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

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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.

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.

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Meta-analysis

Introduction

The aging population inevitably leads to an increase in osteoporosis and associated fractures, entailing substantial medical, social, and economic burdens (1,2). Osteoporosis annually accounts for more than 8.9 million cases of fractures or bone defects globally, and its prevalence gradually rises with the aging population (3,4). Projections anticipate that fractures, the most debilitating consequence of osteoporosis, will increase worldwide with significant disparities among regions and countries (5-7). Between 2010 and 2040, the number of individuals at high risk of fractures globally is anticipated to double, with the most substantial increase observed in Africa, Latin America, and Asia (5). Osteoporotic fractures result in reduced quality of life, increased complications, mortality, and extensive healthcare resource utilization (8). Hip fractures are the costliest and most incapacitating among fractures, causing 10% to 20% of mortality attributable to fractures annually. Fractures in other skeletal sites, including the vertebral column and wrist, also lead to significant disability and functional decline (9,10).

Statins are lipid-lowering drugs with established efficacy in preventing cardiovascular diseases (11). Compared to traditional systemic anti-osteoporotic drugs and biologics, statins are considerably more cost-effective, reducing adverse effects such as liver and kidney damage, rhabdomyolysis, and fractures (12,13). Considering their potential pleiotropic effects on bone metabolism,

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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 (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 I^2 statistic was used to assess heterogeneity. The I^2 statistic has three classifications: low heterogeneity (<25%), moderate heterogeneity (25-75%), and high heterogeneity (>75%). Due to high heterogeneity among studies ($I^2 = 92.1\%$), 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.

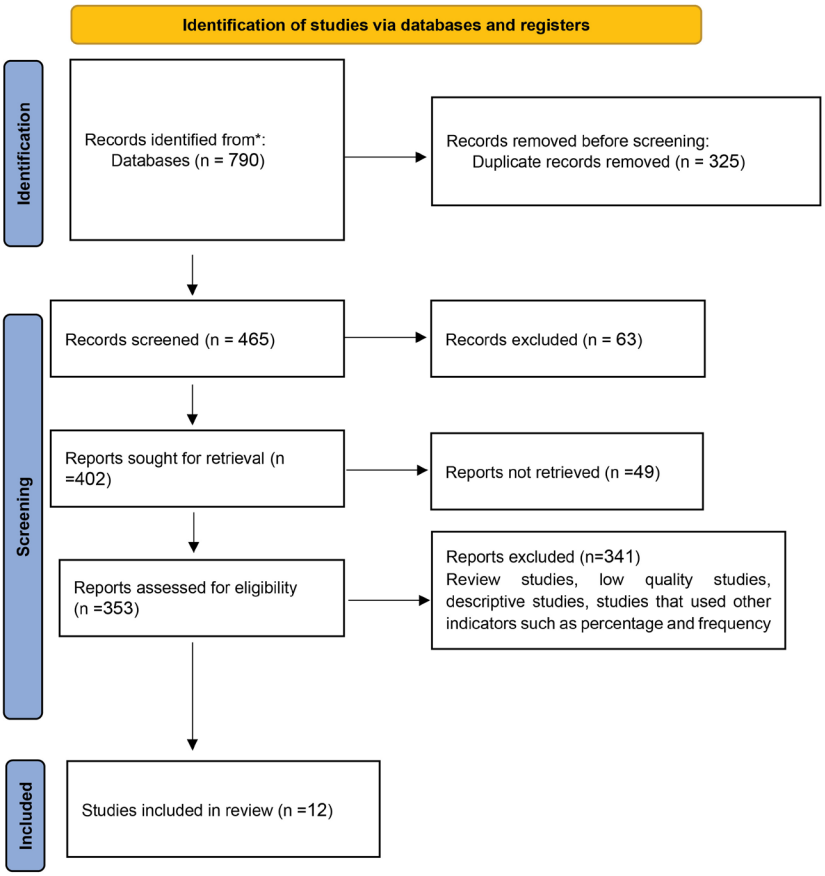

Figure 1. The flow chart of study selection.

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

Table 1. Specifications of articles which entered into the meta-analysis process

Author, year of publication	Country	Type of Study	The number of patients in the statin group	Age of statin group patients	The number of patients in the comparison group	Age of patients in the comparison group	During the study period
Chen HY, 2020 (18)	Taiwan	Case-Control	86 188	64.4	86188	64.5	January 2004 to December 2013
Lin TK, 2018 (23)	Taiwan	Cohort	115 590	67	44943	66.4	from January 2004 to December 2013
Kim KJ, 2021 (19)	Korea	Case-Control	17 041	64	17041	64	January 1, 2004, to December 31, 2014
Seo DH, 2023 (24)	Korea	Cohort	NR	NR	NR	NR	January 1 2004 until December 31 2012
Hong WJ, 2019 (25)	Taiwan	Cohort	405	>40	855	>40	2000 to 2010
Hippisley-Cox J, 2010 (W) (26)	England and Wales	Cohort	104 774	57.2	909423	44.4	between 1 January 2002 and 30 June 2008
Hippisley-Cox J, 2010 (M) (26)	England and Wales	Cohort	121 148	57.2	869347	44.4	between 1 January 2002 and 30 June 2008
Scranton RE, 2005 (27)	USA	Cohort	28 063	65.1	2195	61	between January 1998 and June 2001
Pena JM, 2015 (28)	26 countries	RCT	8901	66	8901	66	2003 to 2006
Ozen G, 2019 (29)	USA	Cohort	4187	NR	NR	NR	from 2001 through 2017
Lin SM, 2018 (30)	Taiwan	Cohort	2627	66.5	2627	66.2	between 2000 and 2012
Adams AL, 2015 (31)	USA	Case-control	1884	>45	2150	>45	1997-2006
Cheng KC, 2019 (32)	Taiwan	Case-control	2420	>65	2447	>65	2000 to 2013

NR, Not reported; RCT, Randomized controlled trial; M, Men; W, Women.

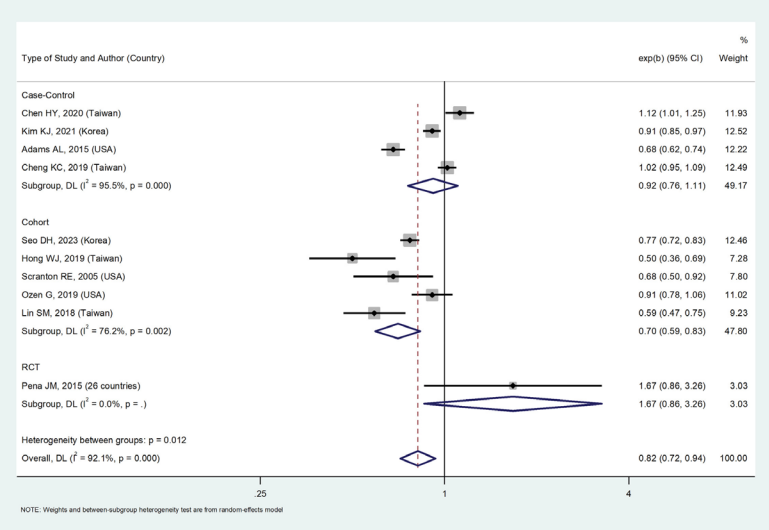

Figure 2. Forest plot of the association between statins and osteoporotic fractures by study type.

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	I^2 (%)
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)	<0.001	99.6

OR, Odds ratio; CI, Confidence interval; cDDD, Cumulative defined daily dose.

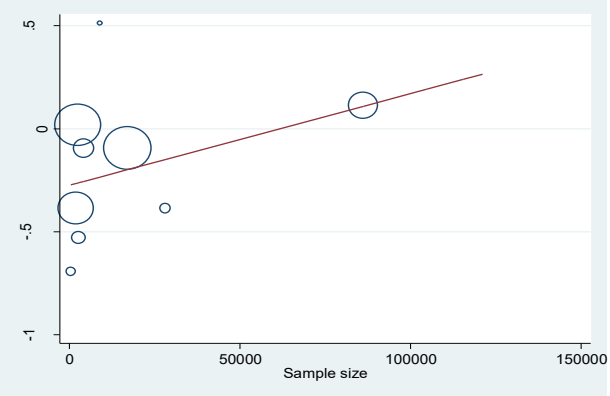

Figure 3. The meta-regression diagram showing the relationship between "the effect of statin on the probability of osteoporosis fractures" and the number of patient samples.

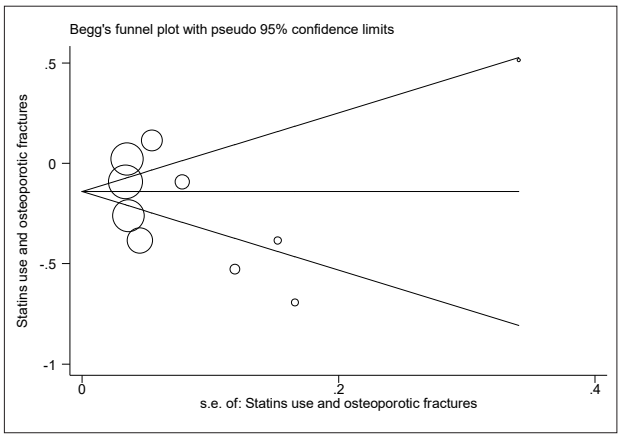

Figure 4. Publication bias diagram.

0.77, 0.60–1.00). 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.

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Authors' contribution

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

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Supplementary files

Supplementary file 1. Search strategy in databases.

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