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# Association between parathyroidectomy and bone fracture risk in patients with primary hyperparathyroidism: a systematic review and meta-analysis

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## Abstract

**Introduction:** Parathyroidectomy is the definitive treatment for primary hyperparathyroidism and enhances bone density; thus, this study aimed to investigate the association between parathyroidectomy and fracture risk in individuals with primary hyperparathyroidism.

**Materials and Methods:** This meta-analysis and systematic review were conducted through simple and advanced searches in PubMed, Cochrane, Web of Science, ProQuest, and Google Scholar. The search was updated until June 25, 2023. Data were collected using SPSS version 19 and analyzed with STATA software version 14.

**Results:** Eleven cohort studies totaling 97,388 patients with primary hyperparathyroidism who had parathyroidectomy were included in the meta-analysis. In individuals with primary hyperparathyroidism, parathyroidectomy decreased the fracture risk by 15% (odds ratio [OR]: 0.85; 95% confidence interval [CI]: 0.74, 0.99) overall and by 22% (OR: 0.78; 95% CI: 0.76, 0.80) in patients aged 70 to 79 years; however, no notable association was found between parathyroidectomy and the fracture risk in patients aged 50 to 59 years (OR: 0.99; 95% CI: 0.55, 1.76) and 60 to 69 years (OR: 0.84; 95% CI: 0.69, 1.02); additionally, parathyroidectomy resulted in a 29% reduction in the fracture risk in the USA (OR: 0.71; 95% CI: 0.61, 0.81) and a 23% reduction in the hip fracture risk (OR: 0.77; 95% CI: 0.60, 0.97); however, no statistically notable correlation was found between parathyroidectomy and the risk of hand, foot, vertebral, femur, forearm, spine, upper extremity, femoral neck, and osteoporotic fractures.

**Conclusion:** Parathyroidectomy reduced fracture risk by 15%, notably preventing bone and hip fractures in people over 70.

**Registration:** This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD42024564707) and Research Registry (UIN: reviewregistry1854 websites).

**Keywords:** Hyperparathyroidism, Bone fractures, Broken bones, Parathyroidectomy

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## Introduction

A parathyroid tumor or hyperplasia of one or more parathyroid glands causes excessive parathyroid hormone (PTH) production, which in turn alters the body's overall metabolism of bone calcium and phosphate levels. This condition is known as primary hyperparathyroidism (1). Approximately 50 occurrences of primary hyperparathyroidism, an endocrine condition, occur for every 100,000 people each year (2). Numerous symptoms, such as recurrent nephrolithiasis, bone pain,

cognitive abnormalities, and neuropsychiatric functional impairment, may be experienced by patients (3).

Conservative medical care and parathyroidectomy are two treatment approaches for these people. Medical treatment normally entails the prescription of bisphosphonates and calcium-lowering medications; parathyroidectomy, on the other hand, usually aims to remove a single adenoma (4). Randomized clinical trials show that whereas non-surgical therapy is linked to a gradual loss of bone mass, parathyroidectomy enhances bone mineral density (5-7).

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### ■ Implication for health policy/practice/research/medical education

In this meta-analysis study, we found that patients diagnosed with primary hyperparathyroidism who undergo parathyroidectomy have been demonstrated to experience a significant reduction in fracture risk, particularly concerning hip fractures, which are known to have serious implications for morbidity and mortality in this population. Interestingly, research indicates that individuals over 70 derive even greater benefits from this surgical intervention, as they exhibit a more pronounced decrease in fracture risk compared to younger cohorts. Despite their advanced age, older patients may experience substantial improvements in bone health following parathyroidectomy, highlighting the importance of considering surgical options for this demographic. The findings underscore the critical role of parathyroidectomy in enhancing skeletal integrity and reducing the likelihood of fractures, thereby contributing to better overall health outcomes in patients with primary hyperparathyroidism, particularly among the elderly.

Parathyroidectomy is still the only effective treatment for patients with primary hyperparathyroidism, even though the fact that it is a costly surgical procedure for both patients and the healthcare system and may result in complications like hypocalcemia, hematoma formation, and damage to the larynx (8,9); nonetheless, parathyroidectomy remains the definitive treatment for patients with primary hyperparathyroidism (10). Given that some studies identify parathyroidectomy as a factor in reducing fracture risk in these patients (11,12), other studies consider it a risk factor for increased fracture risk in these patients (13,14). This study aimed to investigate the association between parathyroidectomy and fracture risk in patients with primary hyperparathyroidism using a meta-analysis and systematic review approach.

### Materials and Methods

This study was designed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol (15), which is tailored for meta-analysis studies and systematic review; the study's protocol was then registered on the PROSPERO (International Prospective Register of Systematic Reviews) website.

### Search strategy

The systematic review and meta-analysis were conducted through simple and advanced searches in PubMed, Cochrane, Web of Science, ProQuest, and Google Scholar search engine. The search was updated until June 25, 2023. The following Medical Subject Headings (MeSH) keywords were employed in the resource search: "Hyperparathyroidism, Primary," "Fractures, Bone," "Broken Bones," "Parathyroidectomy," "Parathyroidectomies." These keywords were combined using the operators (AND, OR). Eligible study resources were reviewed for manual search execution. The search strategy on the PubMed website was as follows: ("parathyroidectomy"[MeSH Terms] OR

"parathyroidectomy"[AllFields]OR"parathyroidectomies"[All Fields] OR ("parathyroidectomy" [MeSH Terms] OR "parathyroidectomy"[All Fields] OR "parathyroidectomies"[All Fields])) AND ("fractures bone"[All Fields] OR ("fractures, bone"[MeSH Terms] OR ("fractures"[All Fields] AND "bone"[All Fields]) OR "bone fractures"[All Fields] OR ("broken"[All Fields] AND "bones"[All Fields]) OR "broken bones"[All Fields]))).

### PICO component:

- Population: Cohort studies examining the association between parathyroidectomy and fracture risk in patients with primary hyperparathyroidism.
- Intervention/Exposure: Parathyroidectomy.
- Comparison: Age and sex-matched individuals with the target group.
- Outcomes: The relationship between parathyroidectomy and fracture risk.

### Exclusion and inclusion criteria

Cohort studies that examined the correlation between parathyroidectomy and fracture risk in individuals with primary hyperparathyroidism were incorporated into the meta-analysis; however, studies that were duplicates, reviews, of low quality, conference papers unrelated to primary hyperparathyroidism patients, lacking full text, reporting the association between primary hyperparathyroidism and fracture risk, or with incomplete data for analysis were excluded.

### Quality assessment

Two authors assessed the quality of the studies using the Newcastle Ottawa Scale questionnaire. Each question was allocated a maximum of one star in this nine-item tool, except for the comparison question, which could receive two stars; therefore, the lowest and highest possible scores for this tool were zero (lowest quality) and ten (highest quality), respectively. Studies that scored seven stars or more were included in our study (16).

### Data extraction

Two individuals performed data extraction. The following data were extracted from the studies: the first author's name, location, year of publication, type of study, duration of the study, sample size, age, and the odds ratio [OR] between parathyroidectomy and fracture risk in patients with primary hyperparathyroidism with its upper and lower limits. A third individual then reviewed the extracted data and resolved any discrepancies.

### Analysis

The research was combined using the logarithm of each index (OR, relative risk [RR], hazard ratio [HR], and incidence rate ratio [IRR]). Heterogeneity was evaluated using the I<sup>2</sup> index. Less than 25% low heterogeneity, 25%

to 75% moderate heterogeneity, and more than 75% high heterogeneity are the three categories of the  $I^2$  index. In this study, a random-effects model was used ( $I^2 = 88.8\%$ ). Using subgroup analysis, the relationship between fracture risk and parathyroidectomy was examined in terms of age and nationality. The relationship between fracture risk and parathyroidectomy was investigated using meta-regression, taking into account the study's year of publication and sample size. Sensitivity analysis and publication bias were conducted for further analyses. STATA 14 was carried out to analyze the data, and tests were carried out with a notable threshold of  $P < 0.05$ .

## Results

### Study selection

Around 409 studies in all were searched through the databases, then 176 duplicate studies were removed after screening the study titles; 22 studies with missing or incomplete abstract information and unavailable full texts were removed from consideration, next of 211 studies that remained for further analysis, 46 were discarded because additional data was required for data analysis; 154 studies' full texts were assessed; 154 studies were removed based

on additional exclusion criteria; and 11 studies were included in the process of systematic review and meta-analysis (Figure 1).

### Summary of reviewed study information

This meta-analysis examined eleven cohort studies. Studies pertaining to the years 2000 to 2023 revealed that 97 388 patients with primary hyperparathyroidism underwent parathyroidectomy surgery in total. Among the 11 studies that were reviewed, five were carried out in the USA, four in Denmark, and two in Sweden (Table 1), although no geographic restrictions were applied during the source search.

The findings demonstrated that patients with primary hyperparathyroidism who had undergone parathyroidectomy had a 15% lower incidence of any fractures (OR: 0.85 (95% CI: 0.74, 0.99) than those who had not (Figure 2).

According to subgroup analysis, patients with primary hyperparathyroidism who underwent parathyroidectomy had a 22% lower fracture risk in the 70–79 age group (OR: 0.78; 95% CI: 0.76, 0.80); however, in the 50–59 age group (OR: 0.99; 95% CI: 0.55, 1.76) and the 60–69 age

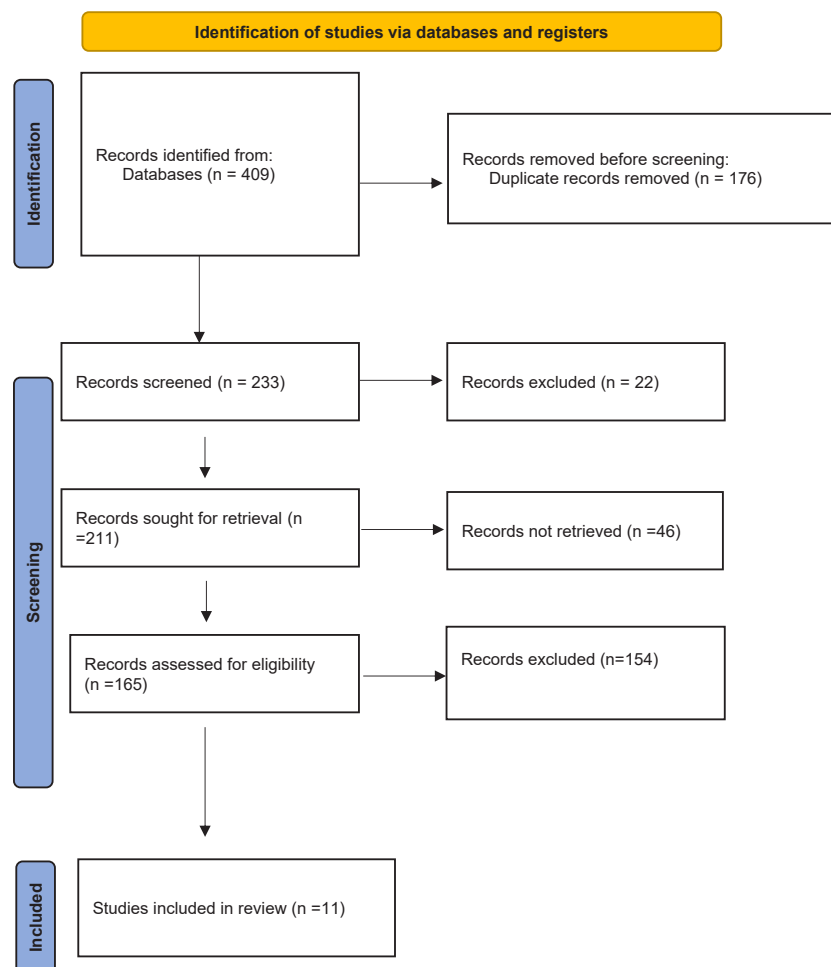


Figure 1. The PRISMA flow chart of study selection.

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

First author, year	Country	Index	Sample size in target group	Mean age in target group	Sample size in compare group	Mean age in compare group	Duration of study	Risk of any fracture		
								Risk	Low	Up
Kanis JA, 2023 (17)	Denmark	HR	6884	65.2	68665	65.2	1997-2015	NR	NR	NR
Nilsson M, 2022 (18)	Sweden	IRR	5009	61.7	14983	61.7	2003-2013	1	0.9	1.1
Seib CD, 2022 (11)	USA	HR	63136	75	147070	75	2006-2017	0.78	0.76	0.8
Axelsson KF, 2022 (12)	Sweden	HR	16374	67.5	163740	67.5	2006-2017	0.83	0.75	0.93
Orr LE, 2020 (19)	USA	HR	303	59	NR	NR	1995-2016	0.55	0.35	0.84
Zheng F, 2018 (20)	USA	HR	1228	59.8	5802	67.7	1995-2014	0.68	0.57	0.82
VanderWalde LH, 2009 (21)	USA	HR	553	>50	NR	NR	NR	0.41	0.18	0.93
VanderWalde LH, 2006 (22)	USA	HR	452	>50	NR	NR	1995-2000	0.68	0.47	0.98
Vestergaard P, 2004 (23)	Denmark	OR	1934	58.3	1279	64.2	1980-1999	0.64	0.51	0.8
Vestergaard P, 2003 (13)	Denmark	IRR	841	58.6	NR	NR	1982-1996	1.45	1.05	1.99
Vestergaard P, 2000 (14)	Denmark	RR	674	58.2	2021	58.2	1979-1997	1.8	1.3	2.3

NR: Not reported; OR: Odds ratio; RR: Risk ratio; HR: Hazard ratio; IRR: Incidence rate ratio.

group (OR: 0.84; 95% CI: 0.69, 1.02), there was no notable reduction in fracture risk (Figure 3).

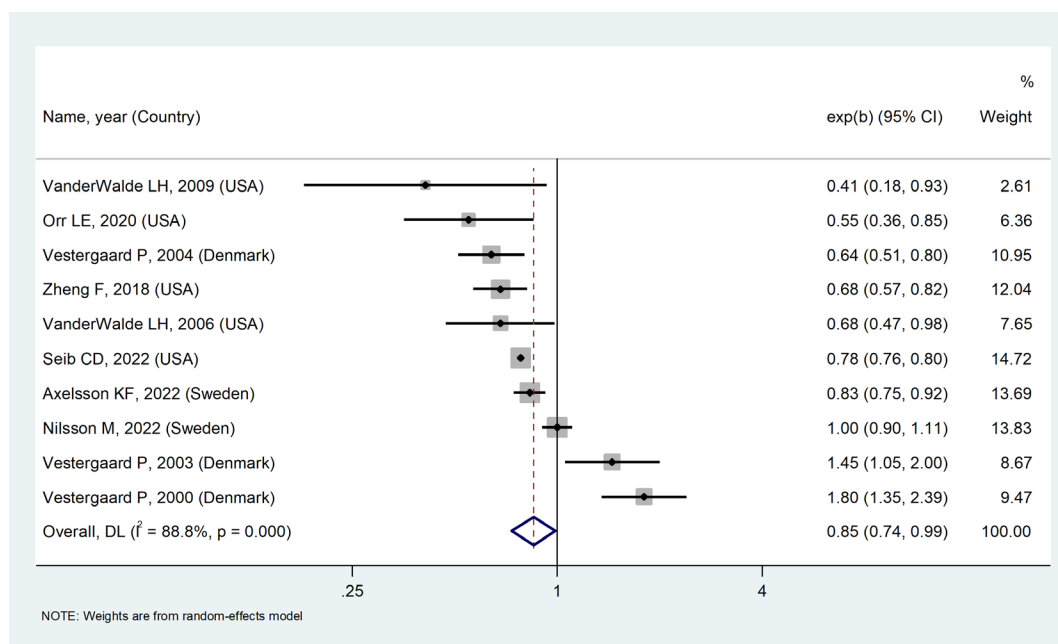
Parathyroidectomy in patients with primary hyperparathyroidism reduced the fracture risk by 29% in the USA (OR: 0.71; 95% CI: 0.61, 0.81); however, it did not affect the fracture risk in patients in Denmark (OR: 1.18; 95% CI: 0.60, 2.32) and Sweden (OR: 0.91; 95% CI: 0.76, 1.09) (Figure 4).

Examining secondary outcomes, the findings indicated that in patients with primary hyperparathyroidism, parathyroidectomy decreased the hip fracture risk by 23% (OR: 0.77; 95% CI: 0.60, 0.97); however, no statistically notable correlation was found between parathyroidectomy and the fractures risk in the upper extremities, vertebrae,

spine, hand, foot, femur, forearm, or femoral neck (Table 2).

Meta-regression revealed that there was no statistically notable association between “the effect of parathyroidectomy on fracture risk in patients with primary hyperparathyroidism” and sample size ( $P=0.880$ ) or year of research publication ( $P=0.282$ ) (Figures 5 and 6).

Figure 7 indicates that this study had no publication bias ( $P=0.502$ ), and the source search stage was fully and unbiasedly conducted. In addition, Figure 8 shows that Vestergaard and colleagues’ study in 2000 (14) and the study by Vestergaard et al in 2004 (23) were the most influential studies in the current meta-analysis result.



**Figure 2.** Forest plot showing the association between parathyroidectomy and fracture risk in patients with primary hyperparathyroidism.

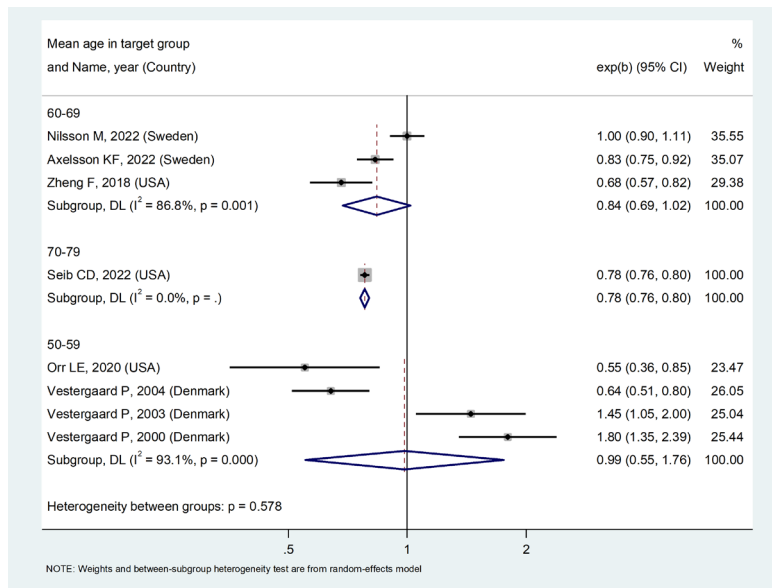


Figure 3. Forest plot showing the association between parathyroidectomy and fracture risk in patients with primary hyperparathyroidism by age group.

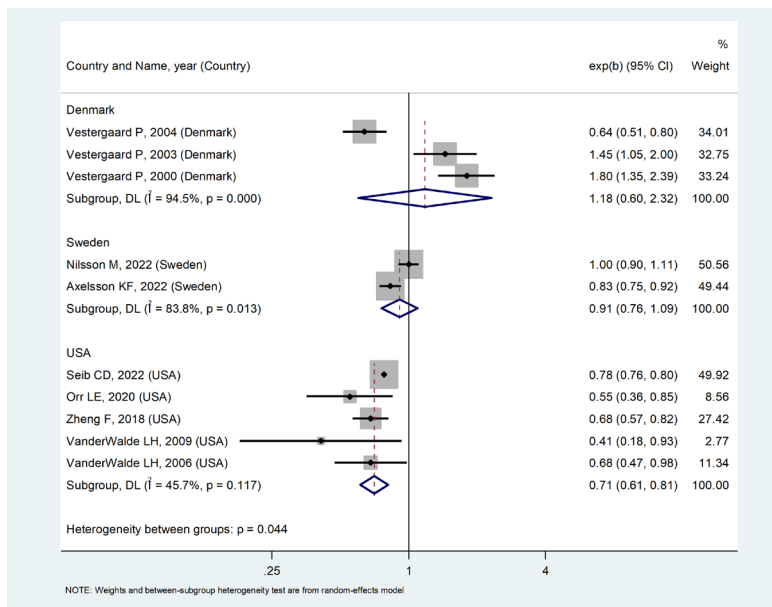
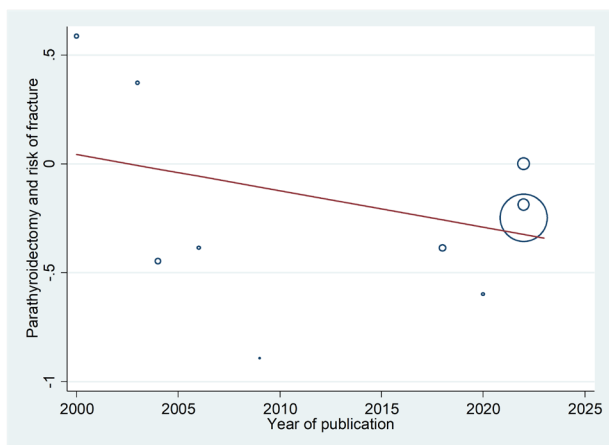


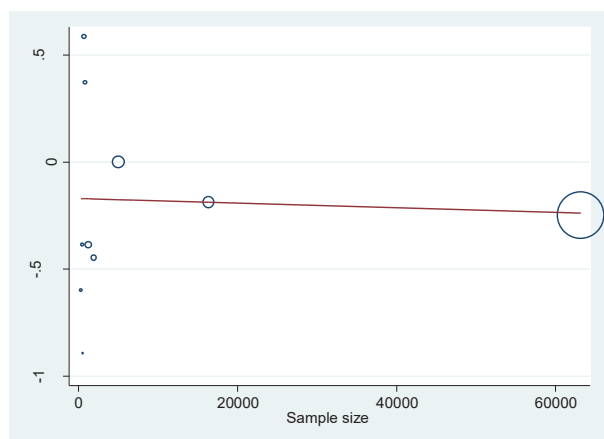
Figure 4. Forest plot showing the association between parathyroidectomy and fracture risk in patients with primary hyperparathyroidism by countries.

Table 2. Evaluation of the relationship between parathyroidectomy and fracture risk in different bones in patients with primary hyperparathyroidism

Variables	OR	Low	Up	I <sup>2</sup> (%)	P value	Significant
Hip fracture	0.77	0.60	0.97	84.2	<0.001	Yes
Vertebral fracture	1.62	0.43	6.07	84.7	0.011	No
Foot fracture	1.39	0.81	2.39	0	0.402	No
Hand fracture	0.73	0.42	1.29	0	0.548	No
Forearm fracture	1.02	0.56	1.89	80.8	0.001	No
Femur fracture	0.88	0.42	1.84	86	0.001	No
Upper extremity fracture	0.94	0.66	1.33	0	0.447	No
Femoral neck fracture	1.22	0.81	1.82	0	0.937	No
Spine fracture	0.61	0.27	1.38	47.2	0.169	No
Osteoporotic fractures	0.99	0.66	1.49	86.8	0.006	No



**Figure 5.** Meta-regression plot showing the association between “parathyroidectomy and fracture risk in patients with primary hyperparathyroidism” with year of publication.



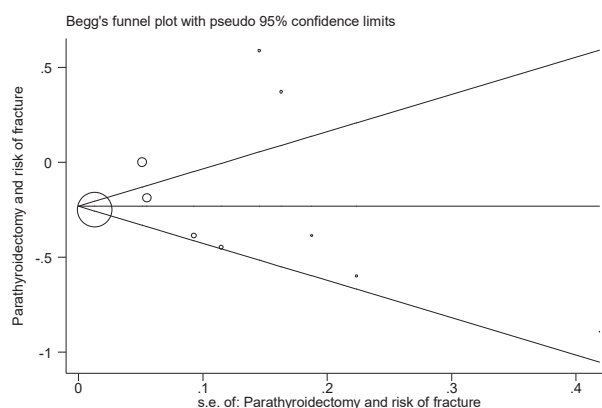
**Figure 6.** Meta-regression plot showing the association between “parathyroidectomy and fracture risk in patients with primary hyperparathyroidism” with sample size.

Removing any of these studies will notably change the final result.

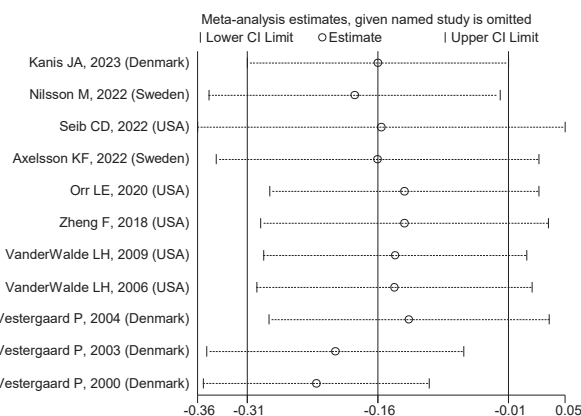
### Discussion

This meta-analysis, which included 11 studies, demonstrated that parathyroidectomy in patients with primary hyperparathyroidism reduced the fracture risk by 15% across all patients and 22% in patients aged 70 to 79. Parathyroidectomy resulted in a 23% reduction in the hip fracture risk; however, no statistically notable association was found between parathyroidectomy and the fracture risk in other bones; additionally, parathyroidectomy decreased the fracture risk in the USA by 29%.

Kongsaree et al conducted a meta-analysis to investigate the skeletal effects of parathyroidectomy on patients with primary hyperparathyroidism. They found that, in comparison to the control group, parathyroidectomy notably reduced the hip fracture risk (RR: 0.63; 95% CI: 0.52-0.76) and the risk of any fracture (RR: 0.80; 95% CI: 0.74-0.86) (24). After undergoing a parathyroidectomy, patients with primary hyperparathyroidism had better



**Figure 7.** Publication bias plot.



**Figure 8.** Sensitivity analysis plot

long-term skeletal results than those who had alternative therapies (RR: 0.64; 95% CI: 0.58-0.71), according to another meta-analysis by Zhang et al (25). These studies were congruent with the current research regarding study type and outcome, indicating that parathyroidectomy can reduce fracture risk in patients with primary hyperparathyroidism and substantially prevent fractures. Since parathyroidectomy leads to increased bone density, these results are justifiable.

Axelsson and colleagues’ cohort study results, which included 163740 participants in the control group and 16374 patients with primary hyperparathyroidism, showed that parathyroidectomy was associated with a reduction in hip fractures (HR: 0.78; 95% CI: 0.61-0.98) and any fracture risk (HR: 0.83; 95% CI: 0.75-0.93) (12). Additionally, a cohort study by Orr et al, which looked at the impact of adding bisphosphonates before or after parathyroidectomy on skeletal outcomes, revealed that parathyroidectomy was associated with a lower risk of fractures (HR: 0.55, 95% CI: 0.35-0.84) (19). In a cohort study, Seib et al found that older patients with primary hyperparathyroidism treated with parathyroidectomy had a lower incidence of fractures than patients receiving non-surgical care (HR: 0.78; 95% CI: 0.76-

0.80) and hip fractures (HR: 0.76; 95% CI: 0.72-0.79) after parathyroidectomy (11). In a follow-up cohort study, Zheng et al demonstrated that, in comparison to the control group, a successful parathyroidectomy was linked to a lower risk of hip fractures (HR: 0.43; 95% CI: 0.27–0.68) and any fracture (HR: 0.68; 95% CI: 0.57–0.82) (20). Every study that was previously mentioned was condensed. They illustrated fractures by lowering the cohort's risk and showed how parathyroidectomy lowers the risk of hip fractures. According to the current study, parathyroidectomy notably lowers the risk of hip and fracture fractures. Given that parathyroidectomy is a treatment option for primary hyperparathyroidism, which is known to induce bone resorption, it stands to reason that this procedure would reduce the likelihood of bone fractures.

There was no difference in the overall fracture risk (RR: 1.2, 95% CI: 0.53–2.75), non-vertebral fracture risk (RR: 1.22, 95% CI: 0.58–2.59), or vertebral fracture risk (RR: 1.37, 95% CI: 0.69–2.72) between the medical management group and the parathyroidectomy group, according to the meta-analysis results by Cironi et al in patients with mild primary hyperparathyroidism (26). There was no difference in fracture risk between parathyroidectomy and active surveillance in a meta-analysis conducted by Anagnostis et al to evaluate the effects of parathyroidectomy versus active surveillance in patients with mild asymptomatic primary hyperparathyroidism (27). These studies results' and the current study's findings disagreed. There was no difference in fracture risk between parathyroidectomy and other treatment methods, possibly because individuals with mild primary hyperparathyroidism were included in the previous meta-analysis; nevertheless, the current meta-analysis did not impose any restrictions on the degree of primary hyperparathyroidism at the time of the search.

## Conclusion

Individuals with primary hyperparathyroidism who have parathyroidectomy have been shown to have a lower fracture risk, especially hip fractures. Notably, despite their late age, individuals over 70 showed a greater benefit from the surgery regarding reduced fracture risk; moreover, fracture incidence was lower in patients with primary hyperparathyroidism who received parathyroidectomy in the United States. For the primary hyperparathyroidism treatment, parathyroidectomy is advised over alternative therapeutic options.

## Limitations of the study

- No information was provided about the length of primary hyperparathyroidism in the reviewed studies.
- There was no information about the gender of patients who underwent parathyroidectomy.
- The severity of primary hyperparathyroidism was not specified in the reviewed studies.

- Some studies did not specify the sample size of the comparison group.
- All of the studies were of the cohort type.
- Only three nations were covered by the published studies.

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## Authors' contribution

**Conceptualization:** Mojtaba Farhadi and Samad Samadzadeh

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**Investigation:** Mohammadreza Naderi and Reza Noktehsanj.

**Methodology:** Seyed Sohrab Vahdati and Hediye Mesbahi.

**Project Management:** Mobin Forghan.

**Resources:** All authors.

**Supervision:** Mojtaba Farhadi.

**Validation:** Hediye Mesbahi and Shahab Emamieh.

**Visualization:** Shahab Emamieh.

**Writing—original draft:** All authors.

**Writing—reviewing and editing:** All authors.

## Conflicts of interest

The authors declare that they have no competing interests.

## Ethical issues

This investigation was conducted in accordance with the PRISMA checklist, and its protocol has been registered on the PROSPERO website (ID: [CRD42024564707](https://doi.org/10.1111/CRD4.2024564707)) and the Research Registry website (Unique Identifying Number (UIN): [reviewregistry1854](https://doi.org/10.1111/reviewregistry1854)). Besides, the authors have observed ethical issues (including plagiarism, data fabrication, and double publication).

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