Original Article
Statin use and risk of fracture: a meta-analysis

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Abstract: This meta-analysis investigates the associations of statins use and fracture risk. Two reviewers independently searched six databases including PubMed, Cochrane Library, Ovid, Embase, China National Knowledge Infrastructure (CNKI) and Wanfang databases. Studies retrieved from database searches were screened using our stringent inclusion and exclusion criteria. A sum of 17 studies, published between 2000 and 2014, were included in this meta-analysis. The results of this meta-analysis suggested that statins use was associated with a decreased risk of fracture (OR=0.80; 95% CI, 0.73-0.88; $P < 0.00001$). In the subgroup analysis by study design, statins was significantly associated with a decreased risk of fracture in both case-control studies (OR=0.67; 95% CI, 0.55-0.87; $P < 0.0001$) and cohort studies (OR=0.86; 95% CI, 0.77-0.97; P=0.02). In the female subgroup analysis, statins user showed decreased fracture risk (OR=0.76; 95% CI, 0.63-0.92; P=0.005). In the subgroup analysis by duration of follow-up, studies with both long and short duration of follow-up showed decreased risk of fracture (OR=0.67; 95% CI, 0.54-0.82; P=0.001 and OR=0.85; 95% CI, 0.74-0.96; P=0.01). Studies with large sample size and small sample size showed decreased risk of fracture (OR=0.85; 95% CI, 0.77-0.94; P=0.002 and OR=0.65; 95% CI, 0.54-0.78; $P < 0.0001$). In conclusion, this meta-analysis suggested a significant association between statins use and decreased fracture risk.

Keywords: Statins, fracture, meta-analysis

Introduction

Osteoporosis, characterized by reduced bone strength and a raised risk for low-trauma fractures, increases dramatically with age [1]. About 40% of women in developed countries will experience an osteoporosis-related fracture in the course of their lifetime, with men experiencing approximately one-third to one-half the risk of women [2]. Osteoporosis is also a major social problem due to increasing financial burden. According to the 2003-2006 survey by the National Ministry of Health in China [3], 69.4 million people over the age of 50 years in China suffer from osteoporosis (15.3 million men and 54.1 million women) and 213.9 million people in that age group have low bone mass (100.4 million men and 113.5 million women).

Statins reduce cholesterol biosynthesis in the liver by inhibiting

3-hydroxy-3-methylglutaryl-coenzyme-A reductase (HMGCR), the rate-limiting enzyme in the mevalonate pathway. Gotoh et al. found that

fluvastatin increases bone mineral density in postmenopausal women [4]. Mandal et al. found that a unique function of statins, which foster enhanced expression of mutant p53R280K to prevent breast cancer cell metastasis to bone [5]. Qi and colleagues showed that both simvastatin and the mesenchymal stem cell sheet contributed to the formation of new bone and that the tibia fracture was completely healed by transplantation of the mesenchymal stem cell sheet with locally applied simvastatin [6].

Recently, many studies reported the significant association between statins use and fracture risk [7-23]. However, the results were inconclusive. Thus, we did a meta-analysis to assess the association between statins use and fracture risk.

Methods

Publication search

A literature research was conducted using PubMed, Cochrane Library, Ovid, Embase,

Table 1. Characteristics of the included studies

First author	Year	Study design	Mean age	Female (%)	Follow-up years	Sample size	Adjusted for
Chan	2000	Case-control	77	100	2	3675	Sex, age, health maintenance organization, chronic disease score, number of hospital admissions in previous year, use of antipsychototics, hypnotics, antidepressants, thiazide diuretics, hypoglycemics, systemic steroids, other LLDs
Meier	2000	Case-control	70	75	3.3	27319	Sex, age, date, general practice, years in database, smoking, BMI, oral or inhaled corticosteroids, HRT, number of physician visits before the fracture date
Wang	2000	Case-control	82	83	NA	6110	Sex, age, race, health insurance, heart disease, heart failure, hypertension, diabetes, cancer, Charlson comorbidity score, healthcare utilization (number of medications, days hospitalized, days in nursing home, number of physician visits), use of HRT , oral corticosteroids, thiazides, psychoactive medication, other LLDs
van Staa	2001	Case-control	70	76	NA	163760	Sex, age, general practice, smoking, BMI, diabetes, rheumatoid arthritis, hyperthyroidism, congestive heart failure, seizures, anemia, dementia, depression, psychotic disorder, cerebrovascular accident, COPD, use of anticonvulsants, Non-steroidal anti-inflammatory drugs, methotrexate, HRT , thiazides, anxiolytics/hypnotics, antipsychotics, antidepressants, anti-Parkinson drugs, systemic and inhaled corticosteroids, bronchodilators, other LLDs
Pasco	2002	Case-control	70	100	NA	1375	Sex, age, body weight, BMD, alcohol use, smoking, physical activity, use of HRT, glucocorticoids, calcium or vitamin D supplements
Ray	2002	Cohort	62	66	1.9	34584	Demographics, calendar year, reason for Medicaid enrollment, use of oral corticosteroids, HRT , thiazides, hypnotics, anxiolytics, skeletal muscle relaxants, antidepressants, anticonvulsants, anti-Parkinson drugs, hospitalization or emergency room visit 365 before the cohort entry
LaCroix	2003	Cohort	66	100	3.9	93934	Sex, age, race, history of fracture, coronary heart disease, smoking, coffee, time spent walking, physical function, alcohol, BMI, use of thiazides, alendronate, corticosteroid, sedative and hypnotics, HRT, dietary supplements (including calcium), other LLDs
Rejnmark	2004	Case-control	78	70	NA	39934	Sex, age, alcoholism, cerebrovascular diseases, diabetes, atherosclerotic diseases, use of thiazides, loop diuretics, other LLDs, bisphosphonates, raloxifene, nitrates, β-blockers, systemic and topic corticosteroids, HRT
Schoofs	2004	Cohort	64	57	6.5	3469	Age, sex, length of available pharmacy data, diabetes, BMI, 5-year Framingham cardiovascular disease risk score, prevalent vertebral fracture, baseline lumbar spine BMD, lower limb disability, smoking, age at menopause, thyroid disease, cholesterol level, Mini Mental State Evaluation score, use of thiazides, HRT
Bauer 1	2004	Cohort	66	100	3.6	6459	Sex, age, BMI, physical activity, smoking, health status, use of HRT or bisphosphonates, allocation to alendronate or placebo
Bauer 2	2004	Cohort	66	100	5.3	4878	Age, BMI, physical disability, smoking, health status, use of HRT
Bauer 3	2004	Cohort	66	100	4.5	2763	Sex, age, BMI, physical activity, smoking, health status, use of HRT or bisphosphonates
Bauer 4	2004	Cohort	75	100	4	8422	Sex, age, BMI, physical activity, smoking, health status, use of HRT or bisphosphonates, allocation to estrogen/progestin or placebo
Scranton	2005	Cohort	65	5	2.5	91052	Sex, race, age, BMI, Charlson comorbidity score, osteoporosis, calcium or bisphosphonates, benzodiazepines, barbiturates, muscle relaxants, antidepressants, antipsychotics, prednisone, anti-Parkinson drugs, anticonvulsants
Rejnmark	2006	Case-control	43	52	NA	498617	Sex, age, Charlson comorbidity index, days in hospital in previous year, previous fractures, diuretics, β-blocker, calcium channel blocker, ace inhibitor, antihypertensives, estrogens, bisphosphonates, raloxifene, antiepileptic drugs, anxiolytics, sedatives, neuroleptics, antidepressants, corticosteroids, thyroid hormones, number of contacts to physician, employed, income, living alone, other LLD
Smeeth	2008	Cohort	63	50	4.3	729529	Sex, age, date, general practice, observation time, BMI, socioeconomic status, consultation rate, prescribing rate, smoking status, drinking habits, diabetes, coronary heart disease, cerebrovascular disease, peripheral vascular disease, other atheoma, other circulatory disease, dementia, cancer atrial fibrillation, heart failure, hepatic disease, renal disease, thyroid disease, hyperlipidemia, hypertension, HRT, antipsychotics, antidepressants, steroids, fibrates, nitrates, cytochrome inhibitors, aspirin, β-blockers, calcium channel blockers, potassium channel activators, diuretics, positive inotropes, anticoagulants, antihypertensives, other cardiovascular drugs
Bakhireva	2010	Case-control	72	100	NA	3608	Sex, age, duration of health plan coverage, number of outpatient visits and prescription fills, ethnicity, Charlson comorbidity index, corticosteroid, bisphosphonate, thiazide diuretic, calcitonin, methotrexate, antiepileptic drug, HRT

Helin-Salmivaara	2012	Cohort	62	100	5	102839	Age, coronary heart disease, rheumatoid arthritis, use of antidiabetic drugs, and use of hormone replacement therapy, the use of diuretics, beta blockers, calcium channel blockers, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers
Peña	2014	Cohort	66	38	1.9	17802	Age, sex, blood pressure of at least 140/90 mmHg or use of antihypertensive medications, randomized treatment assignment, current tobacco use, body mass index, exercise, race, alcohol use, baseline hemoglobin A1c level in quartiles, and history of previous fracture
Ward 1	2014	Cohort	56	46	4	13934	Age, gender, Charlson Comorbidity Index, osteoarthritis during baseline, musculoskeletal injury during baseline, obesity, illicit drug use, tobacco use and alcohol abuse/dependence, number of outpatient medical encounters and inpatient admissions during the baseline period, and use of 14 classes of medications
Ward 2	2014	Cohort	56	100	4	23062	Age, gender, statin use, all comorbid conditions as in the Methods section, total Charlson comorbidity score, presence of osteoarthritis/arthropathy during baseline, presence of musculoskeletal injury during baseline, osteoporosis, obesity, smoking, alcohol use, illicit drug use, number of all admissions in the baseline period, number of all outpatient visits in the baseline period, and use of different classes of medications
Ward 3	2014	Cohort	56	0	4	21411	Age, gender, statin use, all comorbid conditions as in the Methods section, total Charlson comorbidity score, presence of osteoarthritis/arthropathy during baseline, presence of musculoskeletal injury during baseline, osteoporosis, obesity, smoking, alcohol use, illicit drug use, number of all admissions in the baseline period, number of all outpatient visits in the baseline period, and use of different classes of medications

BMI, body mass index; HRT, hormone replacement therapy; LLD, lipid lowering drug; NA, not available.
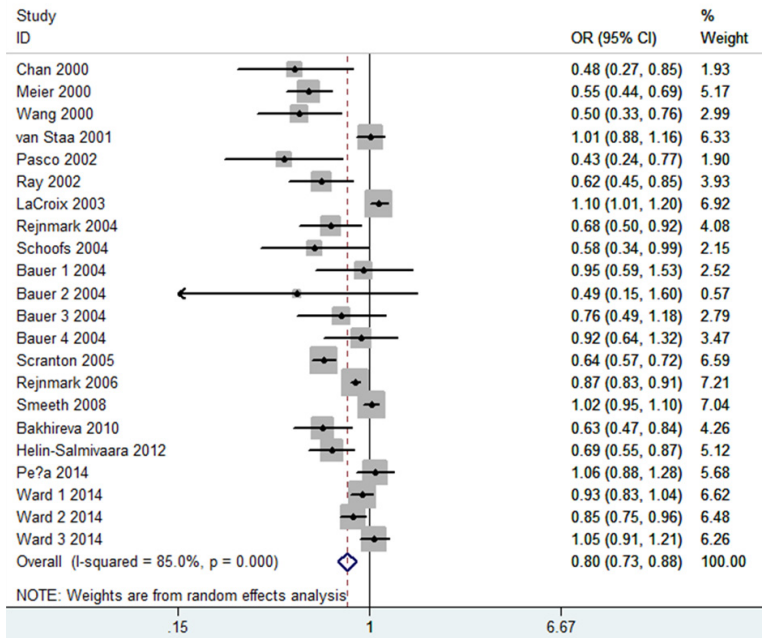
Figure 1. Meta-analysis for the association between statins use and decreased fracture risk.

Wanfang and China National Knowledge Infrastructure (CNKI) databases, to identify studies published prior to October 2014. Relevant studies were identified using the terms: "statins or statin" and "fracture". The search was confined to humans. A manual search of references of the original articles related with this topic was used to identify additional studies. If the data or data subsets were published in more than one paper, only the paper with the largest sample size was enrolled.

Inclusion and exclusion criteria

Studies were selected for meta-analysis if they met the inclusion criteria as follows: (1) case-control study design; (2) studies that investigated the association between statins use and fracture risk; (3) study subjects were fracture patients confirmed by X ray. The exclusion criteria were: (1) reviews and summaries; (2) repetitive publications; (3) no raw data of the association between statins use and fracture risk.

Data extraction

Data from published studies were extracted. For each study, we collected the following information: first author, year of publication, design, age, gender, follow-up duration, numbers of cases and controls, adjustment.

Statistical analysis

Pooled odds risk (OR) and 95% confidence intervals (CI) were calculated with the usage of fixed-effects or random-effects model. Z test was employed to detect the significance of overall effect size, and forest plots were conducted to display values of OR at 95% CI between case and control groups. Heterogeneity of the combined studies was assessed with Cochran's Q-statistic test and I^2 test. The *P* value of Cochran's Q-statistic of below 0.05, was considered statistically significant heterogeneity. The I^2 test provides a measure of the degree of heterogeneity in the results. Typically, values of 0~25% are considered to represent no heterogeneity, 25~50% to modest heterogeneity, 50~75% to large heterogeneity and 75~100% to extreme heterogeneity. A random effects model was applied if there was heterogeneity ($P < 0.05$ or $I^2 > 50\%$), otherwise, a fixed effects model was employed. Sensitivity analysis was conducted by omitting individual studies sequentially to assess stability of the results. The Egger's test and funnel plots were used to identify publication bias.

Results

Study characteristics

Based on the inclusion criteria, a sum of 17 papers, published between 2000 and 2014, were included in this meta-analysis. We noticed that 2 papers reported more than one studies and each group was considered separately. Therefore, 22 studies including 1898536 subjects were included in this meta-analysis. Of the 22 studies, 8 studies were case-control studies; the other 14 studies were designed as cohort studies. Characteristics in this meta-analysis are summarized in **Table 1**.

Results of meta-analysis

Heterogeneity test revealed that significant heterogeneity existed, and thus a random-effects model was used ($P < 0.05$). The results of this

Table 2. Results of this meta-analysis

	Test of association			Heterogeneity		
	OR (95% CI)	Z	P Value	χ^2	P Value	I^2 (%)
All studies	0.80 (0.73-0.88)	4.68	< 0.00001	140.16	< 0.00001	85
Design						
Cohort	0.86 (0.77-0.97)	2.43	0.02	85.58	< 0.00001	85
Case-control	0.67 (0.56-0.81)	4.12	< 0.0001	42.88	< 0.00001	84
Gender						
Female	0.76 (0.63-0.92)	2.81	0.005	43.98	< 0.00001	80
Follow-up						
< 5 years	0.85 (0.74-0.96)	2.56	0.01	101.24	< 0.00001	88
> 5 years	0.67 (0.54-0.82)	3.88	0.0001	0.61	0.74	0
Sample size						
< 10000	0.85 (0.77-0.94)	3.08	0.002	111.78	< 0.00001	89
> 10000	0.65 (0.54-0.78)	4.54	< 0.00001	11.39	0.18	30
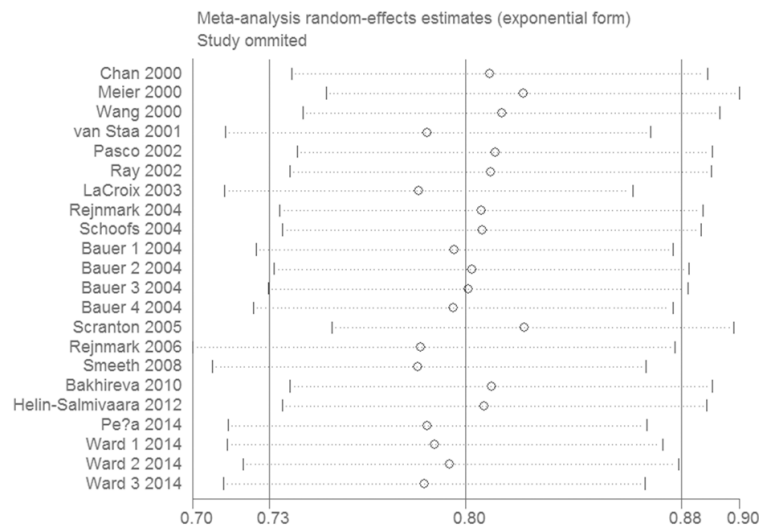
Figure 2. Sensitive analysis for the association between statins use and decreased fracture risk.

and OR=0.85; 95% CI, 0.74-0.96; P=0.01). Studies with large sample size and small sample size showed decreased risk of fracture (OR= 0.85; 95% CI, 0.77-0.94; P=0.002 and OR=0.65; 95% CI, 0.54-0.78; P < 0.0001). All the results of the meta-analysis were listed in **Table 2**.

The results of sensitivity analysis suggested that no single study had marked effect on the pooled ORs (**Figure 2**). The funnel plot was symmetrical (**Figure 3**), suggesting no publication bias. Egger test further verified that no publication bias existed (P=0.07).

meta-analysis suggested that statins use was associated with a decreased risk of fracture (OR=0.80; 95% CI, 0.73-0.88; P < 0.00001; **Figure 1**). In the subgroup analysis by study design, statins was significantly associated with a decreased risk of fracture in both case-control studies (OR=0.67; 95% CI, 0.55-0.87; P < 0.0001) and cohort studies (OR=0.86; 95% CI, 0.77-0.97; P=0.02). In the female subgroup analysis, statins user showed decreased fracture risk (OR=0.76; 95% CI, 0.63-0.92; P=0.005). In the subgroup analysis by duration of follow-up, studies with both long and short duration of follow-up showed decreased risk of fracture (OR=0.67; 95% CI, 0.54-0.82; P=0.001

Discussion

Globally, fracture is known as one of the most frequent disease. Over the past decade, the correlation between statins use and fracture risk, have been extensively investigated, with conflicting results. We conducted the present meta-analysis to explore the correlations between statins use and fracture risk. The present meta-analysis including 22 studies assessed the association between statins use and fracture risk. We found that statins use showed a decreased risk of fracture. This result suggested that statins use may be a protective factor of fracture. Furthermore, we found that
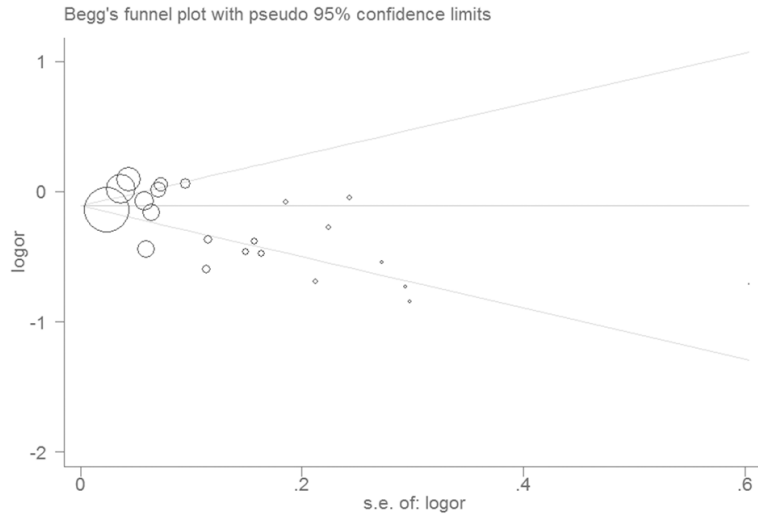
Begg's funnel plot with pseudo 95% confidence limits

Figure 3. Funnel plot for the association between statins use and decreased fracture risk.

bias suggesting that the overall pooled result is unbiased.

In conclusion, this meta-analysis suggested a significant association between statins use and decreased fracture risk.

Disclosure of conflict of interest

None.

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statins use might also be a protective factor for females.

Statins inhibit 3-hydroxy-3-methylglutaryl-CoA (HMGCoA) reductase, and thereby block the synthesis of mevalonate. The biological plausibility of the lipid hypothesis of osteoporosis has led to investigate the association between circulating lipid levels and risk of prevalent or incident fractures at different bone sites. In a cross-sectional study, Yamaguchi et al. [24] evaluated the relationships between plasma lipids and the presence of vertebral fractures in 214 Japanese postmenopausal women. Triglyceride levels were significantly lower in women with vertebral fractures than in those without fractures.

Some limitations in the present meta-analysis should be pointed out. First, due to the publication limitations or incomplete data, several relevant studies were not able to be enrolled in this analysis. Second, our results were not based on the same adjusted estimates, and insufficient information for data analysis might cause confounding bias. Despite these limitations, our analysis also had some advantages. First, substantial number of cases and controls were pooled from different trials, which significantly increased statistical power of the meta-analysis. Second, the quality of studies included in current meta-analysis was relatively satisfactory and met our predefined inclusion criteria. Third, we did not find any publication

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