esposito K et al., RR:0.82,95%CI:0.50–1.32). Recently, two prospective studies on the association of MetS with fracture risk were published [14–15]. With accumulating evidence, we conduct a meta-analysis of prospective cohort studies to evaluate the association between Mets and risk of fractures more precisely.

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2. Methods

2.1. Search strategy

The present meta-analysis was reported in accordance with the proposed MOOSE (Meta-Analysis of Observational Studies in Epidemiology) guidelines [16]. A comprehensive search was conducted by using PubMed and Embase database without restrictions through July 2015 for relevant studies assessing the association between MetS and fractures. The following search terms were used: 1) metabolic syndrome (insulin resistance syndrome or syndrome X); 2) fracture, bone, BMD, osteoporosis, osteopenia, and metabolic bone diseases; 3) cohort studies, prospective studies, and follow-up studies. In addition, the reference lists of retrieved papers and recent reviews were reviewed.

2.2. Study selection

Screening of titles or abstracts was first performed. Then a second screening was based on full-text review. Studies were considered eligible if they met the following criteria: 1) the study design was a prospective cohort study; 2) metabolic syndrome was defined and measured at baseline; 3) the outcome of interest was fracture of any type; and 4) relative risk (RR) or hazard ratio (HR) and its corresponding 95% confidence interval (CI) (or data to calculate them) were reported.

2.3. Data extraction

The key exposure variable in this study was the presence or absence of MetS at baseline. Outcomes of interest were fractures at any sites. Data were extracted using a standardized data-collection form. The following data were abstracted: the first author's name; the publication year; the country of study origin; the number, mean age or age range, and sex of the participants; the diagnostic criteria of MetS, and the type of fracutres, based on the information as provided in the primary studies; the study design details, including starting year of study, study duration; the adjusted covariates when calculating RR or HR, losses of follow-up. If a study did not clearly mention any above key points, we considered that it had been not performed. Two of us (Yang and Lv) independently reviewed the selected studies and extracted data. Discrepancies were resolved by discussion.

2.4. Statistical analyses

The study-specific maximally adjusted RRs or HRs were pooled to examine the association between MetS and risk of fractures. HRs were directly considered as RRs. Heterogeneity across studies was examined by using the Q and I^2 statistic (significance level at $P < 0.10$) [17]. The combined risk estimates were computed using either fixed-effects models or random-effects models with the presence of heterogeneity [18]. Because clinical characteristics were not consistent between studies, we further conducted a subgroup analysis to explore the potential effect modification of these variables on outcomes. Furthermore, we compared the pooled RR estimates derived from the two separate subgroups (men *vs* women) with a test of interaction [19]. We also investigated the influence of a single study on the overall risk estimate by omitting 1 study in each turn. Potential publication bias was assessed by Egger's test (linear regression method) and Begg's test (rank correlation method) to evaluate publication bias [20]. All analyses were performed using STATA version 12.0 (Stata Corp LP, College Station, Texas). A P value <0.05 was considered statistically significant, except where otherwise specified.

3. Results

3.1. Literature search

Of the 1991 titles identified from the two databases, 1981 were excluded after we reviewed titles and abstracts. After reviewing the full text of the remaining 10 studies, we included 5 studies[4] [14–15] [21–22] in the final analysis. The main reasons for exclusion in the final review were as follows: not prospective studies [23–25], the exposure or endpoint was not relevant [26–27]. Fig. 1 showed a flow chart of study selection.

Study characteristics.

The characteristics of 5 studies were presented in Table 1. These studies were published between 2006 and 2015. These studies were conducted in USA [4], Norway [21], France [22], Netherlands [15] and Korea [14] respectively. Most of the studies were population-based except the study by Lee SH et al. [14]. The length of the follow-up period ranged from 2 [4] to 10 y [22]. The sample size ranged from 762 to 27,159 adults. Three studies presented results by gender [4] [15] [21] and other two studies included only male participants [14] [22]. Mets was diagnosed according to NCEP-ATP III (National Cholesterol Education Program's Adult Treatment Panel III) or IDF (International Diabetes Fundation) criteria. Two studies[14 22] did not specify the type of fracture and other two studies [4 21]only had non-vertebral fracture as the study endpoint. The exposure and outcome assessments were mainly from medical record and hospital database. The adjustments were not identical among the included studies. All studies adjusted for a wide range of risk factors for fractures, including age, body mass index (BMI), exercise, and smoking et al. Except the study by Ahmed et al., other four studies presented the results with BMI adjustment both in men and women.

We adopted Newcastle-Ottawa Scale (NOS) [28] for quality assessment. A "YES" was awarded for each included item listed in the top of Table 2. As shown in Table 2, the full score was 9 and all studies scored 8 or higher, indicating a relatively high quality of the included studies.

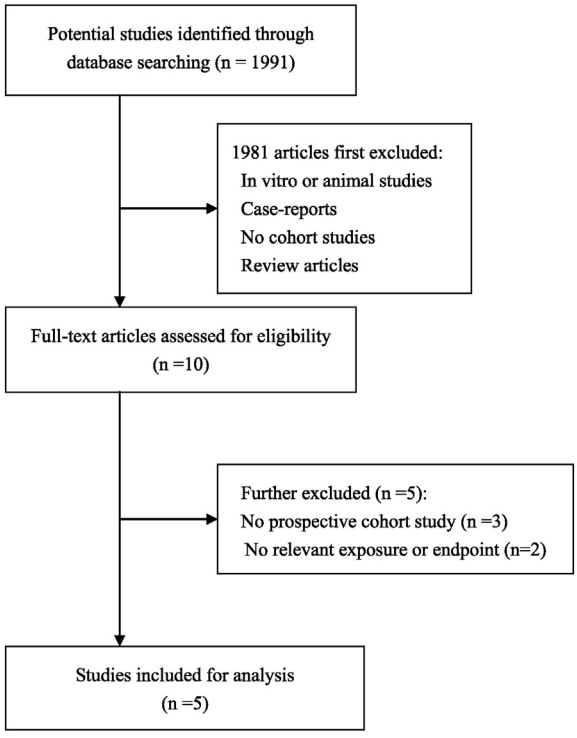

Fig. 1. Flow chart of study selection illustrating literature search for cohort studies.