A systematic review and meta-analysis of the effect of statins on osteoporotic fractures

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**Article History:**
Received: 26 Oct. 2023
Accepted: 12 Jan. 2024
ePublished: 29 Jun. 2024

**Abstract**

**Introduction:** Statins can increase bone density and improve osteoporosis. As fractures are the worst outcome of osteoporosis, our study aimed to investigate the relationship between statins and osteoporotic fractures using a systematic review and meta-analysis.

**Materials and Methods:** A systematic review and meta-analysis were conducted using the PRISMA checklist to draft this article. ProQuest, PubMed, Web of Science, Cochrane, and Google Scholar were searched to access sources without time restrictions until November 10, 2023. Data analysis was performed using STATA 14 software.

**Results:** About 12 studies showed that statins generally reduced osteoporotic fractures (OR: 0.82; 95% CI: 0.72, 0.94). The association between statins and osteoporotic fractures in case-control studies (OR: 0.92; 95% CI: 0.76, 1.11), RCT studies (OR: 1.67; 95% CI: 0.86, 3.26), and cohort studies (OR: 0.70; 95% CI: 0.59, 0.83) was observed. The likelihood of osteoporotic fractures with the use of pravastatin (OR: 0.96; 95% CI: 0.87, 1.07), fluvastatin (OR: 0.88; 95% CI: 0.75, 1.03), atorvastatin (OR: 0.92; 95% CI: 0.76, 1.10), rosuvastatin (OR: 0.85; 95% CI: 0.66, 1.08), and simvastatin (OR: 0.98; 95% CI: 0.92, 1.03) was noted. Additionally, statins led to a reduction in vertebral fractures (OR: 0.74; 95% CI: 0.65, 0.86) but showed no effect on the hip region (OR: 0.78; 95% CI: 0.60, 1.01). In the groups of 30–364 cumulative defined daily doses (cDDD) (OR: 0.84; 95% CI: 0.65, 1.08) and ≥365 cDDD (OR: 0.50; 95% CI: 0.25, 1), no significant association was observed between statins and osteoporotic fractures.

**Conclusion:** Overall, statins resulted in an 18% reduction in the risk of osteoporotic fractures.

**Registration:** This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (CRD42023484864) and Research Registry (UIN: reviewregistry1750) website.

**Keywords:** Osteoporotic fractures, Fracture, Osteoporotic, Hydroxymethylglutaryl-CoA reductase inhibitors, Statin, HMG CoA reductase inhibitors

**Implication for health policy/practice/research/medical education:**
Our meta-analysis, combining the results of 12 reviewed studies, showed that statins overall prevent 18% of osteoporosis fractures and 26% of vertebral fractures, but do not have a significant effect on reducing hip fractures.

**Please cite this paper as:** Asgari-Savadjani S, Tavakoli Chaleshtori M, Mousavi M. A systematic review and meta-analysis of the effect of statins on osteoporotic fractures. J Nephropharmacol. 2024;13(2):e11672. DOI: 10.34172/npj.2024.11672.
including reduced bone resorption and bone formation stimulation, statins may benefit bone mineral density (14-16). Evidence suggests a potential link between cholesterol metabolism and bone health, indicating that improved lipid metabolism may enhance bone health in osteoporosis by modifying osteoblast function (17). Given the hypothesis that statins may reduce osteoporotic fractures and acknowledging the conflicting findings of prior studies (18,19), the present study aimed to investigate the association between statins and fractures resulting from osteoporosis.

Materials and Methods
The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (20) guided the composition of this systematic review and meta-analysis study, and its protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) website.

Search strategy
The Google Scholar search engine and databases, including ProQuest, PubMed, Web of Science, and Cochrane, were searched without time restrictions until November 10, 2023. Medical Subject Headings (MeSH) terms and their equivalents, including “Osteoporotic Fractures,” “Fracture, Osteoporotic,” “Hydroxymethylglutaryl-CoA Reductase Inhibitors,” “Statin,” and “HMG CoA Reductase Inhibitors,” were employed for source exploration. These keywords were combined using Boolean operators (AND, OR) for an advanced search. Additionally, manual searches were conducted by reviewing the reference lists of eligible studies. The search strategy in the Web of Science was based on the following: Osteoporotic Fractures OR “Fracture, Osteoporotic” (All Fields) AND Hydroxymethylglutaryl-CoA Reductase Inhibitors OR Statin OR HMG CoA Reductase Inhibitor (All Fields).

PICO components
Population: Studies investigating the impact of statins on osteoporotic fractures.
Intervention: Statin consumption.
Comparison: Groups not using statins.
Outcomes: The effect of statins on the likelihood of osteoporotic fractures.

Inclusion and exclusion criteria
Studies assessing the impact of statins on osteoporotic fractures were included. Duplicate studies, review studies with low quality, descriptive studies, incomplete-text studies, those lacking necessary data for analysis, and studies using other indices such as percentages and frequencies were excluded from our review.

Quality assessment
For evaluating the Randomized Controlled Trial (RCT) study, the Cochrane Institute checklist (21) was utilized. This checklist consists of seven questions, each with three response options: high risk of bias, low risk of bias, and unclear. Each question evaluates one of the key biases in clinical trials. To assess observational studies (cohort, case-control), the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (22) was employed. This checklist comprises 22 questions with a minimum and maximum score of 0 and 44, respectively. Then, two researchers assessed instances of disagreement regarding responses to the questions and, through consultation, reached a consensus response.

Data extraction
Two researchers independently conducted data extraction. The designed checklist for data extraction included the first author’s name, study type, sample size, patient’s age, study location, study duration, study time, the odds ratio (OR) of statin use, and the probability of osteoporotic fracture with a 95% confidence interval. A third researcher reviewed the extracted data from the previous two researchers and resolved any discrepancies.

Statistical analysis
The logarithm of odds ratio (OR) was utilized to combine studies, and I² statistic was used to assess heterogeneity. The I² statistic has three classifications: low heterogeneity (<25%), moderate heterogeneity (25-75%), and high heterogeneity (>75%). Due to high heterogeneity among studies (I²=92.1%), this study applied a random-effects model. Subgroup analysis was performed to investigate the effect of statins on osteoporotic fractures, considering types of statins, statin doses, study types, and the site of osteoporosis. Meta-regression was used to examine the association between “the effect of statins on osteoporotic fractures” and the number of patient samples. A publication bias assessment was conducted during the source search using a publication bias graph. Data analysis was performed using STATA 14 software, considering statistical significance at $P<0.05$.

Results
A total of 790 studies were retrieved from the databases above. Upon reviewing study titles, 325 duplicates were identified and removed. Subsequently, abstracts of the remaining studies were assessed, leading to the exclusion of 63 studies due to the unavailability of their full texts. Among the remaining 402 studies, 49 were excluded due to incomplete data required for analysis. Further scrutiny of 353 studies resulted in the exclusion of 341 studies based on other exclusion criteria, leaving 12 studies for systematic review and meta-analysis (Figure 1).

Among the 12 scrutinized studies, 7 were cohort studies, 4 were case-control studies, and one was an RCT. A portion of the extracted information from eligible studies is presented in Table 1.
As depicted in Figure 2, statin use significantly reduced osteoporotic fractures (OR: 0.82, 95% CI: 0.72-0.94). The association between statin use and osteoporotic fractures was non-significant in case-control studies (OR: 0.92, 95% CI: 0.76-1.11) and the RCT (OR: 1.67, 95% CI: 0.86-3.26). However, in cohort studies, statin use notably decreased osteoporotic fractures (OR: 0.70, 95% CI: 0.59-0.83).

In Table 2 and within the subgroup analysis, it was observed that statistically significant effects of statins on the likelihood of osteoporotic fractures were not found across any of the statin types (pravastatin, fluvastatin, atorvastatin, rosuvastatin, and simvastatin). Concerning the site of osteoporosis, statins led to a reduction in vertebral fractures (OR: 0.74, 95% CI: 0.65-0.86) but did not exhibit an effect on hip fractures (OR: 0.78, 95% CI: 0.60-1.01). Evaluation of daily dosage revealed that in the group receiving 30–364 cumulative defined daily doses (cDDD) (OR: 0.84, 95% CI: 0.65-1.08) and the group with ≥365 cDDD (OR: 0.50, 95% CI: 0.25-1.00), no significant association between statin use and reduced risk of osteoporotic fractures was found.

In Figure 3, the meta-regression analysis indicated a lack of statistically significant association between “the effect of statins on the probability of osteoporotic fractures” and the number of patient samples examined (P value=0.271). This suggests that the results obtained were not dependent on the number of study samples.

Moreover, Figure 4 displayed no evidence of publication bias (P value=0.538). This indicates an absence of bias in source search, suggesting that all published studies were assessed without considering their outcomes.

Discussion
Our meta-analysis demonstrated that statins may prevent up to 18% of osteoporotic fractures (OR: 0.82, 95% CI: 0.72-0.94). However, upon stratification of studies based on study design, it was evident that the association between statins and osteoporotic fractures was not significant in case-control studies and RCTs. Only in cohort studies statins could prevent up to 30% of osteoporotic fractures. Moreover, concerning the fracture site, statins reduced vertebral fractures by 26%, yet they did not affect hip fractures.

Furthermore, when comparing different types of statins, our analysis revealed no significant reduction in osteoporotic fractures using pravastatin, fluvastatin, atorvastatin, rosuvastatin, or simvastatin. This particular aspect represents a strength of our study, as previous meta-analysis exploring the relationship between statins and bone fractures did not individually evaluate the effects of statins on osteoporotic fractures.
### Table 1. Specifications of articles which entered into the meta-analysis process

<table>
<thead>
<tr>
<th>Author, year of publication</th>
<th>Country</th>
<th>Type of Study</th>
<th>The number of patients in the statin group</th>
<th>Age of statin group patients</th>
<th>The number of patients in the comparison group</th>
<th>Age of patients in the comparison group</th>
<th>During the study period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen HY, 2020 (18)</td>
<td>Taiwan</td>
<td>Case-Control</td>
<td>86188</td>
<td>64.4</td>
<td>86188</td>
<td>64.5</td>
<td>January 2004 to December 2013</td>
</tr>
<tr>
<td>Lin TK, 2018 (23)</td>
<td>Taiwan</td>
<td>Cohort</td>
<td>115590</td>
<td>67</td>
<td>44943</td>
<td>66.4</td>
<td>from January 2004 to December 2013</td>
</tr>
<tr>
<td>Kim KJ, 2021 (19)</td>
<td>Korea</td>
<td>Case-Control</td>
<td>17041</td>
<td>64</td>
<td>17041</td>
<td>64</td>
<td>January 1, 2004, to December 31, 2014</td>
</tr>
<tr>
<td>Seo DH, 2023 (24)</td>
<td>Korea</td>
<td>Cohort</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>January 1 2004 until December 31 2012</td>
</tr>
<tr>
<td>Hong WJ, 2019 (25)</td>
<td>Taiwan</td>
<td>Cohort</td>
<td>405</td>
<td>&gt;40</td>
<td>855</td>
<td>&gt;40</td>
<td>2000 to 2010</td>
</tr>
<tr>
<td>Hippisley-Cox J, 2010 (W) (26)</td>
<td>England and Wales</td>
<td>Cohort</td>
<td>104774</td>
<td>57.2</td>
<td>909423</td>
<td>44.4</td>
<td>between 1 January 2002 and 30 June 2008</td>
</tr>
<tr>
<td>Hippisley-Cox J, 2010 (M) (26)</td>
<td>England and Wales</td>
<td>Cohort</td>
<td>121148</td>
<td>57.2</td>
<td>869347</td>
<td>44.4</td>
<td>between 1 January 2002 and 30 June 2008</td>
</tr>
<tr>
<td>Scranton RE, 2005 (27)</td>
<td>USA</td>
<td>Cohort</td>
<td>28063</td>
<td>65.1</td>
<td>2195</td>
<td>61</td>
<td>between January 1998 and June 2001</td>
</tr>
<tr>
<td>Pena JM, 2015 (28)</td>
<td>26 countries</td>
<td>RCT</td>
<td>8901</td>
<td>66</td>
<td>8901</td>
<td>66</td>
<td>2003 to 2006</td>
</tr>
<tr>
<td>Ozen G, 2019 (29)</td>
<td>USA</td>
<td>Cohort</td>
<td>4187</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>from 2001 through 2017</td>
</tr>
<tr>
<td>Lin SM, 2018 (30)</td>
<td>Taiwan</td>
<td>Cohort</td>
<td>2627</td>
<td>66.5</td>
<td>2627</td>
<td>66.2</td>
<td>between 2000 and 2012</td>
</tr>
<tr>
<td>Adams AL, 2015 (31)</td>
<td>USA</td>
<td>Case-control</td>
<td>1884</td>
<td>&gt;45</td>
<td>2150</td>
<td>&gt;45</td>
<td>1997-2006</td>
</tr>
<tr>
<td>Cheng KC, 2019 (32)</td>
<td>Taiwan</td>
<td>Case-control</td>
<td>2420</td>
<td>&gt;65</td>
<td>2447</td>
<td>&gt;65</td>
<td>2000 to 2013</td>
</tr>
</tbody>
</table>

NR, Not reported; RCT, Randomized controlled trial; M, Men; W, Women.
different statin types. Additionally, in terms of cumulative dosage, no significant association between statins and osteoporotic fractures was observed in groups receiving 30–364 cDDD and ≥365 cDDD.

In the meta-analysis by Bauer et al, aiming to examine the association between statins and fracture risk across 10 studies, observational studies indicated an OR of 0.43; 95% CI: 0.25-0.75) for statin use and hip fractures and an OR of 0.69; 95% CI: 0.55-0.88) for non-spinal fractures. However, in clinical trials, statin administration did not show statistically significant effects on hip fractures (OR: 0.87, 95% CI: 0.48-1.58) or non-spinal fractures (OR: 1.02, 95% CI: 0.83-1.26) (33). In a meta-analysis conducted by Shi et al involving 1,783,123 elderly individuals to investigate fracture risk among statin users, observational studies indicated a reduced risk for all fractures with statin treatment (RR: 0.80, 95% CI: 0.72-0.88). However, no significant effect of statin therapy on fracture risk was observed in the RCT meta-analysis (RR: 1.00, 95% CI: 0.87-1.15) (34). Studies by Shi et al (34) and Bauer et al (33) concurred that a significant association between RCTs and the effect of statins on fractures was not existed. However, they differed in indicating the effectiveness of statin use in reducing fracture risk in observational studies. Since in our study, only in cohort studies, the relationship between statin and reduction of osteoporosis fracture risk was significant, however this relationship was not significant in case-control studies. It should be noted that Bauer et al (33) and Shi et al (34) did not distinguish between observational study types (case-control and cohort), possibly contributing to the difference in our study’s findings compared to the studies by Bauer et al (33) and Shi et al (34).

According to the meta-analysis conducted by Toh et al, statins could reduce the risk of fractures by up to 23% (OR: 0.77, 95% CI: 0.66–0.90). A significant reduction in the risk of hip fractures (OR: 0.58, 0.46–0.74) and vertebral fractures (OR: 0.65, 0.48–0.88) was observed due to statin administration. However, statin use did not exhibit any impact on fractures in other body areas (OR:

| Table 2. Association between statins and osteoporotic fractures by subgroups examined in eligible studies |
|---------------------------------|-------------|----------|-------------|
| Variables                      | Subgroups   | OR (95% CI) | P value | I² (%) |
| Type of statin                 |             |           |          |
| Pravastatin                    | 0.96 (0.87, 1.07) | 0.799 | 0 |
| Fluvastatin                    | 0.88 (0.75, 1.03) | 0.293 | 18.5 |
| Atorvastatin                   | 0.92 (0.76, 1.10) | <0.001 | 89.8 |
| Rosuvastatin                   | 0.85 (0.66, 1.08) | 0.006 | 75.8 |
| Simvastatin                    | 0.98 (0.92, 1.03) | 0.874 | 0 |
| Bone fracture site             |             |           |          |
| Vertebral fracture             | 0.74 (0.65, 0.86) | 0.002 | 74.3 |
| Hip fracture                   | 0.78 (0.60, 1.01) | <0.001 | 94.1 |
| Dose of statin                 |             |           |          |
| 30–364 cDDD                    | 0.84 (0.65, 1.08) | <0.001 | 98.3 |
| ≥365 cDDD                      | 0.50 (0.25, 1.0) | <0.001 | 99.6 |

OR, Odds ratio; CI, Confidence interval; cDDD, Cumulative defined daily dose.
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Additionally, there was an association between statins and fracture risk in women (OR: 0.80, 0.66–0.96) and men (OR: 0.62, 0.36–1.08) (35). The overall conclusion of our study aligns with the findings of the study by Toh et al (35), indicating the protective effects of statin administration against bone fractures. However, some minor differences existed. For instance, contrary to the study by Toh et al (35), our study found no significant impact of statin administration on reducing the risk of osteoporotic fractures in the hip region. Nevertheless, patient characteristics such as mean age, gender distribution and menopausal status were not consistent between the two studies, although these factors were deemed irrelevant.

In the meta-analysis by Gao et al, data indicated that statins could reduce the risk of fractures (OR=0.80; 95% CI, 0.73–0.88). Furthermore, statin use was significantly associated with a considerable reduction in fracture risk among women (OR=0.76; 95% CI, 0.63–0.92) (36). Moreover, Jin et al in a meta-analysis of 17 studies, demonstrated that statin use reduced the risk of fractures (OR: 0.80, 95% CI, 0.73-0.88). Statin receiving was associated with a reduced fracture risk in case-control studies (OR: 0.67, 95% CI, 0.55–0.87) and cohort studies (OR: 0.86, 95% CI, 0.77-0.97) (37). Our study's overall findings were consistent with those of Gao et al (36) and Jin et al (37). However, these studies considered all types of bone fractures, while our current study solely aimed at investigating osteoporotic fractures, leading to differences in the number of studies examined and the total sample size of these meta-analyses. Consequently, these variations in the final results of these meta-analyses are expected. For instance, in our study, unlike the study by Jin et al (37), no significant association between statins and osteoporotic fractures was observed in case-control studies.

Based on the findings of the study conducted by An et al who investigated the impact of statins on osteoporosis, statins reduced the overall fracture risk (OR = 0.81, 95% CI 0.73–0.89) as well as the risk of hip fractures (OR = 0.75, 95% CI 0.60–0.92). However, no positive effect was observed on the spine, upper limb fractures, or bone density in the femoral neck (16). Notably, the conclusion of the study by An et al (16) aligns with our findings. However, concerning the location of bone fractures, the results of the two studies contradicted each other. Unlike the study by An et al (16), our study found that statins were not effective in preventing osteoporotic fractures in the hip region. Nevertheless, differences in the type and dosage of statins used in our studies compared to those mentioned in the study by An et al (16) might contribute to this discrepancy.

**Conclusion**

Our study demonstrated that statins prevented 18% of overall osteoporotic fractures and 26% of vertebral fractures but showed no significant effect on hip fractures. Generally, the use of statins is recommended for elderly patients, postmenopausal women, and individuals with low bone density, as they belong to the high-risk group for osteoporosis and related fractures. By reducing the risk of osteoporotic fractures, Statins contribute to reducing hospitalization costs, enhancing quality of life, and alleviating the economic burden on families.

**Limitations of the study**

A) In eligible studies (except for the Hippisley-Cox and Coupland study), the effect of statins on fractures resulting from osteoporosis was not disaggregated by gender. Hence, the current study did not specify whether the impact of statins on reducing osteoporotic fractures is greater in women or men. B) The age groups of the study participants were not structured in a way that allowed independent classification. Therefore, we could not evaluate age's influence on statins' effectiveness in reducing osteoporotic fractures. C) Full texts of some sources were not accessible. D) The number of published RCT sources in this field was limited, resulting in only one qualified RCT study being included in this meta-analysis.
Acknowledgments
The authors would like to thanks Hamid Nasri and Diana Sarokhani for guidance and editing of manuscript registration on the PROSPERO website.

Authors’ contribution
Conceptualization: Shahin Asgari-Savadjadi, Mohammad Mousavi.
Data curation: Maryam Tavakoli Chaleshtori.
Formal analysis: Mohammad Mousavi.
Investigation: Mohammad Mousavi.
Methodology: Shahin Asgari-Savadjadi, Maryam Tavakoli Chaleshtori.
Project administration: Mohammad Mousavi.
Resources: All authors.
Software: All authors.
Supervision: Mohammad Mousavi.
Validation: Mohammad Mousavi.
Visualization: Shahin Asgari-Savadjadi, Maryam Tavakoli Chaleshtori.
Writing–original draft: Mohammad Mousavi.
Writing–review & editing: Shahin Asgari-Savadjadi, Maryam Tavakoli Chaleshtori.

Conflicts of interest
The authors declare that they have no competing interests.

Ethical issues
This investigation has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) website with (ID: CRD42023484864) and Research Registry website with (Unique Identifying Number (UIN) reviewregistry1750). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

Funding/Support
None.

Supplementary files
Supplementary file 1. Search strategy in databases.

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