Parathyroidectomy for adults with primary hyperparathyroidism

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[Intervention Review]

Parathyroidectomy for adults with primary hyperparathyroidism

Joseph M Pappachan[1,2,3], Ian M Lahart[4], Ananth K Viswanath[5], Farzad Borumandi[6], Ravinder Sodi[7], Maria-Inti Metzendorf[8], Brenda Bongaerts[8]

[1]Department of Endocrinology & Metabolism, Lancashire Teaching Hospitals NHS Trust, Preston, UK. [2]Faculty of Science, Manchester Metropolitan University, Manchester, UK. [3]University of Manchester Medical School, Manchester, UK. [4]Faculty of Education, Health and Wellbeing, University of Wolverhampton, Walsall, UK. [5]Endocrinology, New Cross Hospital, Wolverhampton, UK. [6]Department of Oral and Maxillofacial Surgery, University Hospitals Sussex NHS Foundation Trust, St. Richard's Hospital, Chichester and Worthing Hospital, Worthing, UK. [7]Biochemistry, Pathology Department, Broomfield Hospital, Mid & South Essex NHS Foundation Trust, Chelmsford, UK. [8]Institute of General Practice, Medical Faculty of the Heinrich-Heine University Düsseldorf, Düsseldorf, Germany

Contact: Joseph M Pappachan, drpappachan@yahoo.co.in.

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ABSTRACT

Background

Primary hyperparathyroidism (PHPT), a disorder in which the parathyroid glands produce excessive amounts of parathyroid hormone, is most common in older adults and postmenopausal women. While most people with PHPT are asymptomatic at diagnosis, symptomatic disease can lead to hypercalcaemia, osteoporosis, renal stones, cardiovascular abnormalities and reduced quality of life. Surgical removal of abnormal parathyroid tissue (parathyroidectomy) is the only established treatment for adults with symptomatic PHPT to prevent exacerbation of symptoms and to be cured of PHPT. However, the benefits and risks of parathyroidectomy compared to simple observation or medical therapy for asymptomatic and mild PHPT are not well established.

Objectives

To evaluate the benefits and harms of parathyroidectomy in adults with PHPT compared to simple observation or medical therapy.

Search methods

We searched CENTRAL, MEDLINE, LILACS, ClinicalTrials.gov and WHO ICTRP from their date of inception until 26 November 2021. We applied no language restrictions.

Selection criteria

We included randomised controlled trials (RCTs) comparing parathyroidectomy with simple observation or medical therapy for the treatment of adults with PHPT.

Data collection and analysis

We used standard Cochrane methods. Our primary outcomes were 1. cure of PHPT, 2. morbidity related to PHPT and 3. serious adverse events. Our secondary outcomes were 1. all-cause mortality, 2. health-related quality of life and 3. hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis. We used GRADE to assess the certainty of the evidence for each outcome.

Main results

We identified eight eligible RCTs that included 447 adults with (mostly asymptomatic) PHPT; 223 participants were randomised to parathyroidectomy. Follow-up duration varied from six months to 24 months.

Of the 223 participants (37 men) randomised to surgery, 164 were included in the analyses, of whom 163 were cured at six to 24 months (overall cure rate 99%). Parathyroidectomy compared to observation probably results in a large increase in cure rate at six to 24 months follow-up: 163/164 participants (99.4%) in the parathyroidectomy group and 0/169 participants in the observation or medical therapy group were cured of their PHPT (8 studies, 333 participants; moderate certainty).

No studies explicitly reported intervention effects on morbidities related to PHPT, such as osteoporosis, osteopenia, kidney dysfunction, urolithiasis, cognitive dysfunction or cardiovascular disease, although some studies reported surrogate outcomes for osteoporosis and cardiovascular disease. A post-hoc analysis revealed that parathyroidectomy, compared to observation or medical therapy, may have little or no effect after one to two years on bone mineral density (BMD) at the lumbar spine (mean difference (MD) 0.03 g/cm^2,95% CI −0.05 to 0.12; 5 studies, 287 participants; very low certainty). Similarly, compared to observation, parathyroidectomy may have little or no effect on femoral neck BMD after one to two years (MD −0.01 g/cm^2, 95% CI −0.13 to 0.11; 3 studies, 216 participants; very low certainty). However, the evidence is very uncertain for both BMD outcomes. Furthermore, the evidence is very uncertain about the effect of parathyroidectomy on improving left ventricular ejection fraction (MD −2.38%, 95% CI −4.77 to 0.01; 3 studies, 121 participants; very low certainty).

Four studies reported serious adverse events. Three of these reported zero events in both the intervention and control groups; consequently, we were unable to include data from these three studies in the pooled analysis. The evidence suggests that parathyroidectomy compared to observation may have little or no effect on serious adverse events (RR 3.35, 95% CI 0.14 to 78.60; 4 studies, 168 participants; low certainty).

Only two studies reported all-cause mortality. One study could not be included in the pooled analysis as zero events were observed in both the intervention and control groups. Parathyroidectomy compared to observation may have little or no effect on all-cause mortality, but the evidence is very uncertain (RR 2.11, 95% CI 0.20 to 22.60; 2 studies, 133 participants; very low certainty).

Three studies measured health-related quality of life using the 36-Item Short Form Health Survey (SF-36) and reported inconsistent differences in scores for different domains of the questionnaire between parathyroidectomy and observation.

Six studies reported hospitalisations for the correction of hypercalcaemia. Two studies reported zero events in both the intervention and control groups and could not be included in the pooled analysis. Parathyroidectomy, compared to observation, may have little or no effect on hospitalisation for hypercalcaemia (RR 0.91, 95% CI 0.20 to 4.25; 6 studies, 287 participants; low certainty). There were no reported hospitalisations for renal impairment or pancreatitis.

Authors' conclusions

In accordance with the literature, our review findings suggest that parathyroidectomy, compared to simple observation or medical (etidronate) therapy, probably results in a large increase in cure rates of PHPT (with normalisation of serum calcium and parathyroid hormone levels to laboratory reference values). Parathyroidectomy, compared with observation, may have little or no effect on serious adverse events or hospitalisation for hypercalcaemia, and the evidence is very uncertain about the effect of parathyroidectomy on other short-term outcomes, such as BMD, all-cause mortality and quality of life. The high uncertainty of evidence limits the applicability of our findings to clinical practice; indeed, this systematic review provides no new insights with regard to treatment decisions for people with (asymptomatic) PHPT. In addition, the methodological limitations of the included studies, and the characteristics of the study populations (mainly comprising white women with asymptomatic PHPT), warrant caution when extrapolating the results to other populations with PHPT.

Large-scale multi-national, multi-ethnic and long-term RCTs are needed to explore the potential short- and long-term benefits of parathyroidectomy compared to non-surgical treatment options with regard to osteoporosis or osteopenia, urolithiasis, hospitalisation for acute kidney injury, cardiovascular disease and quality of life.

PLAIN LANGUAGE SUMMARY

Parathyroidectomy for adults with primary hyperparathyroidism

What is primary hyperparathyroidism?

Primary hyperparathyroidism (PHPT) is a disorder in which the parathyroid glands (four glands located near or on the thyroid in the neck) become enlarged and produce too much parathyroid hormone. The disease affects 1% of adults. Overproduction of parathyroid hormone disrupts calcium levels in the body, which can lead to various other health issues, such as osteoporosis (a health condition that weakens bones) and bone fractures, chronic kidney disease, cardiovascular disease, and cognitive dysfunction (decline in mental ability), along with a reduced health-related quality of life.

How is hyperparathyroidism treated?

Parathyroidectomy (surgical removal of the abnormal parathyroid gland or glands) is a well-established treatment option for people with PHPT. Parathyroidectomy is expected to cure PHPT and improve the unwanted complications of the disease.

What did we want to find out?

We wanted to know if parathyroidectomy was better than medical therapy or simple observation for curing mild PHPT with no symptoms and improving disease-associated complications such as osteoporosis, low bone density, kidney stones, kidney disease, cardiovascular disease (conditions affecting the heart and blood vessels) and cognitive dysfunction. We also wanted to determine if parathyroidectomy had any unwanted effects and whether it improved the health-related quality of life of people with PHPT.

What did we do?

We searched for randomised controlled trials (RCTs) that examined parathyroidectomy compared to non-surgical treatment options in adults with PHPT. We compared and summarised the results of the studies and rated our confidence in the evidence based on factors such as study methods and sizes.

What did we find?

We identified only eight RCTs, which enrolled 433 adults. In total, 164 adults had a parathyroidectomy, and 163 (99%) were cured after six to 24 months. Compared to medical therapy or simple observation, parathyroidectomy probably results in a large increase in cure rates. We have no information on the effect of parathyroidectomy on osteoporosis or cardiovascular disease. However, the included studies reported measures that are closely related to these conditions. Parathyroidectomy may have little or no effect on the bone mineral density of the lower spine and hip after one to two years, but we are very uncertain about the results. The evidence on the effect of parathyroidectomy on left ventricular ejection fraction (the percentage of blood leaving the left heart chamber at each heartbeat) was also very uncertain. Parathyroidectomy, compared to observation, may have little or no effect on unwanted severe events or the occurrence of hospitalisation for the correction of abnormally high calcium levels in the blood. The evidence is very uncertain about the impact of parathyroidectomy on death from any cause. Finally, three RCTs reported results for health-related quality of life. The findings differed widely, and we are uncertain about the effect of parathyroidectomy on health-related quality of life compared to observation.

What are the limitations of the evidence?

We are moderately confident in the evidence on cure rates because the reports of the RCTs did not contain enough information to prove their methods were reliable. However, we have little or very little confidence in the other results because the methods may have been unreliable, the studies did not measure complications of PHPT directly, and the studies enrolled few people.

How up-to-date is the evidence?

The evidence is up to date to 26 November 2021.

SUMMARY OF FINDINGS

Summary of findings 1. Parathyroidectomy compared to observation in adults with primary hyperparathyroidism

Parathyroidectomy compared to observation for primary hyperparathyroidism

Patient or population: people with primary hyperparathyroidism

Settings: inpatients/outpatient follow-up

Intervention: parathyroidectomy

Comparison: observation

Outcomes	Anticipated absolute effects (95% CI)*		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with observation	Risk with parathyroidectomy				
Cure of PHPT Assessed with: normalisation of hypercalcaemia Follow-up: 6–24 months	0 per 1000	994 per 1000 (163 to 164)	**RR 0.04** (0.02 to 0.08)	333 (8)	⊕⊕⊕⊝ **Moderate**[a]	—
Morbidity related to PHPT Assessed with: osteoporosis, kidney dysfunction/urolithiasis, cognitive function and cardiovascular disease Follow-up: 12–24 months	Mean BMD of the lumbar spine ranged across control groups from 0.68 to 1.12 g/cm^2.	Mean BMD at the lumbar spine in the intervention groups was on average **0.03 g/cm^2 higher** (95% CI 0.05 lower to 0.12 higher).	—	287 (5)	⊕⊝⊝⊝ **Very low**[b]	—
	Mean BMD of the femoral neck ranged across control groups from 0.79 to 0.82 g/cm^2.	Mean BMD at the femoral neck in the intervention groups was on average **0.01 g/cm^2 lower** (95% CI	—	216 (3)	⊕⊝⊝⊝ **Very low**[b]	—

		0.13 lower to 0.11 g/cm^2 higher).				
	Mean LVEF ranged across control groups from 65.7 to 68.0%.	Mean LVEF in the intervention groups was on average **2.38% lower** (95% CI 4.77% lower to 0.01% higher).	—	121 (3)	⊕⊝⊝⊝ **Very low**[c]	Ambrogini 2007 did not provide mean values for the echocardiographic parameters but reported that all parameters were within the normal range and did not change during follow-up in either group. We could not include this study in the statistical analysis.
Serious adverse events Follow-up: 6–24 months	0 per 1000	12 per 1000 (1 to 164)	**RR3.35** (0.14 to 78.60)	168 (4)	⊕⊕⊝⊝ **Low**[d]	The pooled relative effect is based on only 1 study, the other three could not be included as they had zero events in both intervention and control group.
All-cause mortality Follow-up: 6–24 months	15 per 1000	31 per 1000 (3 to 339)	**RR2.11** (0.20 to 22.60)	133 (2)	⊕⊝⊝⊝ **Very low**[e]	The pooled relative effect is based on only 1 study, the other study could not be included as it had zero events in both intervention and control group.
Health-related quality of life Assessed with: SF-36 scores (higher scores indicate better quality of life) Follow-up: 12–24 months	See comment	See comment	See comment	195 (3)	⊕⊝⊝⊝ **Very low**[c]	1 study observed no differences in scores for in any SF-36 domains between groups; 1 study reported higher scores for the parathyroidectomy group in 2 domains (social and emotional role function); 1 study showed higher scores for the parathyroidectomy group in 4 domains (bodily pain, general health, vitality and mental health).
Hospitalisation for hypercalcaemia, renal impairment or pancreatitis Follow-up: 6–24 months	**54 per 1000**	**35 per 1000** **(1 to 164)**	**RR 0.91** (0.20 to 4.25)	287(6)	⊕⊕⊝⊝ **Low**[d]	All reported hospitalisations were due to (recurrent) hypercalcaemia. The pooled relative effect was based on 4 studies, the other 2 could not be included as they had zero events in both intervention and control group.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BMD: bone mineral density; **CI:** confidence interval; **LVEF:** left ventricular ejection fraction; **MD:** mean difference; **PHPT:** primary hyperparathyroidism; **RR:** risk ratio; **SF-36:** 36-Item Short Form Health Survey.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

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[a] Downgraded one level due to unclear risk of bias (sequence generation, allocation concealment and selective reporting).
[b] Downgraded three levels due to unclear risk of bias (sequence generation, allocation concealment and selective reporting), inconsistency in the direction of the effect, indirectness (surrogate outcome) and serious imprecision (small sample size).
[c] Downgraded three levels due to unclear risk of bias (sequence generation, allocation concealment and selective reporting), indirectness (surrogate outcome) and serious imprecision (small sample size).
[d] Downgraded two levels due to unclear risk of bias (sequence generation, allocation concealment and selective reporting) and imprecision (low sample size).
[e] Downgraded three levels due to high risk of bias (sequence generation, allocation concealment and lack of blinding of the outcome assessor) and serious imprecision (low median sample size).

BACKGROUND

Description of the condition

Primary hyperparathyroidism (PHPT) is an endocrine disorder that affects approximately 1% of adults; it is the third most common endocrine disorder after diabetes mellitus and hypothyroidism (Best 2017). The incidence of PHPT increases with age, and the highest prevalence (around 2%) is observed in postmenopausal women in the USA (Ning 2009). The causes of PHPT include benign parathyroid adenoma (in around 80% of cases), multi-gland disorder (multiple adenomas or multi-gland hyperplasia; in 15% to 20% of cases) and, in rare cases, parathyroid carcinoma (Bilezikian 2018). PHPT is usually associated with hypercalcaemia, elevated or high normal parathyroid hormone (PTH) concentrations, hypercalciuria, renal stones and bone demineralisation that results in osteopenia or osteoporosis. Although most people with PHPT remain asymptomatic prior to diagnosis, with only mild disease, some people may present with symptomatic hypercalcaemia, dehydration leading to acute kidney injury, fragility fractures from osteoporosis, hypertension, renal stone disease or chronic kidney disease. Elevated PTH levels result in increased bone turnover and skeletal demineralisation, and increased bone turnover leads to gradual loss of cortical bone mineral density (BMD) with relative sparing of trabecular bones and predominant osteopenia or osteoporosis of the lumbar spine, neck of femur and forearm bones (Khan 2017; Silverberg 2014). This BMD loss can lead to bone fractures at these sites even with minimal trauma (fragility fractures), which increases morbidity and premature mortality risk, especially in older people. Alterations in calcium metabolism and bone turnover can result in hypercalcaemia, hypercalciuria and urolithiasis in a large proportion of people with PHPT. Research suggests that 10% to 20% of individuals with PHPT have urolithiasis (Cipriani 2015; Verdelli 2017) and that 40% to 60% have hypertension, which increases the risk of cardiovascular morbidity and premature mortality (Pepe 2017). Studies have also associated PHPT with psychoneurological and cognitive dysfunction (Kreidieh 2013; Trombetti 2016). In some people with the disease, serum calcium levels may be consistently within the normal laboratory range; these cases are known as normocalcaemic PHPT. The metabolic and end-organ complications in these individuals may be similar to those with classical PHPT (Yener 2016). Overall, PHPT is associated with excess morbidity risk and a higher risk of premature mortality (Pepe 2017).

Description of the intervention

Surgical removal of abnormal parathyroid tissue (parathyroidectomy) is an established treatment for people with proven PHPT, especially those with symptomatic disease. Operative resection of the diseased parathyroid gland(s) removes the source of excess PTH production and thereby cures the disease in most individuals (Kreidieh 2013). International consensus recommends that all people with symptomatic PHPT should be considered for parathyroidectomy. Parathyroidectomy is an effective treatment to prevent or improve end-organ complications such as abnormal BMD, urolithiasis, renal failure and possibly cardiovascular disease. Additionally, a curative parathyroidectomy may improve neurocognitive functions (Silverberg 2014). Studies have associated the intervention with improvements in functional capacity and health-related quality of life (HRQOL), even in individuals with asymptomatic PHPT (Ambrogini 2007; Morris 2010). Based on consensus recommendations, an international task force of experts updated the guidelines on the management of PHPT in 2022 (Bilezikian 2022). This consensus recommends parathyroidectomy for people with PHPT who meet any of the following criteria.

- Age under 50 years
- Serum calcium levels greater than 1 mg/dL (0.25 mmol/L) above the upper limit of the normal laboratory reference range
- BMD by T-score of −2.5 or lower at the lumbar spine, femoral neck, total hip or distal third of radius for postmenopausal women or men older than 50 years
- Low trauma fragility fracture
- Glomerular filtration rate (GFR) of less than 60 mL/min or a consistent annual decline in calculated GFR of 3 mL/min over the years to below 60 mL/min
- Kidney stones, nephrocalcinosis or high risk for kidney stone formation
- Urinary calcium of more than 250 mg/day in women or more than 300 mg/day in men

Most parathyroid tumours are eutopic in the neck region, but in 6% to 16 % of cases, one or more hyperfunctioning parathyroid glands are in an ectopic location such as the mediastinum (Roy 2013). Prior to surgery, the abnormal parathyroid gland is localised using technetium ^{99m}Tc-Sestamibi Scintigraphy, an ultrasound scan, or a combination of the two. The sestamibi scan has relatively good sensitivity for locating hyperfunctioning parathyroid glands, as well as single and multiple parathyroid adenomas (Borumandi 2019). The accurate localisation of parathyroid tumours aids with surgical planning and reduces surgical time and associated morbidity. Further imaging modalities have been developed to improve the precise localisation of parathyroid tumours. Multi-phase or four-dimensional computed tomography (4-D CT) scans are performed for the visualisation of parathyroid tumours not detectable on conventional imaging (Kuzminski 2018; Borumandi 2019). A 4-D CT scan of the neck is also useful as an imaging modality for the localisation of parathyroid adenomas, especially when other imaging modalities fail to identify the diseased gland and in people with recurrent PHPT (Kattar 2022). The reported sensitivity of a 4-D CT scan for localising parathyroid adenomas is higher than that of the sestamibi scan.

The targeted approach for parathyroidectomy is the ideal treatment option for people with well-localised disease identified in preoperative parathyroid imaging (Khan 2017). People with no clear localisation of the parathyroid tumour undergo a bilateral exploration of the neck. Both the targeted approach and bilateral neck exploration can achieve high cure rates, although success depends on surgical expertise (Wilhelm 2016).

Targeted approach for parathyroidectomy

In people with well-localised parathyroid tumours, surgical exploration is limited to the tumour site. Surgeons can confirm the correct removal of the parathyroid tumour driving the PHPT through intraoperative monitoring of PTH levels, which should drop by more than 50% within 20 minutes of resection to normal laboratory reference values (Graceffa 2022). If elevated PTH falls below 40 pg/mL within 15 minutes of parathyroidectomy, cure of PHPT is very likely (Claflin 2019; Graceffa 2022). Intraoperative PTH monitoring also helps to detect multi-gland disease and plays an important role in cases of equivocal preoperative localisation that require bilateral neck exploration (Borumandi 2019, Dobrinja 2017).

Common approaches to minimally invasive parathyroidectomy involve open focal mini-incision (70% of cases), video-assisted approach (around 20% of cases; Alesina 2013) or total endoscopic approach (around 10% of cases), depending on the clinical situation and the surgeons' ability to perform the technique (Brunaud 2016; Taieb 2013). Gagner 1996 first described total endoscopic parathyroidectomy with subsequent refinements of the technique to current day surgical practice. Video-assisted parathyroidectomy, first described in 1997, also involves the use of an endoscope but does not require gas to view the surgical field (Miccoli 1997). To avoid a neck scar, surgeons occasionally use extra-cervical endoscopic approaches through the chest wall, breast, oral cavity, retro-auricular region or axilla. Robotic parathyroidectomy that places a computer interface between patient and surgeon to optimise the feasibility and quality of surgery is a new approach in minimally invasive parathyroidectomy (Garas 2015).

Bilateral neck exploration for parathyroidectomy

Until the late 1970s, bilateral neck exploration was the standard approach to parathyroidectomy in people with PHPT; it was successful in around 97% of cases, with reported complication rates of 1% to 2% (Brunaud 2016). Today, surgeons use bilateral neck exploration in cases of equivocal preoperative localisation, lack of clear surgical target, and four-gland hyperplasia of the parathyroid gland with familial or genetic disorders and concomitant thyroid disease. The surgery involves the exploration of all four parathyroid glands to locate the diseased gland under general anaesthesia with a slightly larger neck incision compared to the targeted approach.

Adverse effects of the intervention

In general, parathyroidectomy is associated with low rates of surgical and postoperative complications. One systematic review of 82 observational studies and six randomised controlled trials (RCTs) at moderate risk of bias concluded that targeted parathyroidectomy and bilateral neck exploration are both effective techniques for surgical treatment of PHPT, though the safety profile of the targeted approach was slightly superior to bilateral neck exploration (Singh 2016a). The review reported an increased risk of hypocalcaemia in the bilateral neck exploration group compared to the minimally invasive parathyroidectomy group (13.6% versus 2.3%, $P < 0.001$). Postoperative hypocalcaemia in people who undergo bilateral neck exploration is caused by iatrogenic hypoparathyroidism. Singh 2016a also reported a lower risk of injury to the recurrent laryngeal nerve after the targeted approach compared to bilateral neck exploration (0.3% versus 0.9%). This complication can cause temporary or permanent postoperative hoarseness. The risk of infection was comparable in the two groups (0.5% in both), as was premature mortality (0.1% with a targeted approach versus 0.5% with a bilateral neck exploration).

Another important complication of parathyroidectomy is haematoma formation, which may cause neck pain, respiratory distress, dysphagia and increased drainage from the surgical wound (Kreidieh 2013). Hungry bone syndrome – associated with severe and prolonged postoperative hypocalcaemia requiring intense medical management – can complicate some cases of severe PHPT after parathyroidectomy (Witteveen 2013). Although postoperative hypoparathyroidism with symptomatic hypocalcaemia is usually transient, some cases may warrant long-term follow-up and medical management (Fyrsten 2016).

Persistent PHPT with postoperative hypercalcaemia within six months of parathyroidectomy occurs in up to 5% of individuals because of incomplete removal of abnormal parathyroid tissue (Silverberg 2014). Recurrent disease (new-onset PHPT) can also occur in up to 8% of people with sporadic parathyroid adenomas after three to 11 years. One cause of recurrent or persistent disease is ectopic parathyroid tumours, which can be detected on a localisation scan prior to repeat surgery (Khan 2017; Silverberg 2014). If the tumour is well localised, the best approach to reoperation is targeted parathyroidectomy; otherwise, the recommended technique is unilateral exploration on the contralateral side to previous exploration. The reported success rate of reoperation exceeds 90%, especially when the abnormal parathyroid tissue is localised before surgery and when parathyroidectomy is coupled with intraoperative PTH assay. Postoperative complications, including hyperparathyroidism, are higher in people undergoing reoperation (Khan 2017; Silverberg 2014).

How the intervention might work

As PHPT is a consequence of excess production of PTH from one or more of the parathyroid glands, complete surgical removal of the abnormal parathyroid tissues is expected to cure the disease. Biochemical evidence of normalised PTH levels with resolution of hypercalcaemia after parathyroidectomy usually indicates a cure of the disease. In individuals with normocalcaemic PHPT, normalisation of elevated PTH levels usually indicates a cure. Regardless of the surgical technique used, studies have observed high cure rates in people who have undergone successful parathyroidectomy (Anagnostis 2020; Khan 2017; Kreidieh 2013; Silverberg 2014; Singh 2016b). Although there is a small risk of disease recurrence even in sporadic cases of PHPT, the health benefits of successful parathyroidectomy observed during postoperative follow-up provides a clear rationale for recommending this treatment option in appropriately selected patients.

Why it is important to do this review

The prevalence of PHPT increases steadily with age, and older people tend to develop more complications related to the disease compared to younger people (Oltmann 2014). Improved healthcare has led to a marked increase in the proportion of older people in the global population. The cumulative risk of adverse hormonal effects from elevated PTH levels on target organs increases with the duration of PHPT, and older age groups are more vulnerable to end-organ complications related to the disease, such as osteoporosis, kidney disease, cognitive dysfunction and cardiovascular morbidity (Bilezikian 2018). Increased healthcare burden and related economic loss are the consequences of such complications.

Multiple observational studies and RCTs have shown that parathyroidectomy improves bone-related health outcomes in PHPT (Axelsson 2022; Hansen 2012; Khosla 1999; Koumakis 2013; Lundstam 2015; Nilsson 2017; Seib 2022; Vestergaard 2000; Yeh 2016). Other studies have demonstrated the benefits of this intervention for preventing renal function deterioration (Tassone

2015), improving cardiovascular morbidity (Best 2017; McMahon 2015), and improving HRQOL (Aberg 2015).

Although there are a few published systematic reviews on this topic, data suggest moderate health benefits of parathyroidectomy in people with PHPT in terms of improvements in BMD, cognitive functions and HRQOL (Anagnostis 2020; Cheng 2015; McMahon 2015; Singh 2016a; Singh 2016b). However, there are still uncertainties regarding the overall health benefits of parathyroidectomy, the populations that benefit most from surgery, the severity of hyperparathyroidism that should represent a definite indication for parathyroidectomy, and the economic impact of surgery over medical therapy. Therefore, there is a need to compile the latest RCT evidence to examine the benefits of parathyroidectomy as a treatment option for managing PHPT.

OBJECTIVES

To evaluate the benefits and harms of parathyroidectomy in adults with PHPT compared to simple observation or medical therapy.

METHODS

Criteria for considering studies for this review

Types of studies

We included only RCTs.

Types of participants

We limited participants to adults (aged 18 years or older) with PHPT who underwent parathyroidectomy for the first time. We excluded studies of people who had secondary hyperparathyroidism, tertiary hyperparathyroidism or different types of hyperparathyroidism (if the study did not provide separate results for each type).

We defined PHPT by one or more of the following diagnostic criteria (Bilezikian 2018).

- Elevated or high normal PTH levels with serum calcium levels above normal laboratory reference values
- Elevated serum PTH with normal calcium levels and exclusion of secondary causes for elevation of PTH (mainly decreased calcium intake, vitamin D deficiency, renal insufficiency and hypercalciuria of renal origin)
- Exclusion of secondary causes for hyperparathyroidism (e.g. chronic renal insufficiency and vitamin D deficiency)

Types of interventions

We included the following interventions.

- Minimally invasive parathyroidectomy (focal mini-incision, video-assisted approach, totally endoscopic or robotic approach)
- Parathyroidectomy by bilateral surgical neck exploration

We considered the following controls.

- Observation (biochemical, clinical and imaging follow-up without surgical interventions)
- Pharmacotherapy such as bisphosphonates and calcium-lowering drugs (calcimimetics) without parathyroidectomy

For comparing interventions with control interventions, we combined both the interventions and the comparators. In sensitivity analyses, we planned to compare the different parathyroidectomy surgical techniques separately. We did not plan to analyse the control interventions separately, since neither observation nor pharmacotherapy has the goal of curing PHPT.

Any concomitant interventions had to be the same in the intervention and control groups to establish fair comparisons. If a study included multiple arms, we included all study arms that met our inclusion criteria.

The minimum duration of follow-up was six months after the surgical procedure.

Types of outcome measures

Had we identified any studies that reported none of our primary or secondary outcomes, we would have provided some basic information in an additional table but not included the studies in our analysis.

Primary outcomes

- Cure of PHPT
  - Defined as improvement of hypercalcaemia and elevated PTH levels to normal laboratory reference values
  - Measured at six months or later after randomisation
- Morbidity related to PHPT
  - For example, improvement or lack of progression of established osteoporosis or osteopenia after parathyroidectomy, lack of progression or development of kidney dysfunction or nephrolithiasis/urolithiasis, improvement or lack of progression of cognitive dysfunction, improvement or lack of worsening of cardiovascular disease
  - Measured at six months or later after randomisation
- Serious adverse events
  - For example, postoperative bleeding requiring prolonged hospitalisation or surgical drainage insertion, hypocalcaemia, local haematoma, voice change from injury to recurrent laryngeal nerve, infection
  - Measured at any time after randomisation

Secondary outcomes

- All-cause mortality
  - Defined as death from any cause
  - Measured at any time after randomisation
- HRQOL
  - Evaluated by a validated instrument such as the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36)
  - Short-term: measured up to six months after randomisation; long-term: measured more than six months after randomisation
- Hospitalisation
  - Due to hypercalcaemia, defined as calcium level more than 3.0 mmol/L
  - Due to acute renal impairment, defined as requiring intravenous hydration or dialysis
  - Due to pancreatitis, defined as a systemic inflammatory response in the context of severe acute upper abdominal

pain with biochemical confirmation (elevated pancreatic enzymes)
  - Measured within six months of randomisation

Search methods for identification of studies

Electronic searches

We searched the following sources from inception to 26 November 2021 with no restrictions on language of publication.

- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO)
- MEDLINE Ovid (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE; from 1946)
- LILACS (Latin American and Caribbean Health Science Information database)
- ClinicalTrials.gov (www.clinicaltrials.gov)
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; www.who.int/trialsearch/)

We did not include Embase in our search, as RCTs indexed in Embase are now prospectively added to CENTRAL via a highly sensitive screening process (CENTRAL 2021). The search strategies for all databases are available in Appendix 1.

Searching other resources

We tried to identify other potentially eligible or ancillary publications by searching the reference lists of included studies, systematic reviews and health technology assessment reports. In addition, we contacted authors of included to identify any additional information on the retrieved studies and establish whether we may have missed further studies.

We did not include studies published only as abstracts or conference proceedings for data extraction unless full data were available from study authors, because these types of publication do not meet the CONSORT requirements ("an evidence-based, minimum set of recommendations for reporting randomised trials"; CONSORT 2016; Scherer 2007). We had planned to present information on abstracts or conference proceedings in the Characteristics of studies awaiting classification table.

Data collection and analysis

Selection of studies

After deduplication, two review authors (JMP and AKV) independently screened the abstract and title of every record retrieved by the searches. We obtained the full text of all potentially eligible records and screened them against out eligibility criteria. We resolved any disagreements through consensus or by recourse to a third review author (RS). If we could not resolve a disagreement, we categorised the study as 'awaiting classification' and contacted the study authors for clarification. We created a PRISMA flow diagram showing the study selection process (Page 2021). We listed all articles excluded after full-text assessment in the Characteristics of excluded studies table and provided the reasons for exclusion (Page 2021).

Data extraction and management

Two review authors (JMP and RS) independently extracted the data from studies that met our eligibility criteria to identify key participant and intervention characteristics. We described interventions using the template for intervention description and replication (TIDieR) checklist (Hoffmann 2014; Hoffmann 2017). We provided relevant information about each trial in the Characteristics of included studies table (we summarised the checklist information for ease of reading) and in two appendices (Appendix 2; Appendix 3). We reported data on efficacy outcomes and adverse events using standardised data extraction sheets from the CMED Group. We resolved any disagreements by discussion or by consulting a third review author (AKV).

We provided information about potentially relevant ongoing studies in the Characteristics of ongoing studies table. For each included study, we searched for the protocol and reported primary, secondary and other outcomes in comparison with data in publications in a joint appendix (Appendix 4).

We emailed the authors of all included studies for additional information and presented the results of this survey in an appendix (Appendix 5).

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents or multiple reports of a primary study, we maximised the information yield by collating all available data and using the most complete data set aggregated across all known publications. For all included and excluded studies, we listed duplicate publications, companion documents, multiple reports of a primary study and other study documents (such as trial registry information) as secondary references under the study ID.

Data from clinical trials registers

We made full use of any relevant data identified in clinical trial registers such as ClinicalTrials.gov. If there was also a full publication of the study, we collated and critically appraised all available data. Had we identified any studies marked completed in a clinical trial register but with no available results, we would have added them to the Characteristics of studies awaiting classification table.

Assessment of risk of bias in included studies

Two review authors (JMP and IML) independently assessed the risk of bias in each included study. We resolved any disagreements by consensus or by consulting a third review author (AKV). We assessed the following domains.

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other potential sources of bias

We judged the risk of bias domains as 'low risk', 'high risk' or 'unclear risk', according to the recommendations presented in the Cochrane *Handbook for Systematic Reviews of Interventions*

(Higgins 2011). We assessed risk of performance bias, detection bias and attrition bias for each outcome individually. If the information contained in study publications, study protocols or other identified sources was insufficient to judge risk of bias, we contacted the study authors for further details. We created a risk of bias graph and a risk of bias summary figure to illustrate out judgements.

We considered HRQOL to be a self-reported outcome.

We defined the following outcomes as investigator-assessed.

- Cure of PHPT
- Morbidity related to PHPT
- All-cause mortality
- Serious adverse events
- Hospitalisation for hypercalcaemia, renal impairment or pancreatitis

We considered that serious adverse events could be either self-reported or investigator-assessed.

Risk of bias for a study across outcomes

Some risk of bias domains, such as selection bias (random sequence generation and allocation concealment), affect the risk of bias across all outcome measures in a study. Where there was high risk bias in these domains, we marked all endpoints investigated in the associated study as being at high risk.

Risk of bias for an outcome within a study and across domains

We assessed the risk of bias for an outcome measure by including all entries relevant to that outcome (i.e. both study-level entries and outcome-specific entries). We considered low risk of bias to denote a low risk of bias for all key domains, unclear risk to denote an unclear risk of bias for one or more key domains and high risk to denote a high risk of bias for one or more key domains.

Risk of bias for an outcome across studies and across domains

We judged outcomes at low risk of bias when most information came from studies at low risk of bias, unclear risk when most information came from studies at low or unclear risk of bias, and high risk when a sufficient proportion of information came from studies at high risk of bias. We incorporated these summary assessments into our judgements about the certainty of evidence in the summary of findings table.

Measures of treatment effect

We expressed dichotomous data as risk ratios (RRs), with 95% confidence intervals (CIs). For continuous outcomes measured on the same scale (e.g. BMD in g/cm^2), we estimated the intervention effect using the mean differences (MDs) with 95% CIs. For data pooled across studies that used different instruments to measure the same outcome, we had planned to calculate standardised mean differences (SMDs) with 95% CIs, entering data on a scale with a consistent direction of effect and multiplying the MD by a representative standard deviation (SD), for example the SD from a well-known scale used by several of the studies.

Unit of analysis issues

We took into account the level at which randomisation occurred, such as for cross-over trials, cluster-randomised trials and multiple observations for the same outcome. If more than one comparison from the same study was eligible for inclusion in the same meta-analysis, we either combined groups to create a single pair-wise comparison, or we spit the 'shared' group into two or more groups so that each participant contributed data to the meta-analysis only once. While the latter approach offers some solution to adjust the precision of the comparison, it only partially overcomes this unit of analysis issue, as it does not account for correlation arising from the same set of participants being in multiple comparisons (Higgins 2022).

Had we identified any cluster-RCTs that had not appropriately adjusted for clustering, we would have inflated the variance of the intervention effects using a design effect. Calculation of a design effect involves the estimation of an intracluster correlation coefficient (ICC), as specified in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022). We would have obtained estimates of ICCs by contacting study authors or by imputing the ICC values from estimates in other included studies or from external estimates based on empirical research (e.g. Bell 2013). We had planned to examine the impact of clustering using sensitivity analyses.

Dealing with missing data

If possible, we obtained missing data from the authors of the included studies. We carefully evaluated important numerical data such as number of people screened, randomised and analysed. We investigated attrition rates (e.g. dropouts, losses to follow-up, withdrawals), and we critically appraised issues concerning missing data and use of imputation methods (e.g. last observation carried forward).

Where the SD of an outcome was not reported and we could not recreate it, we standardised by the mean of the pooled baseline SD reported in the other studies that measured the same outcome.

Where included studies did not report means and SDs for outcomes and we did not receive the necessary information from study authors, we imputed these values by estimating the mean and variance from the median, range and sample size (Hozo 2005).

We had planned to investigate the impact of imputation on meta-analyses through sensitivity analyses, reporting which studies had imputed SDs for every outcome.

Assessment of heterogeneity

In the event of substantial clinical or methodological heterogeneity, we did not report study results as the pooled effect estimate in a meta-analysis, but rather visually examined point estimates and CI overlap.

We used the I^2 statistic to estimate the degree of heterogeneity present among the studies in each analysis. If we identified substantial unexplained heterogeneity, we reported it and explored possible causes by prespecified subgroup analysis. We used the rough guide to interpretation as outlined in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions*, as follows (Higgins 2022).

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

We avoided using absolute cut-off values, but interpreted I^2 in relation to the size and direction of effects and the strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or CI of the I^2 statistic).

Assessment of reporting biases

Had we included 10 or more studies that investigated a particular outcome, we would have used funnel plots to assess small study effects. There are several possible explanations for funnel plot asymmetry, including true heterogeneity of effect with respect to study size, poor methodological design (and hence bias of small studies) and selective non-reporting (Kirkham 2010). If we create funnel plots in future updates, we will interpret the results with caution (Sterne 2011).

Data synthesis

We performed meta-analysis only if we judged the participants, interventions, comparisons and outcomes to be sufficiently similar to ensure a clinically meaningful result. Unless there was good evidence of homogeneous effects across studies of different methodological quality, we summarised data using a random-effects model (Wood 2008). We interpreted random-effects meta-analyses with due consideration for the whole distribution of effects and presented a CI. We performed statistical analyses according to the statistical guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022).

Subgroup analysis and investigation of heterogeneity

We expected the following characteristics to introduce clinical heterogeneity, and we planned to carry out the following subgroup analyses including an investigation of interactions (Altman 2003).

- Different surgical techniques
- Severity of PHPT
- Differences in the demographics of study populations such as sex, age and ethnic differences

Had we performed subgroup analyses, we would have used the formal test for subgroup interactions in Review Manager (RevMan Web 2022), acknowledging its limitations (observational nature and low power to detect differences with fewer than 10 studies per category; Higgins 2022).

Sensitivity analysis

We had planned to perform sensitivity analyses to explore the influence of risk of bias on effect sizes, as specified in the Assessment of risk of bias in included studies section.

Summary of findings and assessment of the certainty of the evidence

We presented the overall certainty of the evidence for each outcome according to the GRADE approach, which takes into account issues related to internal validity (overall risk of bias, inconsistency, imprecision, publication bias) and external validity (directness of results). Two review authors (JMP and IML) independently rated the certainty of the evidence for each outcome. We resolved any differences in rating by discussion or by consulting a third review author (RS).

We created a summary of findings table according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2022), using GRADEpro software (GRADEpro GDT). Summary of findings tables provide key information about the best estimate of the magnitude of effect (in relative terms and as absolute differences for each relevant comparison of alternative management strategies), the numbers of participants and studies addressing each important outcome, and a rating of overall confidence in effect estimates for each outcome. Our summary of findings table included all of our prespecified primary and secondary outcomes.

If meta-analysis was not possible, we presented the results in narrative format in the summary of findings table. We justified all decisions to downgrade the certainty of the evidence in informative footnotes, following GRADE guidelines (Santesso 2016; Santesso 2020).

RESULTS

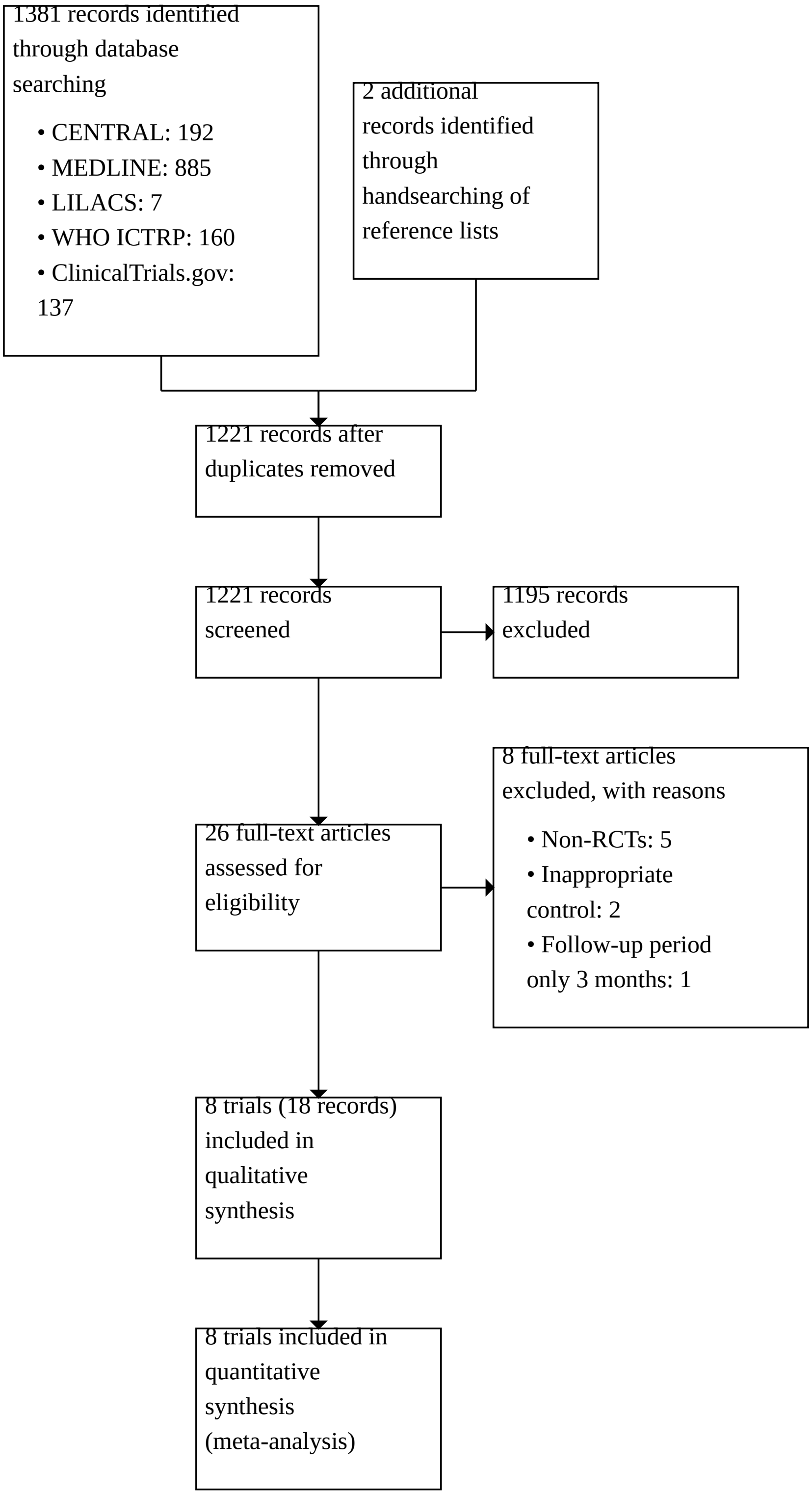
Description of studies

For a detailed description of studies, see the Characteristics of included studies, Characteristics of excluded studies, and Characteristics of ongoing studies tables.

Results of the search

The combined search strategy identified 1126 records after deduplication (Figure 1). After screening the titles and abstracts, we assessed 26 full-text publications for eligibility. Eighteen publications reporting the results of eight RCTs met our inclusion criteria (Almqvist 2004; Ambrogini 2007; Bollerslev 2007; Horiuchi 2002; Morris 2010; Pepe 2013; Pepe 2018; Talpos 2000). We identified one ongoing clinical trial (EudraCT2013-005027-16); we may include the results in future updates.

Figure 1. The Search strategy and the study flow diagram



Included studies

Comparisons

Seven studies compared parathyroidectomy with observation (Almqvist 2004; Ambrogini 2007; Bollerslev 2007; Morris 2010; Pepe 2013; Pepe 2018; Talpos 2000). Horiuchi 2002 compared parathyroidectomy with medical therapy (etidronate).

Overview of study populations

The studies included 447 participants in total; 223 participants were randomised to parathyroidectomy, 215 to observation and nine to etidronate medical therapy. The sample sizes of individual studies ranged from 21 to 191 people.

See Characteristics of included studies and Table 1.

Study design

All eight studies were parallel-group RCTs.

Seven studies were single-centre RCTs (Almqvist 2004; Ambrogini 2007; Horiuchi 2002; Morris 2010; Pepe 2013; Pepe 2018; Talpos 2000); Bollerslev 2007 was a multi-centre RCT conducted in three countries.

Because the intervention was a surgical procedure, no studies could blind participants or personnel. Five studies did not report blinding conditions (Almqvist 2004; Horiuchi 2002; Pepe 2013; Pepe 2018; Talpos 2000). Two studies mentioned blinding of outcome assessors (Ambrogini 2007; Morris 2010).

Participant recruitment took place between 1994 and 2015. The duration of follow-up ranged from six months to 24 months. Pepe 2018 had a one-month run-in period with vitamin D (cholecalciferol) and calcium supplementation for some participants in both groups. No study was terminated early.

Settings

This review compiles evidence from RCTs performed in 14 hospitals in seven countries.

Three RCTS were conducted in Italy (Ambrogini 2007; Pepe 2013; Pepe 2018), two in the USA (Morris 2010; Talpos 2000), one in Sweden (Almqvist 2004) and one in Japan (Horiuchi 2002). The multi-centre study was conducted in Denmark, Sweden and Norway (Bollerslev 2007).

Participants

Women accounted for 75% to 100% of the study populations. The mean age of participants ranged from 59 years to 77 years at baseline. All studies except Morris 2010 mentioned the ethnicity of participants. All studies reported data on either cointerventions or comorbidities, and two studies reported data for both cointerventions and comorbidities (Almqvist 2004; Pepe 2018).

The mean serum calcium levels in participants randomised to parathyroidectomy ranged from 2.59 mmol/L to 2.74 mmol/L. The participants in the control arm had comparable mean serum calcium levels, ranging from 2.56 mmol/L to 2.73 mmol/L. No studies provided information on the duration of PHPT.

Most participants had mild PHPT, and few met the current criteria for parathyroidectomy (e.g. osteoporosis and calcium levels of 2.85 mmol/L or above).

Diagnosis

PHPT diagnosis was based on elevated serum calcium levels and PTH levels in plasma. Six studies described their study population as having mild or asymptomatic PHPT, Pepe 2018 did not define PHPT severity, and Pepe 2013 reported that only 3/24 participants had mild PHPT, while the rest were symptomatic.

Interventions

Five studies did not specify the surgical approach to parathyroidectomy (Almqvist 2004; Horiuchi 2002; Pepe 2013; Pepe 2018; Bollerslev 2007). In Talpos 2000, all participants underwent parathyroidectomy by bilateral neck exploration, a standard surgical approach in the absence of a parathyroid adenoma. Morris 2010 used the minimally invasive parathyroidectomy approach for all operations, which is preferred in cases of PHPT where a parathyroid adenoma is evident. Finally, in Ambrogini 2007, 20/24 participants in the intervention arm underwent minimally invasive parathyroidectomy and the remaining four participants underwent parathyroidectomy by bilateral neck exploration.

Comparators

In all studies except Horiuchi 2002, the control was clinical and biochemical observation. Horiuchi 2002 compared the surgical intervention with a medical intervention consisting of etidronate therapy. Etidronate is a drug in the class of bisphosphonates that reduces bone resorption in favour of bone formation, hence strengthening the bone.

Outcomes

Only Ambrogini 2007 explicitly stated primary and secondary endpoints.

All studies reported postintervention serum calcium levels and plasma PTH concentration; consequently, we were able to evaluate whether the surgery had successfully resolved PHPT. Five studies assessed morbidity related to PHPT through BMD measurements at various locations in the body (Almqvist 2004; Ambrogini 2007; Bollerslev 2007; Horiuchi 2002; Talpos 2000), while four studies reported various echocardiography measures. (Almqvist 2004; Ambrogini 2007; Bollerslev 2007; Pepe 2013). Only two studies specifically reported all-cause mortality (Bollerslev 2007; Morris 2010), four reported serious adverse events (Almqvist 2004; Ambrogini 2007; Morris 2010; Talpos 2000), and five studies assessed hospitalisation due to severe hypercalcaemia (Ambrogini 2007; Bollerslev 2007; Morris 2010; Pepe 2018; Talpos 2000). Three studies reported HRQOL, all of which used the SF-36 (Ambrogini 2007; Bollerslev 2007; Talpos 2000).

Ongoing studies

We identified one ongoing study that met our inclusion criteria (EudraCT2013-005027-16). There was no available publication of study results, and the trialists did not respond to our request for information,

Excluded studies

We excluded eight studies after careful evaluation of the full publications. For further details, see Characteristics of excluded studies.

Risk of bias in included studies

For details on the risk of bias of the included studies see Characteristics of included studies.

For an overview of review authors' judgements about each risk of bias item for individual studies and across all studies, see Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies (blank cells indicate that the particular outcome was not measured in some studies).

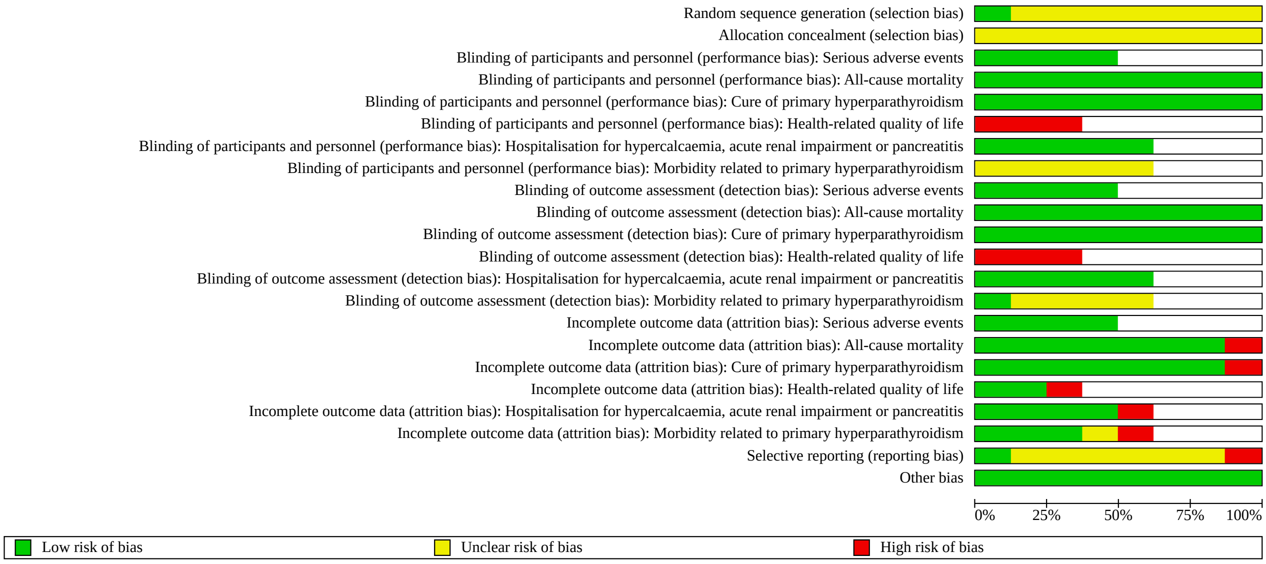
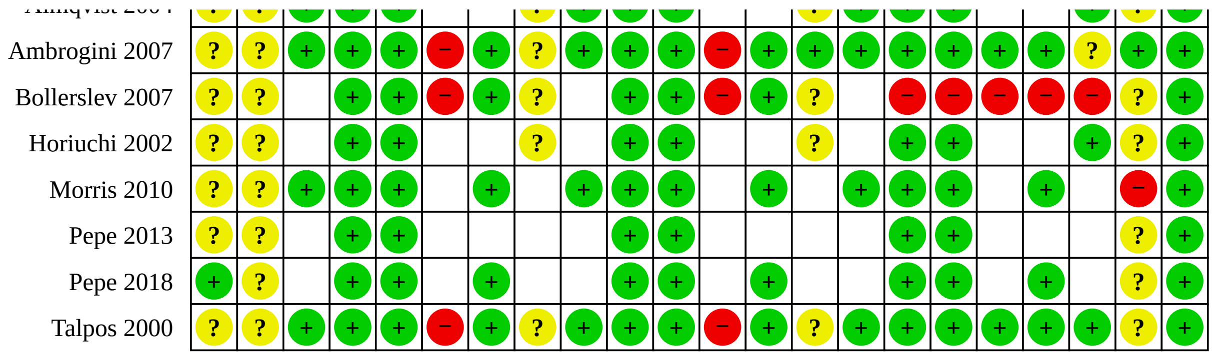


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study (blank cells indicate that the particular outcome was not measured in some studies).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): Serious adverse events	Blinding of participants and personnel (performance bias): All-cause mortality	Blinding of participants and personnel (performance bias): Cure of primary hyperparathyroidism	Blinding of participants and personnel (performance bias): Health-related quality of life	Blinding of participants and personnel (performance bias): Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis	Blinding of participants and personnel (performance bias): Morbidity related to primary hyperparathyroidism	Blinding of outcome assessment (detection bias): Serious adverse events	Blinding of outcome assessment (detection bias): All-cause mortality	Blinding of outcome assessment (detection bias): Cure of primary hyperparathyroidism	Blinding of outcome assessment (detection bias): Health-related quality of life	Blinding of outcome assessment (detection bias): Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis	Blinding of outcome assessment (detection bias): Morbidity related to primary hyperparathyroidism	Incomplete outcome data (attrition bias): Serious adverse events	Incomplete outcome data (attrition bias): All-cause mortality	Incomplete outcome data (attrition bias): Cure of primary hyperparathyroidism	Incomplete outcome data (attrition bias): Health-related quality of life	Incomplete outcome data (attrition bias): Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis	Incomplete outcome data (attrition bias): Morbidity related to primary hyperparathyroidism	Selective reporting (reporting bias)	Other bias
Almqvist 2004	?	?	+	+	+			?	+	+	+			?	+	+	+			+	?	+
Ambrogini 2007	?	?	+	+	+	−	+	?	+	+	+	−	+	+	+	+	+	+	+	?	+	+

Figure 3. (Continued)



Allocation

Risk of bias related to random sequence generation was unclear in all studies except Pepe 2018, which was at low risk. Risk of bias related to allocation concealment was unclear in all eight studies.

Blinding

Because the intervention was a surgical procedure, no studies could blind participants or personnel. Only two studies explicitly mentioned blinding of outcome assessors (the technician who performed BMD measurements in Ambrogini 2007), and the technician who performed functional testing in Morris 2010). Nevertheless, we considered that lack of blinding was unlikely to affect several outcomes (cure of PHPT, serious adverse effects, all-cause mortality and hospitalisation for hypercalcaemia), and we were unsure whether lack of blinding would affect the outcome morbidity related to PHPT.

Incomplete outcome data

All studies described the number of withdrawals; dropout rates were low and the reasons for dropping out were balanced between the intervention and control groups. In three studies, the authors reported that they had performed an intention-to-treat analysis (Ambrogini 2007; Bollerslev 2007; Talpos 2000). We judged Bollerslev 2007 at high risk of attrition bias because data were missing for 38% to 42% of the study population.

Selective reporting

We considered Morris 2010 at high risk of selective reporting and Ambrogini 2007 at low risk of selected reporting (after the study authors shared their study protocol). No protocols were available for the remaining studies, which we judged at unclear risk of reporting bias.

Other potential sources of bias

We did not identify any other sources of bias in the eight included studies.

Effects of interventions

See: **Summary of findings 1** Parathyroidectomy compared to observation in adults with primary hyperparathyroidism

Baseline characteristics

For details of baseline characteristics, see Appendix 2 and Appendix 3.

Parathyroidectomy versus observation or medical therapy

See Summary of findings 1.

Primary outcomes

Cure of PHPT

All eight studies reported postintervention serum calcium levels and PTH levels. A cure was biochemically defined as a return of serum calcium and PTH levels to normal laboratory reference values. Follow-up times were six months (Morris 2010; Pepe 2013; Pepe 2018), 12 months (Almqvist 2004; Ambrogini 2007; Bollerslev 2007; Horiuchi 2002), and 24 months (Bollerslev 2007; Talpos 2000). Three studies reported a cure rate of 98% (Almqvist 2004; Ambrogini 2007; Horiuchi 2002), and five reported a 100% cure rate (Bollerslev 2007; Morris 2010; Pepe 2013; Pepe 2018; Talpos 2000). Parathyroidectomy compared to observation probably results in a large increase in cure rate at six to 24 months' follow-up: 163/164 participants (99.4%) in the parathyroidectomy group and 0/169 participants in the observation or medical therapy group were cured of their PHPT (RR 0.04 95% CI 0.02 to 0.08; I^2 = 0%; 8 studies, 333 participants; moderate-certainty evidence; Analysis 1.1).

Morbidity related to PHPT

Osteoporosis or osteopenia

No studies reported actual improvement or lack of progression of established osteoporosis or osteopenia. However, five studies reported comparisons between the intervention and control arm regarding BMD measurements at various locations in the body (Almqvist 2004; Ambrogini 2007; Bollerslev 2007; Horiuchi 2002; Talpos 2000). All five of these studies reported BMD at the lumbar spine, and three studies reported BMD at the femoral neck (Almqvist 2004; Bollerslev 2007; Talpos 2000). At 12 to 24 months, parathyroidectomy compared to observation or medical therapy may have little or no effect on BMD values at the lumbar spine (MD 0.03 g/cm^2, 95% CI −0.05 to 0.12; I^2 = 71%; 5 studies, 287 participants; very low-certainty evidence; Analysis 1.2), and parathyroidectomy compared to observation may have little or no effect on BMD values at the femoral neck (MD −0.01 g/cm^2, 95% CI −0.13 to 0.11; I^2 = 82%; 3 studies, 216 participants; very low-certainty evidence; Analysis 1.2), but the evidence is very uncertain.

Cardiovascular disease

Four studies reported different echocardiographic measurements (Almqvist 2004; Ambrogini 2007; Bollerslev 2007; Pepe 2013). The evidence is very uncertain about the effect of parathyroidectomy compared to observation on the echocardiographic parameter of left ventricular ejection fraction (LVEF) at six to 24 months' follow-up (MD −2.38%, 95% CI −4.77 to 0.01; I^2 = 0%; 3 studies, 121 participants; very low-certainty evidence; Analysis 1.2). Ambrogini 2007 did not present any echocardiographic data but did report that all echocardiographic parameters were within the normal range and did not change during one year of follow-up.

Serious adverse events

Four studies did not mention the presence or absence of any serious adverse effects (Bollerslev 2007; Horiuchi 2002; Pepe 2013; Pepe 2018), while three studies explicitly reported that no participants in either study arm experienced any serious adverse events (Almqvist 2004; Ambrogini 2007; Morris 2010). Furthermore, Talpos 2000 reported that one participant experienced postoperative bleeding after parathyroidectomy, requiring an overnight drain. Therefore, based on the four studies that reported this outcome, 1/81 participants in the parathyroidectomy group and 0/87 participants in the observation group experienced a serious adverse event. With the three studies that reported zero adverse events in both groups excluded from the pooled analysis, the evidence suggests that parathyroidectomy compared to observation may result in little or no difference in serious adverse events (RR 3.35, 95% CI 0.14 to 78.60; 4 studies, 168 participants; low-certainty evidence; Analysis 1.3). No studies reported the development of postoperative hypocalcaemia after parathyroidectomy.

Secondary outcomes

All-cause mortality

Only two studies specifically reported all-cause mortality. No participants died in either study arm in Morris 2010, while three participants died in Bollerslev 2007 (two in the parathyroidectomy group and one in the observation group). However, the reasons for death were not reported. In total, 2/65 participants in the parathyroidectomy group and 1/68 participants in the observation group died. Excluding the study that reported no events in both groups from the pooled analysis, parathyroidectomy compared to observation may have little or no effect on all-cause mortality, but the evidence is very uncertain (RR 2.11, 95% CI 0.20 to 22.60; 2 studies; 133 participants; very low-certainty evidence; Analysis 1.4). While the remaining studies did not specifically report all-cause mortality, they did state that all participants completed follow-up (Almqvist 2004; Ambrogini 2007; Horiuchi 2002; Pepe 2013; Pepe 2018; Talpos 2000).

Health-related quality of life

Three studies assessed HRQOL, and all three used the SF-36 (Ambrogini 2007; Bollerslev 2007; Talpos 2000). Appendix 6 describes the different domains of this self-administered survey. All three studies reported the scores for the individual domains, but only Bollerslev 2007 additionally reported the physical and mental component summary scores. Bollerslev 2007 and Talpos 2000 observed that baseline scores for the single domains were similar in both study arms. Ambrogini 2007 reported that the baseline emotional role function score was lower in the observation group than in the parathyroidectomy group. After one year of follow-up, Ambrogini 2007 observed higher scores in 4/9 SF-36 domains (bodily pain, general health, vitality and mental health) in the parathyroidectomy group compared to the observation group. After two years of follow-up, Bollerslev 2007 reported no differences in scores for any domain between the study arms, whereas Talpos 2000 reported higher scores in 2/9 domains (social function and emotional role function) in the parathyroidectomy group.

Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis

Six studies reported hospitalisation of participants for the correction of hypercalcaemia (Almqvist 2004; Ambrogini 2007; Bollerslev 2007; Morris 2010; Pepe 2018; Talpos 2000), two of which reported no events in either study arm (Morris 2010; Pepe 2013). In total, 5/141 participants in the parathyroidectomy and 8/146 participants in the observation group underwent surgery for (recurrent) hypercalcaemia. Excluding the two studies that reported no events in both groups from the pooled analysis, the evidence suggests that parathyroidectomy compared to observation may have little or no effect on hospitalisation for hypercalcaemia (RR 0.91, 95% CI 0.20 to 4.25; P = 0.91; 6 studies, 287 participants, low-certainty evidence; Analysis 1.5). There were no reported hospitalisations due to acute renal impairment or for pancreatitis.

Long-term follow-up

In addition to reporting outcomes after one and two years of follow-up, Bollerslev 2007 reported study outcomes after five and ten years (Lundstam 2015; Lundstam 2017; Pretorius 2021; Pretorius 2022). We did not include these data in our analyses due to the high risk of attrition bias: 46/191 randomised participants (24%) had dropped out after five years, and 62/191 (32%) had dropped out after ten years. In addition, 12 participants in the observation group (13%) had undergone a parathyroidectomy after five years (in five cases due to hypercalcaemia), and this number had increased to 17 (18%) by year 10 (no explicit mention of hypercalcaemia). Therefore, we decided to summarise the long-term findings of Bollerslev 2007 narratively.

Validated BMD measurements were available for 111/191 randomised participants at five years of follow-up. In the parathyroidectomy group, BMD Z-scores for the lumbar spine and femoral neck had improved; in the observation group, BMD Z-scores for the lumbar spine were stable, whereas those for the femoral neck had decreased (Lundstam 2015; Lundstam 2017). The difference in change between the two groups was slightly higher in the parathyroidectomy group compared to the observation group. No BMD scores were reported at 10 years of follow-up, but the study authors observed no difference in the incidence of new peripheral bone fractures (15 in the parathyroidectomy group versus 17 in the observation group; Pretorius 2022). Similarly, there were no differences reported for the incidence of overall cardiovascular disease, with 10 cases in each study arm, or for all-cause mortality, with eight deaths in the parathyroidectomy group and seven in the observation group (Pretorius 2022). After 10 years of follow-up, 122 participants had SF-36 questionnaire data available for analysis. Compared to the observation group, the parathyroidectomy group had a modest improvement in the mental subscales of the SF-36. There were no differences reported between the treatment arms in the four physical subscales.

Subgroup analyses

We could not perform subgroup analyses due to the small number of studies and participants and the absence of information on the parathyroidectomy surgical technique.

Sensitivity analyses

We did not perform sensitivity analyses due to a lack of data from studies at low risk of bias.

Assessment of reporting bias

We did not generate funnel plots due to the limited number of studies per comparison.

DISCUSSION

Summary of main results

We identified eight RCTs involving 447 participants with PHPT, of whom 223 were randomised to parathyroidectomy, 215 were randomised to observation, and nine were randomised to medical etidronate therapy. The studies were small (sample sizes ranged from 21 to 191 participants), with variable duration of follow-up (between six months and 24 months). From 75% to 100% of the study participants were women. The outcome cure of PHPT had moderate-certainty evidence, while the overall certainty of the evidence for the remaining outcomes assessed by GRADE was low or very low, mainly due to the short duration of follow-up and small sample sizes of the studies.

Short-term outcomes

We found moderate-certainty evidence that parathyroidectomy compared to observation or etidronate therapy results in a large increase in PHPT cure rates. Regarding morbidity related to PHPT, there was very low-certainty evidence that parathyroidectomy compared to observation or etidronate therapy has little or no effect on the surrogate outcome of BMD at the lumbar spine and that parathyroidectomy compared to observation has little or no effect on BMD at the femoral neck or on LVEF. We found low-certainty evidence that parathyroidectomy has little or no effect on serious adverse events or hospitalisation for hypercalcaemia, and very-low-certainty evidence that parathyroidectomy has little or no effect on all-cause mortality.

Long-term outcomes

Bollerslev 2007 reported several study outcomes for five and ten years of follow-up (Lundstam 2015; Lundstam 2017; Pretorius 2021; Pretorius 2022). The improvements in BMD Z-scores for the lumbar spine and femoral neck were slightly larger in the parathyroidectomy group compared to the observation group after five years; there were no between-group differences for overall cardiovascular disease and all-cause mortality after ten years; and only participants in the observation arm required hospitalisation for hypercalcaemia.

Overall completeness and applicability of evidence

Considering the relatively high prevalence of PHPT, the number of participants in the individual studies included in this review was small. In addition, several characteristics of the population limited the external validity of our results: most participants had an asymptomatic disease, there was a general lack of ethnic diversity, more than 75% of the overall study population were women, and the average age of participants in all studies was 59 years or older.

Only Ambrogini 2007, Bollerslev 2007 and Talpos 2000 assessed immediate or long-term HRQOL; this outcome should be explored in large long-term RCTs. Because the follow-up duration of most studies was short, the results for outcomes that have a lag time to benefit, such as cardiovascular disease and all-cause mortality, should be interpreted with caution.

Subgroup analysis for different types of parathyroidectomy was not possible because individual studies did not report or compare these subtypes of surgical techniques.

Most study participants had mild and asymptomatic PHPT that did not meet the classical NIH criteria for parathyroidectomy. PHPT is common in older individuals and may significantly increase their morbidity and decrease their quality of life, as even a long duration of mild PHPT can increase the risk of skeletal, renal and cardiovascular complications. This is bound to have negative consequences for public health given the increasing proportion of older adults in the global population.

Overall, parathyroidectomy is associated with the cure of PHPT in most people without significant surgery-related adverse events. However, long-term, large-scale multi-national RCTs in ethnically diverse populations are necessary to clarify the degree of benefits conferred by the surgery on bone-related outcomes, cardiovascular morbidity, HRQOL and socioeconomic factors.

Quality of the evidence

The certainty of the evidence for cure of PHPT was moderate according to GRADE. The evidence for other clinical outcomes was of low and very low certainty.

Most studies provided an adequate description of randomisation, but the nature of the intervention made it impossible to conceal allocation or blind participants or personnel. It should have been possible to blind the outcome assessor for some outcomes, but not for self-reported outcomes such as adverse events of surgery, quality of life and hospitalisation for complications of the disease.

Concerning serious adverse events, a precise assessment of the evidence was not possible because only one study reported a serious adverse event. Reasons for downgrading the certainty of the evidence were the small number of study participants, the unclear risk of bias and indirectness. Further research may change these estimates. Moreover, the low number of male participants in the studies likely affects the generalisability of our observations from a population perspective. HRQOL outcomes provided very low-certainty evidence, mainly due to inconsistency, imprecision and substantial attrition.

Potential biases in the review process

We conducted a comprehensive search for high-quality RCTs that evaluated the effectiveness of parathyroidectomy in people with asymptomatic PHPT. We believe that we have identified all published studies in this review, though we may have missed additional unpublished work. Our search strategy and study selection criteria were robust and were agreed upon in advance.

Two review authors extracted data independently, and then we compared the extracted data. We requested missing data from study authors for inclusion in the review whenever available.

Although we could not assess the predefined primary outcome of improvement in osteoporosis or osteopenia, we were able to perform post-hoc analyses on surrogate outcomes during the review process.

Agreements and disagreements with other studies or reviews

One Cochrane Review reported the effects of minimally invasive parathyroidectomy guided by intraoperative PTH monitoring (IOPTH) and preoperative imaging versus bilateral neck exploration for PHPT in adults from five studies (Ahmadieh 2020). The overall cure rate among 236 participants was 98.1%, comparable to the cure rate of 98.4% in our review. However, we could not perform a subgroup analysis of participants who underwent minimally invasive parathyroidectomy or bilateral neck exploration because no data on surgical procedures were available for comparison. Perioperative adverse events such as symptomatic hypocalcaemia, vocal cord palsy, bleeding, fever and infection were reported in 25.9% of participants in Ahmadieh 2020, whereas there was only one reported case of postoperative bleeding in our review. The discrepancy may be related to improvements in surgical techniques and expertise in the more recent studies included in our review. The European Society of Endocrine Surgeons (ESES) position statement recommends that parathyroidectomy be performed in dedicated settings, with an adequate annual volume of these surgical procedures and by experts in the field (Iacobone 2019). For other outcomes such as HRQOL and all-cause mortality, the findings of Ahmadieh 2020 were comparable to ours,

Another systematic review and meta-analysis of four RCTs compared the efficacy of parathyroidectomy with that of active surveillance in people with mild asymptomatic PHPT (Anagnostis 2020). The four included RCTs were also included in our review, and Anagnostis 2020 reported similar findings to our review for the outcomes serum calcium concentrations, BMD measurements, incidence of adverse events (nephrolithiasis) and HRQOL. Our review included an additional four RCTs with some moderately severe cases of PHPT. Unfortunately, despite additional data, the low overall certainty of evidence prevented us from reaching clearer conclusions about the potential benefits of parathyroidectomy over observation that could aid decision-making in clinical practice.

Other systematic reviews assessed the effects of parathyroidectomy versus observation in a mixture of RCTs and observational cohort studies (Cheng 2015; Singh 2016b; Singh 2016a; Zhang 2018); owing to the differing study designs, the results of these reviews are not directly comparable with ours.

AUTHORS' CONCLUSIONS

Implications for practice

As the total number of participants undergoing parathyroidectomy in our review was relatively low, and the certainty of the evidence was low or very low for most outcomes, our findings have very limited applicability in clinical practice and must be interpreted with caution. The external validity of our findings is further limited by the inadequate representation of more advanced disease, ethnically diverse populations and male sex. As such, the decision of whether to perform parathyroidectomy should be based on a shared decision-making process, where the physician and the person with primary hyperparathyroidism (PHPT) discuss the benefits and risks of the available treatment options in the context of the person's expectations, values and preferences.

Implications for research

Based on the available evidence, we were unable to draw solid conclusions on the benefits of parathyroidectomy compared to observation or medical treatment on morbidity related to mild or asymptomatic PHPT (osteoporosis, osteopenia and cardiovascular disease), serious adverse events, all-cause mortality, hospitalisation for hypercalcaemia and most domains of health-related quality of life assessed by the SF-36 questionnaire. There is a need for long-term multi-centre randomised controlled trials (RCTs) to examine these issues in people with PHPT, especially in cases that do not meet the current international criteria for surgery (Bilezikian 2018; Khan 2017). This is particularly important considering the growing proportion of older adults in the global population.

It is also worth investigating the benefits of medical treatment options such as bisphosphonates and calcimimetics for managing PHPT in place of parathyroidectomy, especially in people unfit for parathyroidectomy or who decline surgery. As no RCTs in our review evaluated the cost-effectiveness of parathyroidectomy versus simple observation or medical therapy, future studies should also look into this area of uncertainty.

Given the low certainty of RCT-based evidence, we are unable to provide new insights regarding treatment decisions for people with (asymptomatic) PHPT. Large multi-national RCTs with multi-ethnic participant representation and a larger proportion of men are required to mitigate the uncertainties related to the effects of parathyroidectomy on morbidity related to PHPT and its socioeconomic impact.

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- Sign-off Editor (final editorial decision): René Rodríguez Gutierrez
- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Juan Victor Ariel Franco, Institute of General Practice, Medical Faculty of the Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany
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School of Medicine, Canada; Carolyn Dacey Seib, MD, MAS, Stanford University School of Medicine.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Almqvist 2004

Study characteristics	
Methods	**Design:** single-centre RCT **Title:** Cardiac dysfunction in mild primary hyperparathyroidism assessed by radionuclide angiography and echocardiography before and after parathyroidectomy **Setting:** outpatients (1 centre, Sweden) **Recruitment period:** not clearly mentioned and the study authors did not respond to our enquiry. Appears to be before 2002.
Participants	**Inclusion criteria** • Increased total serum concentration of calcium in the range of 2.55 mmol/L–2.95 mmol/L • Elevated serum concentration of PTH

Almqvist 2004 *(Continued)*

	• Age > 45 years **Exclusion criteria** • Unstable angina pectoris • Renal disease with serum creatinine level > 130 µmol/L **Diagnostic criteria** • Increased total serum calcium concentration in the range of 2.55 mmol/L–2.95 mmol/L • Serum PTH > 40 ng/L **Number randomised:** 50 (intervention: 25; control: 25) **Number who completed follow-up:** 50 (intervention: 25; control: 25) **Age:** intervention: mean 70.5 (SD 8.2) years; control: mean 68.0 (SD 9.1) years
Interventions	**Intervention:** parathyroidectomy at trial entry • Why: to evaluate the effects of parathyroidectomy on cardiac function and bone parameters in people with mild PHPT • What (procedures): bilateral neck exploration to find 4 parathyroid glands as the standard procedure • Who provided: surgeons with expertise in parathyroidectomy • Tailoring: abnormal parathyroid glands were removed for histological examination. Normal looking glands were left intact. **Control:** biochemical and clinical follow-up **Duration of follow-up:** 1 year **Run-in period:** no
Outcomes	**Cure of PHPT** • Measure: total serum calcium concentrations < 2.55 mmol/L and serum PTH levels ≤ 40 ng/L • Time point measured: within 24 hours of surgery, at 1 year • Time point reported: not reported **Morbidity related to PHPT** • Measure: BMD measurements by dual-energy X-ray absorptiometry; echocardiography • Time point measured: baseline and 1 year • Time point reported: baseline and 1 year **Serious adverse events** • Measure: postoperative hypocalcaemia requiring supplementation with calcium or vitamin D, not further defined • Time point measured: any point within 1 year of randomisation • Time point reported: not reported **All-cause mortality** • Not reported **HRQOL** • Not reported **Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis** • Measure: not defined

Almqvist 2004 *(Continued)*

	• Time point measured: any point within 1 year of randomisation • Time point reported: not reported
Study details	**Trial identifier:** not registered **Early termination:** no
Publication details	The study results were presented at the 23rd Annual Meeting of the American Association of Endocrine Surgeons, Banff, Alberta, Canada, 7–9 April 2002. The study results were published as original research papers in the journal Surgery in December 2002 and December 2004 (Almqvist 2004).
Stated aim of the study	To elucidate whether parathyroidectomy in people with PHPT influences their cardiac function and BMD.
Notes	Recruitment period is not clear from the study report and the study protocol is not visible in clinical trial registries. We contacted the study authors by email on several occasions to clarify study details but received no reply. **Funders:** the study was supported by grants from the Skaraborg Institute for Research and Development, the Heart Foundation of Central Hospital, Skövde, and Kommunförbundet Västra Götaland.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "Fifty consecutive eligible patients who agreed to participate in the study were randomized to parathyroid surgery either at inclusion (group A) or 1 year later (group B)." **Comment**: no further details.
Allocation concealment (selection bias)	Unclear risk	**Comment**: not reported.
Blinding of participants and personnel (performance bias) Serious adverse events	Low risk	**Comment**: blinding not possible, but outcome (hypocalcaemia) unlikely to be influenced by lack of blinding.
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Comment**: blinding not possible, but outcome measure unlikely influenced by lack of blinding.
Blinding of participants and personnel (performance bias) Cure of primary hyperparathyroidism	Low risk	**Comment**: blinding not possible, but outcome measure unlikely influenced by lack of blinding.
Blinding of participants and personnel (performance bias) Morbidity related to primary hyperparathyroidism	Unclear risk	**Comment**: blinding not possible, unclear if outcome measure could be influenced by lack of blinding.
Blinding of outcome assessment (detection bias)	Low risk	**Comment**: not reported, but outcome measure (hypocalcaemia) unlikely influenced by lack of blinding.

Almqvist 2004 *(Continued)*

Serious adverse events		
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Comment**: not reported, but outcome measure unlikely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Cure of primary hyperparathyroidism	Low risk	**Comment**: not reported, but outcome measure unlikely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Morbidity related to primary hyperparathyroidism	Unclear risk	**Comment**: not reported, unclear if outcome measure (echocardiographic measures) could be influenced by lack of blinding.
Incomplete outcome data (attrition bias) Serious adverse events	Low risk	**Comment**: all participants were followed up for 1 year.
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Comment**: all participants were followed up for 1 year.
Incomplete outcome data (attrition bias) Cure of primary hyperparathyroidism	Low risk	**Comment**: all participants were followed up for 1 year.
Incomplete outcome data (attrition bias) Morbidity related to primary hyperparathyroidism	Low risk	**Comment**: all participants were followed up for 1 year.
Selective reporting (reporting bias)	Unclear risk	**Comment**: no study protocol available.
Other bias	Low risk	**Comment**: none detected.

Ambrogini 2007

Study characteristics	
Methods	**Design:** single-centre RCT **Title:** Surgery or surveillance for mild asymptomatic primary hyperparathyroidism: a prospective, randomized clinical trial **Setting:** outpatients (1 centre, Italy) **Recruitment period:** January 2002–September 2005
Participants	**Inclusion criteria** • Asymptomatic PHPT • Albumin-corrected serum calcium < 1 mg/dL above upper limit of normal (11.2 mg/dL (2.8 mmol/L)) on ≥ 3 occasions

Ambrogini 2007 *(Continued)*

	• 24-hour urine calcium excretion < 400 mg (10 mmol) • Creatinine clearance in normal range or reduced by ≤ 30% compared with age-matched healthy people • Age- and sex-matched BMD at distal third of radius > 2.0 (Z-score) • Age 50–75 years **Exclusion criteria** • Symptomatic disease (nephrolithiasis, osteitis fibrosa cystica, prevalent fragility fractures) • Familial PHPT • Menopause for < 3 years • Diseases or therapies affecting the skeleton • Current thyroid disease requiring surgery • Contraindications to surgery • Previous neck surgery **Diagnostic criteria** • Increased ionised serum calcium (1.32 mmol/L) or albumin-corrected serum calcium (10.2 mg/dL (2.55 mmol/L)), with increased PTH (65 pg/mL (65 ng/L)) or inappropriately normal intact PTH **Number randomised:** 50 (46 women; intervention: 24; control: 26) **Number who completed follow-up:** 50 (intervention: 24; control: 26) **Age:** intervention: mean 64 (SD 6) years; control: mean 65 (SD 6) years
Interventions	**Intervention:** parathyroidectomy within 2 months of trial inclusion • Why: to study the effects of parathyroidectomy on lumbar spine, hip and forearm BMD after 1 year along with changes in bone markers of osteoporosis, echocardiographic indices, quality of life and psychosocial well-being • What (procedures): minimally invasive surgery removing abnormal gland tissue • Who provided: surgeons with expertise in parathyroidectomy • Tailoring: abnormal gland tissue was identified by preoperative imaging. In case of equivocal or negative imaging, a standard neck exploration was performed. **Control:** no parathyroidectomy **Duration of follow-up:** 1 year **Run-in period:** no
Outcomes	**Cure of PHPT** • Measure: ionised serum calcium ≤ 1.32 mmol/L or albumin-corrected serum calcium ≤ 10.2 mg/dL, without increased PTH (> 65 pg/mL) or inappropriately normal intact PTH • Time point measured: 6 months, 1 year • Time point reported: not reported **Morbidity related to PHPT** • Measure: BMD measurements by dual-energy X-ray absorptiometry; echocardiography • Time point measured: baseline, 6 months and 1 year • Time point reported: baseline, 6 months and 1 year **Serious adverse events** • Measure: hypocalcaemia, not further defined • Time point measured: any point within 1 year of randomisation • Time point reported: not reported

Ambrogini 2007 *(Continued)*

	All-cause mortality • Not reported **HRQOL** • Measure: SF-36 • Time point measured: baseline, 6 months and 1 year • Time point reported: baseline, 6 months and 1 year **Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis** • Measure: not defined • Time point measured: any point within 1 year of randomisation (hypercalcaemia) • Time point reported: not reported
Study details	**Trial identifier:** not registered **Early termination:** no
Publication details	The work was published in the Journal of Clinical Endocrinology and Metabolism in 2007 (Ambrogini 2007).
Stated aim of the study	To compare changes (percentage of basal) of lumbar spine BMD between the 2 groups at 1 year follow-up. Secondary endpoints were a comparison of changes at 1 year of total hip and forearm BMDs, bone markers, echocardiographic indices, quality of life and psychosocial well-being, and complications of surgery. Appearance of NIH criteria for parathyroidectomy in the control group during the follow-up period was also a secondary outcome measure.
Notes	**Funders:** this work was partly supported by grants from the Italian Ministry of Education, Universities and Scientific Research (Ministero dell'Istruzione, dell'Università e della Ricerca Scientifica) in Rome, Italy, and the University of Pisa.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "patients randomly assigned to surgery (PTx group) or to no surgery (no-PTx group)"; "Randomization blocks comprised six patients each." **Comment**: no further details.
Allocation concealment (selection bias)	Unclear risk	**Comment**: not reported.
Blinding of participants and personnel (performance bias) Serious adverse events	Low risk	**Comment**: blinding not possible, but outcome measure unlikely influenced by lack of blinding.
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Comment**: blinding not possible, but outcome measure unlikely influenced by lack of blinding.
Blinding of participants and personnel (performance bias)	Low risk	**Comment**: blinding not possible, but outcome measure unlikely influenced by lack of blinding.

Ambrogini 2007 *(Continued)*

Cure of primary hyperparathyroidism		
Blinding of participants and personnel (performance bias) Health-related quality of life	High risk	**Comment**: blinding not possible, and outcome measure likely influenced by lack of blinding.
Blinding of participants and personnel (performance bias) Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis	Low risk	**Comment**: blinding not possible, but outcome measure unlikely influenced by lack of blinding.
Blinding of participants and personnel (performance bias) Morbidity related to primary hyperparathyroidism	Unclear risk	**Comment**: blinding not possible, unclear if outcome measure could be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Serious adverse events	Low risk	**Comment**: blinding not reported, but outcome measure unlikely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Comment**: blinding not reported, but outcome measure unlikely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Cure of primary hyperparathyroidism	Low risk	**Comment**: blinding not reported, but outcome measure unlikely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Health-related quality of life	High risk	**Comment**: participant-reported outcome, and outcome measure likely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis	Low risk	**Comment**: blinding not possible, but outcome measure unlikely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Morbidity related to primary hyperparathyroidism	Low risk	**Quote:** "The technologist performing dual-energy x-ray absorptiometry was blinded to the patient treatment category." **Comment**: outcome assessor was blinded.
Incomplete outcome data (attrition bias) Serious adverse events	Low risk	**Comment:** 1 patient in control group developed chronic myeloid leukaemia after 4 months of trial start and was not included in the final analysis.
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Comment:** 1 patient in control group developed chronic myeloid leukaemia after 4 months of trial start and was not included in the final analysis.

Ambrogini 2007 *(Continued)*

Incomplete outcome data (attrition bias) Cure of primary hyperparathyroidism	Low risk	**Comment:** 1 patient in control group developed chronic myeloid leukaemia after 4 months of trial start and was not included in the final analysis.
Incomplete outcome data (attrition bias) Health-related quality of life	Low risk	**Comment:** 1 patient in control group developed chronic myeloid leukaemia after 4 months of trial start and was not included in the final analysis.
Incomplete outcome data (attrition bias) Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis	Low risk	**Comment:** 1 patient in control group developed chronic myeloid leukaemia after 4 months of trial start and was not included in the final analysis.
Incomplete outcome data (attrition bias) Morbidity related to primary hyperparathyroidism	Unclear risk	**Comment:** 1 patient in control group developed chronic myeloid leukaemia after 4 months of trial start and was not included in the final analysis.
Selective reporting (reporting bias)	Low risk	**Comment**: study protocol was shared by the study authors. There was no discrepancy between the protocol and outcome reporting.
Other bias	Low risk	**Comment**: none detected.

Bollerslev 2007

Study characteristics	
Methods	**Design:** multi-centre RCT **Title:** Medical observation, compared with parathyroidectomy, for asymptomatic primary hyperparathyroidism: a prospective, randomized trial **Setting:** outpatients (multiple centres, Sweden, Denmark and Norway) **Recruitment period:** 1999–July 2005
Participants	**Inclusion criteria** • Untreated asymptomatic PHPT • Serum calcium 2.60 mmol/L–2.85 mmol/L • Age 50–80 years • No medications interfering with calcium metabolism • Informed consent **Exclusion criteria** • Hyperparathyroid bone disease • Previous neck surgery • Impaired kidney function (creatinine level 130 mol/L) • Kidney stones • Complicating medical conditions • Psychiatric disorders • Multiple endocrine neoplasia

Bollerslev 2007 *(Continued)*

	• Familial hypocalciuric hypercalcaemia • Familial HPT **Diagnostic criteria** • Elevated fasting serum calcium values (measured on 3 occasions and corrected for variation in albumin levels) > mean of reference interval at local laboratory • Serum intact PTH (measured at least twice) > mean of reference interval at local laboratory • Thiazide diuretics stopped at least 4 weeks before diagnostic evaluation **Number randomised:** 191 (intervention: 96 (83 women); control: 95 (82 women)) **Number who completed follow-up:** 129 (113 women; intervention: 65; control: 64) **Age:** intervention: mean 63.8 (SD 7.1) years; control: mean 64.5 (SD 7.8) years
Interventions	**Intervention**: parathyroidectomy at trial entry (after randomisation) • Why: to study the effects of parathyroidectomy on lumbar spine, hip and forearm BMD after 1 year of intervention along with changes in bone markers of osteoporosis, cardiovascular markers, fat mass, lipid and glucose metabolism, quality of life and psychosocial well-being. • What (procedures): parathyroidectomy, not further specified • Who provided: surgeons with expertise in parathyroidectomy • Tailoring: not reported **Control:** medical observation (biochemical, clinical and imaging follow-up for 10 years along with assessment of appearance of indications for parathyroidectomy) **Duration of follow-up:** 1 year (extended follow-up: 2 years, 5 years, 10 years) **Run in period:** no
Outcomes	**Cure of PHPT** • Measure: based on fasting serum calcium levels and serum levels of intact PTH, not further defined • Time point measured: 1 and 2 years after randomisation • Time point reported: 1 and 2 years after randomisation **Morbidity related to PHPT** • Measure: BMD measurements by dual-energy X-ray absorptiometry; echocardiography • Time point measured: baseline, 6 months and 1 year (BMD); baseline and 2 years (echocardiography) • Time point reported: baseline, 6 months and 1 year (BMD); baseline and 2 years (echocardiography) **Serious adverse events** • Not reported **All-cause mortality** • Measure: not defined • Time point measured: any point after randomisation • Time point reported: during follow-up, not further specified **HRQOL** • Measure: SF-36 • Time point measured: baseline, 1 and 2 years • Time point reported: baseline, 6 months, 1 year and 2 years **Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis**

Bollerslev 2007 *(Continued)*

	• Measure: not defined • Time point measured: any point after randomisation (hypercalcaemia) • Time point reported: within 2 years of randomisation; > 2 years after randomisation
Study details	**Trial identifier:** NCT00522028 **Early termination:** no
Publication details	Various aspects of the trial results were published in the Journal of Clinical Endocrinology and Metabolism in 2007 (Bollerslev 2007), 2009 (Bollerslev 2009) and 2015 (Lundstam 2015); in Clinical Endocrinology in 2011 (Persson 2011), in the Journal of Bone and Mineral Research in 2017 (Lundstam 2017), and in Endocrine Connections in 2018 (Godang 2018).
Stated aim of the study	To compare changes in lumbar spine, femoral neck and forearm BMD between the 2 groups from baseline to 1 and 2 years' follow-up, and to assess quality of life and psychosocial well-being during these time periods (Bollerslev 2007); to assess the effects of parathyroidectomy on cardiovascular risk factors after 2 years' follow-up (Bollerslev 2009); to assess the effects of parathyroidectomy on cardiac structure and function (Persson 2011); to compare lumbar spine and femoral neck BMD at baseline and at 5 years' follow-up and fractures at 5 years' follow-up after parathyroidectomy (Lundstam 2015; Lundstam 2017); and to assess the effects of parathyroidectomy on body composition, serum lipids and glucose metabolism at 5 years' follow-up (Godang 2018).
Notes	The study is part of the Scandinavian Investigation on Primary Hyperparathyroidism (the SIPH Study) in people with PHPT. The study authors reported that the 10-year follow-up data are being processed for publication after completion of the study in 2018. **Funders:** this work was supported by grants from the Norwegian Research Council and from Swedish Government grants under the ALF agreement (ALF VGR-71 120), and unrestricted research grants from Novo Nordisk Norway AS, Biovitrium AB, Sweden and Amgen AB, Sweden.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "The patients were included and randomized by block randomization to medical observation or parathyroidectomy by an experienced parathyroid surgeon." **Comment**: no further details.
Allocation concealment (selection bias)	Unclear risk	**Comment**: not reported.
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Quote:** "... neither the subjects nor the investigators were blinded to the treatment given." **Comment:** outcome measure unlikely influenced by lack of blinding.
Blinding of participants and personnel (performance bias) Cure of primary hyperparathyroidism	Low risk	**Quote:** "... neither the subjects nor the investigators were blinded to the treatment given." **Comment:** outcome measure unlikely influenced by lack of blinding.
Blinding of participants and personnel (performance bias) Health-related quality of life	High risk	**Quote:** "... neither the subjects nor the investigators were blinded to the treatment given." **Comment:** outcome measure likely influenced by lack of blinding.

Bollerslev 2007 *(Continued)*

Blinding of participants and personnel (performance bias) Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis	Low risk	**Quote:** "... neither the subjects nor the investigators were blinded to the treatment given." **Comment:** outcome measure unlikely influenced by lack of blinding.
Blinding of participants and personnel (performance bias) Morbidity related to primary hyperparathyroidism	Unclear risk	**Quote:** "... neither the subjects nor the investigators were blinded to the treatment given." **Comment:** unclear if outcome measure could be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Comment**: not reported, but outcome measure unlikely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Cure of primary hyperparathyroidism	Low risk	**Comment**: not reported, but outcome measure unlikely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Health-related quality of life	High risk	**Comment**: participant-reported outcome, outcome measure likely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis	Low risk	**Comment**: not reported, but outcome measure unlikely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Morbidity related to primary hyperparathyroidism	Unclear risk	**Comment**: not reported, but unclear if outcome measure (BMD and echocardiographic parameters) could be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All-cause mortality	High risk	**Comment**: high attrition rate (32%) during follow-up, reasons not clear in the publication.
Incomplete outcome data (attrition bias) Cure of primary hyperparathyroidism	High risk	**Comment**: high attrition rate (32%) at 10 years, reasons not clear in the publication.
Incomplete outcome data (attrition bias) Health-related quality of life	High risk	**Comment**: high attrition rate (32%) at 10 years, reasons not clear in the publication.
Incomplete outcome data (attrition bias) Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis	High risk	**Comment**: high attrition rate (32%) at 10 years, reasons not clear in the publication.

Bollerslev 2007 *(Continued)*

Incomplete outcome data (attrition bias) Morbidity related to primary hyperparathyroidism	High risk	**Comment**: high attrition rate (32%) at 10 years, reasons not clear in the publication.
Selective reporting (reporting bias)	Unclear risk	**Comment**: scarce information in trials register.
Other bias	Low risk	**Comment**: none detected.

Horiuchi 2002

Study characteristics	
Methods	**Design:** single-centre RCT **Title:** A strategy for the management of elderly women with primary hyperparathyroidism: a comparison of etidronate therapy with parathyroidectomy **Setting:** outpatients (1 centre, Japan) **Recruitment period:** 1998–1999
Participants	**Inclusion criteria** • Older age • Female sex • Proven PHPT • Informed consent **Exclusion criteria** • Not reported **Diagnostic criteria** • Serum calcium levels • PTH concentrations • Location of parathyroid adenoma confirmed by ultrasonography, computed tomographic scanning and 99mTc-MIBI scintigraphy **Number randomised:** 22 (intervention: 13; control: 9) **Number completing follow-up:** 22 (intervention: 13; control: 9) **Age:** intervention: mean 76.8 (SD 10.1) years; control: mean 76.3 (SD 5.2) years
Interventions	**Intervention**: parathyroidectomy at trial entry (after randomisation) • Why: to study the effects of parathyroidectomy on lumbar spine BMD, vertebral fractures and urinary markers of bone turn over. • What (procedures): parathyroidectomy, not further specified • Who provided: parathyroidectomy was performed by surgeons • Tailoring: not reported **Comparator:** medical therapy with etidronate **Duration of follow-up:** 1 year

Horiuchi 2002 *(Continued)*

	Run-in period: no
Outcomes	**Cure of PHPT** • Measure: not defined • Time point measured: within 1 year of randomisation • Time point reported: not reported **Morbidity related to PHPT** • Measure: BMD measurements by dual-energy X-ray absorptiometry • Time point measured: baseline and 1 year • Time point reported: baseline and 1 year **Serious adverse events** • Not reported **All-cause mortality** • Not reported **HRQOL** • Not reported **Hospitalisation for hypercalcaemia, renal impairment or pancreatitis** • Not reported
Study details	**Trial identifier:** not registered **Early termination:** no
Publication details	The study was published in the journal Gerontology (Horiuchi 2002).
Stated aim of the study	To compare improvements in lumbar spine BMD and total BMD induced by etidronate treatment and parathyroidectomy in older women with PHPT.
Notes	The study appears to have no registration in clinical trials registries and the study authors did not respond to email requests to share the study details. **Funders**: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "Twenty-two PHPT patients were enrolled and randomized into two groups." **Comment**: no further details.
Allocation concealment (selection bias)	Unclear risk	**Comment**: not reported.
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Comment**: blinding not possible, but outcome measure unlikely influenced by lack of blinding.

Horiuchi 2002 *(Continued)*

Blinding of participants and personnel (performance bias) Cure of primary hyperparathyroidism	Low risk	**Comment**: blinding not possible, but outcome measure unlikely influenced by lack of blinding.
Blinding of participants and personnel (performance bias) Morbidity related to primary hyperparathyroidism	Unclear risk	**Comment**: blinding not possible, unclear if outcome measure could be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Comment**: not reported, but outcome measure unlikely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Cure of primary hyperparathyroidism	Low risk	**Comment**: not reported, but outcome measure unlikely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Morbidity related to primary hyperparathyroidism	Unclear risk	**Comment**: not reported, unclear if outcome measure could be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Comment**: no losses.
Incomplete outcome data (attrition bias) Cure of primary hyperparathyroidism	Low risk	**Comment**: no losses.
Incomplete outcome data (attrition bias) Morbidity related to primary hyperparathyroidism	Low risk	**Comment**: no losses.
Selective reporting (reporting bias)	Unclear risk	**Comment**: no study protocol available.
Other bias	Low risk	**Comment**: none detected.

Morris 2010

Study characteristics	
Methods	**Design:** single-centre RCT **Title**: Parathyroidectomy improves functional capacity in "asymptomatic" older patients with primary hyperparathyroidism: a randomized control trial **Setting:** outpatients (1 centre, USA)

Morris 2010 *(Continued)*

	Recruitment period: October 2005 –December 2006

Participants	**Inclusion criteria**
	• Biochemically confirmed mild PHPT that does not meet the 1990 NIH criteria for parathyroidectomy
	• Age > 50 years
	• No surgical contraindications
	• Ability to speak English
	Exclusion criteria
	• PHPT meeting NIH parathyroidectomy criteria for immediate surgical intervention
	  ○ Nephrolithiasis
	  ○ Fractures
	  ○ Osteoporosis (T score 2.5)
	  ○ Neuromuscular syndrome
	  ○ Serum calcium level > 11.2 mg/dL
	  ○ Creatinine clearance 30%
	  ○ Urinary calcium level > 400 mg/24 hours
	• Current use of thiazide-type diuretics or lithium
	• Recent myocardial infarction or stroke making patients unable to walk or to return to the institution for follow-up
	Diagnostic criteria
	• Serum calcium > 10.2 mg/dL (2.55 mmol/L) and synchronous yet inappropriately elevated PTH levels above 80 pg/mL (ng/L) in the setting of a normal serum 25-hydroxyvitamin D3
	Number randomised: 21 (intervention: 10; control: 11)
	Number who completed follow-up: 18 (intervention: 9 (1 protocol violation); control: 9 (2 protocol violations))
	Age: intervention: mean 65.7 (SD 9.6) years; control: mean 65.3 (SD 10.3) years

Interventions	**Intervention:** minimally invasive parathyroidectomy at trial entry (after randomisation) • Why: to study the effects of parathyroidectomy on functional capacity and sleep quality in older people with asymptomatic parathyroidism • What (procedures): minimally invasive surgery by a directed targeted surgical approach to remove the hyperfunctioning parathyroid adenoma • Who provided: parathyroid surgeons • Tailoring: preoperative imaging was used for operative planning **Control:** observation (biochemical and clinical follow-up) **Duration of follow-up:** 6 months **Run-in period:** no
Outcomes	**Cure of PHPT** • Measure: serum calcium levels ≤ 10.2 mg/dL without synchronous elevated PTH levels > 80 pg/mL • Time point measured: 6 weeks and 6 months • Time point reported: not reported **Morbidity related to PHPT** • Not reported **Serious adverse events**

Morris 2010 *(Continued)*

	• Measure: not defined • Time point measured: not defined • Time point reported: not defined **All-cause mortality** • Measure: not defined • Time point measured: not defined • Time point reported: not defined **HRQOL** • Not reported **Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis** • Measure: not defined • Time point measured: 6 weeks and 6 months • Time point reported: not reported
Study details	**Trial identifier:** NCT00501215 **Study terminated early:** no
Publication details	The study results were published in the journals Surgery in 2009 (Perrier 2009) and Annals of Surgery in 2010 (Morris 2010).
Stated aim of the study	To determine whether parathyroidectomy improves functional capacity and sleep quality in older people with asymptomatic PHPT
Notes	**Funders:** the study was supported by a Jahnigen Career Development Award from the American Geriatrics Society (NDP).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "Twenty-one patients were electronically randomized to 1 of 2 groups." **Comment**: no further details.
Allocation concealment (selection bias)	Unclear risk	**Comment**: not reported.
Blinding of participants and personnel (performance bias) Serious adverse events	Low risk	**Comment**: blinding not possible, but outcome measure unlikely influenced by lack of blinding.
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Comment**: blinding not possible, but outcome measure unlikely influenced by lack of blinding.
Blinding of participants and personnel (performance bias) Cure of primary hyperparathyroidism	Low risk	**Comment**: blinding not possible, but outcome measure unlikely influenced by lack of blinding.

Morris 2010 *(Continued)*

Blinding of participants and personnel (performance bias) Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis	Low risk	**Comment**: blinding not possible, but outcome measure unlikely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Serious adverse events	Low risk	**Comment**: blinding not possible, but outcome measure unlikely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Comment**: open label, but outcome measure unlikely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Cure of primary hyperparathyroidism	Low risk	**Comment**: open label, but outcome measure unlikely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis	Low risk	**Comment**: open label, but outcome measure unlikely influenced by lack of blinding.
Incomplete outcome data (attrition bias) Serious adverse events	Low risk	**Comment**: 1 person in each group did not receive the intervention; there was 1 drop out unrelated to the intervention in the control group.
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Comment**: 1 person in each group did not receive the intervention; there was 1 drop out unrelated to the intervention in the control group.
Incomplete outcome data (attrition bias) Cure of primary hyperparathyroidism	Low risk	**Comment**: 1 person in each group did not receive the intervention; there was 1 drop out unrelated to the intervention in the control group.
Incomplete outcome data (attrition bias) Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis	Low risk	**Comment**: 1 person in each group did not receive the intervention; there was 1 drop out unrelated to the intervention in the control group.
Selective reporting (reporting bias)	High risk	**Comment**: The registered protocol reports the outcomes related to sleep parameters only.
Other bias	Low risk	**Comment**: none detected.

Pepe 2013

Study characteristics	
Methods	**Design:** single-centre RCT

Pepe 2013 *(Continued)*

	Title: Parathyroidectomy eliminates arrhythmic risk in primary hyperparathyroidism, as evaluated by exercise test **Setting:** outpatients (1 centre, Italy) **Recruitment period:** November 2009–April 2011
Participants	**Inclusion criteria** • Biochemically proven PHPT • Informed consent **Exclusion criteria** • Absolute contraindications to exercise stress test or uninterpretable ECG (left bundle branch block, presence of pacemaker and pre-excitation) • Hypertrophic cardiomyopathy • Severe valvular disease • Use of medications that could interfere with the QT interval • Known coronary artery disease • T1DM/T2DM • Hypothyroidism/hyperthyroidism • Hypokalaemia/hyperkalaemia • Hypomagnesaemia/hypermagnesaemia • Creatinine clearance < 60 mL/min • BMI > 30 kg/m^2 **Diagnostic criteria** • Hypercalcaemia with an inappropriately high plasma level of PTH **Number randomised:** 30 (intervention: 15; control: 15) **Number who completed follow-up:** 24 (intervention: 12; control: 12) **Age:** intervention: mean 59.8 (SD 7.2) years; control: mean 60.2 (SD 9) years
Interventions	**Intervention**: parathyroidectomy • Why: to study the effects of parathyroidectomy on risk factors for cardiac arrhythmias related to electrocardiographic QT dynamic changes • What (procedures): parathyroidectomy, not further specified • Who provided: parathyroid surgeons • Tailoring: not reported **Control:** conservative management (biochemical and clinical follow-up) **Duration of follow-up:** 6 months **Run-in period:** no
Outcomes	**Cure of PHPT** • Measure: a significant reduction in ionised calcium levels and PTH levels, not further defined • Time point measured: 6 months • Time point reported: 6 months **Morbidity related to PHPT** • Measure: echocardiography • Time point measured: baseline and 6 months

Pepe 2013 *(Continued)*

	• Time point reported: baseline and 6 months **Serious adverse events** • Not reported **All-cause mortality** • Not reported **Health-related quality of life** • Not reported **Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis** • Not reported
Study details	**Trial identifier:** trial not registered **Early termination:** no
Publication details	The results were published in the European Journal of Endocrinology (Pepe 2013). A companion paper was published in the Journal of Bone and Mineral Research.
Stated aim of the study	To investigate whether parathyroidectomy can eliminate risk factors for the occurrence of arrhythmias related to QT dynamic changes evaluated by exercise testing
Notes	The chief investigator confirmed that all participants in the intervention arm received bilateral neck exploration for parathyroidectomy and that the trial was not registered in any registry, although it complied with local ethical requirements. **Funders:** this research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "Following initial assessment, the remaining 30 patients were randomized to either PTx or conservative management; randomization blocks comprised six patients each. However, six patients (three in each group) did not accept this randomization strategy because they wanted to have immediate neck exploration; therefore, they abandoned the study" **Comment**: no further details.
Allocation concealment (selection bias)	Unclear risk	**Comment**: not reported.
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Comment**: blinding not possible, but outcome measure unlikely influenced by lack of blinding.
Blinding of participants and personnel (performance bias) Cure of primary hyperparathyroidism	Low risk	**Comment**: blinding not possible, but outcome measure unlikely influenced by lack of blinding.

Pepe 2013 *(Continued)*

Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Comment**: not reported, but outcome measure unlikely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Cure of primary hyperparathyroidism	Low risk	**Comment**: not reported, but outcome measure unlikely influenced by lack of blinding.
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Comment**: 3 participants from each group dropped out because they did not accept the randomization strategy.
Incomplete outcome data (attrition bias) Cure of primary hyperparathyroidism	Low risk	**Comment**: 3 participants from each group dropped out because they did not accept the randomization strategy.
Selective reporting (reporting bias)	Unclear risk	**Comment**: no study protocol available.
Other bias	Low risk	**Comment**: none detected.

Pepe 2018

Study characteristics	
Methods	**Design:** single-centre RCT **Title:** Reduction of arrhythmias in primary hyperparathyroidism, by parathyroidectomy, evaluated with 24-h ECG monitoring **Setting:** outpatients (1 centre, Italy) **Recruitment period**: January 2015–July 2016
Participants	**Inclusion criteria** • Biochemically proven PHPT • Informed consent **Exclusion criteria** • Left bundle branch block • Pre-excitation presence of pacemaker • History of severe valvular disease • Hypertrophic cardiomyopathy • Sokolow-Lyon index > 3.5 mV in the ECG (diagnostic threshold for left ventricular hypertrophy • Coronary artery disease • T1DM/T2DM • Hypothyroidism/hyperthyroidism • History of hypokalaemia/hyperkalaemia • Hypomagnesaemia/hypomagnesaemia • Renal disease with serum creatinine > 1.35 mg/dL • BMI >30 kg/m^2 • Caffeine intake > 80 mg/day

Pepe 2018 *(Continued)*

	Diagnostic criteria • Finding of hypercalcaemia with inappropriately high plasma level of PTH **Number randomised:** 30 (intervention: 15; control: 15) **Number who completed follow-up:** 26 (intervention: 13; control: 13) **Age:** intervention: mean 66 (SD 6.5) years; control: 70.6 (SD 8.4) years
Interventions	**Intervention**: parathyroidectomy • Why: to study the effects of parathyroidectomy on the prevalence of arrhythmias in participants with PHPT following surgery evaluated by 24-hour electrocardiographic monitoring • What (procedures): parathyroidectomy, not further specified • Who provided: parathyroid surgeons • Tailoring: not reported **Control:** Conservative management (biochemical and clinical follow-up) **Duration of follow-up:** 6 months **Run-in period:** 1 month (treatment with cholecalciferol 50,000 IU weekly)
Outcomes	**Cure of PHPT** • Measure: reduction in total ionised calcium and PTH levels, not further defined • Time point measured: 6 months • Time point reported: not reported **Morbidity related to PHPT** • Not reported **Serious adverse events** • Not reported **All-cause mortality** • Not reported **HRQOL** • Not reported **Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis** • Not defined • Time point measured: any point after randomisation • Time point reported: not reported
Study details	**Trial identifier:** trial not registered **Early termination:** no
Publication details	The study was published in the European Journal of Endocrinology in 2018 (Pepe 2018).
Stated aim of the study	To investigate the prevalence of arrhythmias in people affected by PHPT compared to controls by 24-hour ECG monitoring, and the effect of parathyroidectomy on arrhythmias.

Pepe 2018 *(Continued)*

Notes	The chief investigator confirmed that all participants in the intervention arm received bilateral neck exploration for parathyroidectomy and that the trial was not registered in any registry, although it complied with local ethical requirements. **Funders:** this research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "30 patients were randomized to either PTx within 15 days or conservative management for 6 months prior surgery; randomization was performed using a computer-generated numbers and blocks comprised 15 patients each." **Comment**: randomisation method appears adequate.
Allocation concealment (selection bias)	Unclear risk	**Comment**: not reported.
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Comment**: blinding not possible, but outcome measure unlikely influenced by lack of blinding.
Blinding of participants and personnel (performance bias) Cure of primary hyperparathyroidism	Low risk	**Comment**: blinding not possible, but outcome measure unlikely influenced by lack of blinding.
Blinding of participants and personnel (performance bias) Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis	Low risk	**Comment**: blinding not possible, but outcome measure unlikely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Comment**: not reported, but outcome measure unlikely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Cure of primary hyperparathyroidism	Low risk	**Comment**: not reported, but outcome measure unlikely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis	Low risk	**Comment**: not reported, but outcome measure unlikely influenced by lack of blinding.
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Comment**: 2 dropouts in both groups for similar reasons.

Pepe 2018 *(Continued)*

Incomplete outcome data (attrition bias) Cure of primary hyperparathyroidism	Low risk	**Comment**: 2 dropouts in both groups for similar reasons.
Incomplete outcome data (attrition bias) Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis	Low risk	**Comment**: 2 dropouts in both groups for similar reasons.
Selective reporting (reporting bias)	Unclear risk	**Comment**: no study protocol available.
Other bias	Low risk	**Comment**: none detected.

Talpos 2000

Study characteristics	
Methods	**Design:** single-centre RCT **Title:** Randomized trial of parathyroidectomy in mild asymptomatic primary hyperparathyroidism: patient description and effects on the SF-36 health survey **Setting:** outpatients (1 centre, USA) **Recruitment period:** June 1994–March 1997
Participants	**Inclusion criteria** • Age 50–75 years • Either sex, any ethnicity • Albumin-adjusted serum calcium 2.52 mmol/L–2.87 mmol/L • Intact PTH level > 20 pg/mL (20 ng/L) • Normal renal function (serum creatinine < 1.5 mg/dL (133 µmol/L)) • Forearm BMD within 2 SD adjusted for age, sex, and race (Z-scores) • Absence of relevant symptoms and complications directly attributable to hypercalcaemia or excess PTH secretion • Willingness to participate and ability to give informed consent • Living within 150-mile radius of Henry Ford Hospital **Exclusion criteria** • Familial hyperparathyroidism • Previous neck surgery or current thyroid disease requiring surgical intervention • Nontraumatic vertebral or hip fractures • Nephrolithiasis within past 2 years • Menopause within past 5 years • Use of medications known to affect bone and mineral metabolism (glucocorticoids, anticonvulsants, bisphosphonates) • Unexpected echocardiographic findings that preclude surgery **Diagnostic criteria**

Talpos 2000 *(Continued)*

	• Persistent albumin-adjusted serum calcium level of 10.1 mg/dL–11.5 mg/dL (2.53 mmol/L–2.88 mmol/L), from ≥ 3 measurements over ≥ 3 months • Intact PTH level > 20 pg/mL (20 ng/L), determined by immunoradiometric assay **Number randomised:** 53 (intervention: 25; control: 28) **Number who completed follow-up:** 48 (intervention: 23; control: 25) **Age:** intervention: mean 67 (SD 7) years; control: 63 (SD 7) years
Interventions	**Intervention**: parathyroidectomy • Why: to study the effects of parathyroidectomy on the disease-specific complications of hyperparathyroidism and quality of life • What (procedures): standard parathyroidectomy with a bilateral approach, removing enlarged glands • Who provided: a single experienced surgeon (over 600 parathyroid procedures before study start) • Tailoring: preoperative localising studies were not performed; enlarged glands were removed; if all glands were found enlarged, a 50 mg–70 mg fragment of vascularised parathyroid was left intact. **Control:** observation (biochemical and clinical follow-up) **Duration of follow-up:** 24 months **Run-in period:** no
Outcomes	**Cure of PHPT** • Measure: normalisation of corrected calcium and PTH levels • Time point measured: baseline, 6 months, 12 months, 18 months and 24 months • Time point reported: not reported **Morbidity related to PHPT** • Measure: BMD measurements by dual-energy X-ray absorptiometry • Time point measured: baseline, 6 months, 12 months, 18 months and 24 months • Time point reported: baseline and 24 months **Serious adverse events** • Measure: not defined • Time point measured: any point after randomisation • Time point reported: not reported **All-cause mortality** • Not reported **HRQOL** • Measure: SF-36 • Time point measured: baseline, 6 months, 12 months, 18 months and 24 months • Time point reported: baseline, 6 months, 12 months, 18 months and 24 months **Hospitalisation for hypercalcaemia, renal impairment or pancreatitis** • Measure: not defined • Time point measured: any point after randomisation • Time point reported: not reported
Study details	**Trial identifier:** not registered

Talpos 2000 *(Continued)*

	Early termination: no
Publication details	The study was reported in the journal Surgery (Talpos 2000) and in the Journal of Clinical Endocrinology and Metabolism (Rao 2004).
Stated aim of the study	To determine the feasibility of an RCT investigating the effects of parathyroidectomy in apparently healthy people in whom the disease-specific complications (e.g. kidney stones or skeletal fractures) are not always serious or inevitable.
Notes	This was the first RCT to investigate the benefits of parathyroidectomy in people with asymptomatic mild PHPT. **Funders:** this work was supported by National Institute of Health, USA, Grant number DK 43858.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "Block randomization of patients to surgery or no surgery was performed within 4 strata that were defined by gender (female:male ratio, 3-4:1) and ethnicity to promote balance in the 2 treatment groups and within the strata." **Comment:** no further details.
Allocation concealment (selection bias)	Unclear risk	**Comment**: not reported.
Blinding of participants and personnel (performance bias) Serious adverse events	Low risk	**Comment**: blinding not possible, but outcome measure (bleeding) unlikely influenced by lack of blinding.
Blinding of participants and personnel (performance bias) All-cause mortality	Low risk	**Comment**: blinding not possible, but outcome measure unlikely influenced by lack of blinding.
Blinding of participants and personnel (performance bias) Cure of primary hyperparathyroidism	Low risk	**Comment**: blinding not possible, but outcome measure unlikely influenced by lack of blinding.
Blinding of participants and personnel (performance bias) Health-related quality of life	High risk	**Comment**: blinding not possible, and outcome measure likely influenced by lack of blinding.
Blinding of participants and personnel (performance bias) Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis	Low risk	**Comment**: blinding not possible, but outcome measure unlikely influenced by lack of blinding.

Talpos 2000 *(Continued)*

Blinding of participants and personnel (performance bias) Morbidity related to primary hyperparathyroidism	Unclear risk	**Comment**: blinding not possible, unclear if outcome measure influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Serious adverse events	Low risk	**Comment**: not reported, but outcome measure (bleeding) unlikely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All-cause mortality	Low risk	**Comment**: not reported, but outcome measure unlikely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Cure of primary hyperparathyroidism	Low risk	**Comment**: not reported, but outcome measure unlikely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Health-related quality of life	High risk	**Comment**: participant-reported outcome, outcome measure likely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis	Low risk	**Comment**: not reported, but outcome measure unlikely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Morbidity related to primary hyperparathyroidism	Unclear risk	**Comment**: not reported, unclear if outcome measure (bone parameters) could be influenced by lack of blinding.
Incomplete outcome data (attrition bias) Serious adverse events	Low risk	**Quote**: "Two of the patients who were randomized to the operative group refused parathyroidectomy. They were followed in the surgery group with an "intent to treat" philosophy"; "Of 25 patients who were randomized to surgery, 23 patients actually underwent parathyroidectomy"; "Three of the 28 patients who were randomized to no surgery (11%) became symptomatic during the trial and underwent parathyroidectomy." **Comment**: low number of violations from protocol, balanced between groups. Primary analyses based on intention-to-treat principle.
Incomplete outcome data (attrition bias) All-cause mortality	Low risk	**Quote**: "Two of the patients who were randomized to the operative group refused parathyroidectomy. They were followed in the surgery group with an "intent to treat" philosophy"; "Of 25 patients who were randomized to surgery, 23 patients actually underwent parathyroidectomy"; "Three of the 28 patients who were randomized to no surgery (11%) became symptomatic during the trial and underwent parathyroidectomy." **Comment**: low number of violations from protocol, balanced between groups. Primary analyses based on intention-to-treat principle.
Incomplete outcome data (attrition bias) Cure of primary hyperparathyroidism	Low risk	**Quote**: "Two of the patients who were randomized to the operative group refused parathyroidectomy. They were followed in the surgery group with an "intent to treat" philosophy"; "Of 25 patients who were randomized to surgery, 23 patients actually underwent parathyroidectomy"; "Three of the 28 patients

Talpos 2000 *(Continued)*

		who were randomized to no surgery (11%) became symptomatic during the trial and underwent parathyroidectomy." **Comment**: low number of violations from protocol, balanced between groups. Primary analyses based on intention-to-treat principle.
Incomplete outcome data (attrition bias) Health-related quality of life	Low risk	**Quote**: "Two of the patients who were randomized to the operative group refused parathyroidectomy. They were followed in the surgery group with an "intent to treat" philosophy"; "Of 25 patients who were randomized to surgery, 23 patients actually underwent parathyroidectomy"; "Three of the 28 patients who were randomized to no surgery (11%) became symptomatic during the trial and underwent parathyroidectomy." **Comment**: low number of violations from protocol, balanced between groups. Primary analyses based on intention-to-treat principle.
Incomplete outcome data (attrition bias) Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis	Low risk	**Quote**: "Two of the patients who were randomized to the operative group refused parathyroidectomy. They were followed in the surgery group with an "intent to treat" philosophy"; "Of 25 patients who were randomized to surgery, 23 patients actually underwent parathyroidectomy"; "Three of the 28 patients who were randomized to no surgery (11%) became symptomatic during the trial and underwent parathyroidectomy." **Comment**: low number of violations from protocol, balanced between groups. Primary analyses based on intention-to-treat principle.
Incomplete outcome data (attrition bias) Morbidity related to primary hyperparathyroidism	Low risk	**Quote**: "Two of the patients who were randomized to the operative group refused parathyroidectomy. They were followed in the surgery group with an "intent to treat" philosophy"; "Of 25 patients who were randomized to surgery, 23 patients actually underwent parathyroidectomy"; "Three of the 28 patients who were randomized to no surgery (11%) became symptomatic during the trial and underwent parathyroidectomy." **Comment**: low number of violations from protocol, balanced between groups. Primary analyses based on intention-to-treat principle.
Selective reporting (reporting bias)	Unclear risk	**Comment**: no study protocol available.
Other bias	Low risk	**Comment**: none detected.

BMD: bone mineral density; ECG: electrocardiogram; HbA1c: glycosylated haemoglobin A1c; HPT: hyperparathyroidism; HRQOL: health-related quality of life; NA: not applicable; NIH: National Institutes of Health; PHPT: primary hyperparathyroidism; PTH: parathyroid hormone; RCT: randomised controlled trial; SD: standard deviation; SF-36: 36-Item Short Form Health Survey; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Beysel 2019	Case-control study (participants in control arm were healthy adults without PHPT).
Ejlsmark-Svensson 2019	Follow-up at 3 months only.
Espiritu 2011	Case-control study.
Hansen 2012	Control arm comprised healthy individuals.

Study	Reason for exclusion
Keutgen 2012	Prospective observational study.
Koman 2019	Observational study.
Niederle 2019	Intervention and control groups did not match our study protocol (both underwent parathyroidectomy).
Vera 2014	Not an RCT, longitudinal follow-up of people who received antiresorptive therapy (medical intervention) and those who underwent parathyroidectomy (control).

RCT: randomised controlled trial.

Characteristics of ongoing studies *[ordered by study ID]*

EudraCT2013-005027-16

Study name	Impact of vitamin D supplementation on skeletal and non skeletal manifestations in patients with primary hyperparathyroidism submitted to parathyroidectomy or followed without surgery
Methods	**Type of trial:** interventional clinical trial of medicinal product **Allocation**: randomised controlled **Intervention model**: parallel group assignment **Masking:** no blinding
Participants	**Condition**: PHPT Enrolment: 100 cases **Inclusion criteria** • Postmenopausal PHPT • Age 45–80 years **Exclusion criteria** • Familial forms of PHPT • Serum calcium > 12.5 mg/dL • Malignancy other than non-melanoma skin cancer • Diseases or medications known to affect mineral metabolism
Interventions	**Intervention:** use of normal or high-dose vitamin D prior to parathyroidectomy **Control:** no supplementation
Outcomes	**Primary outcome** • BMD measured at lumbar spine/femoral neck/forearm at baseline, 12 months and 24 months after parathyroidectomy **Secondary outcomes** • Number of falls • Clinical and morphometric vertebral fractures • Quality of life and neuropsychological aspects • Lipids and glucose metabolism

EudraCT2013-005027-16 *(Continued)*

	• Cardiac and vascular damage (diastolic dysfunction, left ventricular hypertrophy, cardiac calcium deposits in the myocardium, aortic and mitral valve calcification + carotid intima-media thickness + presence of carotid plaque + percent of carotid stenosis) • Renal function • Vitamin D binding protein (DBP) • Polymorphic genetic variants of CYP2R1 CYP24A1 genes that could influence the effect of vitamin D supplementation, affecting the circulating levels of vitamin D **Other outcomes** • None **Relevant proposed outcome measures for summary of findings table** • None
Starting date	**Trial start date**: 24 September 2015 **Trial completion date**: ongoing
Contact information	**Responsible party:** Casa Sollievo Della Sofferenza Irccs, Italy **Principal investigator**: Annamaria Ciaccio
Study identifier	EudraCT number: 2013-005027-16
Official title	Impact of vitamin D supplementation on skeletal and non skeletal manifestations in patients with primary hyperparathyroidism submitted to parathyroidectomy or followed without surgery
Stated purpose of study	To evaluate if normal or high vitamin D3 supplementation versus no supplementation could affect the complications of PHPT in postmenopausal women with asymptomatic PHPT (not fulfilling the current surgical criteria plus osteoporosis) and in postmenopausal women with symptomatic PHPT (undergoing parathyroidectomy)
Notes	We requested an update on the status of the trial from the primary investigator on multiple occasions but received no response.

BMD: bone mineral density.

DATA AND ANALYSES

Comparison 1. Parathyroidectomy versus observation

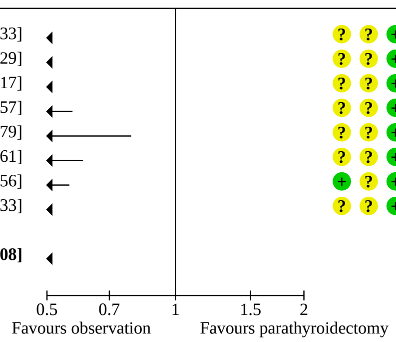
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Cure of primary hyperparathyroidism	8	333	Risk Ratio (M-H, Random, 95% CI)	0.04 [0.02, 0.08]
1.2 Morbidity related to primary hyperparathyroidism	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.2.1 Bone mineral density at lumbar spine (g/cm ^{2})	5	287	Mean Difference (IV, Random, 95% CI)	0.01 [-0.07, 0.10]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.2 Bone mineral density at femoral neck (g/cm 2)	3	216	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.13, 0.11]
1.2.3 Left ventricular ejection fraction (%)	3	121	Mean Difference (IV, Random, 95% CI)	-2.38 [-4.77, 0.01]
1.3 Serious adverse events	4		Risk Ratio (IV, Random, 95% CI)	Totals not selected
1.4 All-cause mortality	2		Risk Ratio (IV, Random, 95% CI)	Totals not selected
1.5 Hospitalisation for correction of hypercalcaemia	6	287	Risk Ratio (IV, Random, 95% CI)	0.91 [0.20, 4.25]

Analysis 1.1. Comparison 1: Parathyroidectomy versus observation, Outcome 1: Cure of primary hyperparathyroidism

Study or Subgroup	Parathyroidectomy Events	Parathyroidectomy Total	Observation Events	Observation Total	Weight	Risk Ratio (Non-event) M-H, Random, 95% CI	A	B	C	D	E	F	G
Almqvist 2004	23	23	0	25	9.8%	0.02 [0.00 , 0.33]	?	?	+	+	+	?	+
Ambrogini 2007	23	24	0	25	30.7%	0.06 [0.01 , 0.29]	?	?	+	+	+	+	+
Bollerslev 2007	47	47	0	48	9.7%	0.01 [0.00 , 0.17]	?	?	+	+	-	?	+
Horiuchi 2002	13	13	0	9	9.9%	0.04 [0.00 , 0.57]	?	?	+	+	+	?	+
Morris 2010	9	9	0	9	10.1%	0.05 [0.00 , 0.79]	?	?	+	+	+	-	+
Pepe 2013	12	12	0	12	10.0%	0.04 [0.00 , 0.61]	?	?	+	+	+	?	+
Pepe 2018	13	13	0	13	10.0%	0.04 [0.00 , 0.56]	+	?	+	+	+	?	+
Talpos 2000	23	23	0	28	9.8%	0.02 [0.00 , 0.33]	?	?	+	+	+	?	+
Total (95% CI)		**164**		**169**	**100.0%**	**0.04 [0.02 , 0.08]**							
Total events:	163		0										

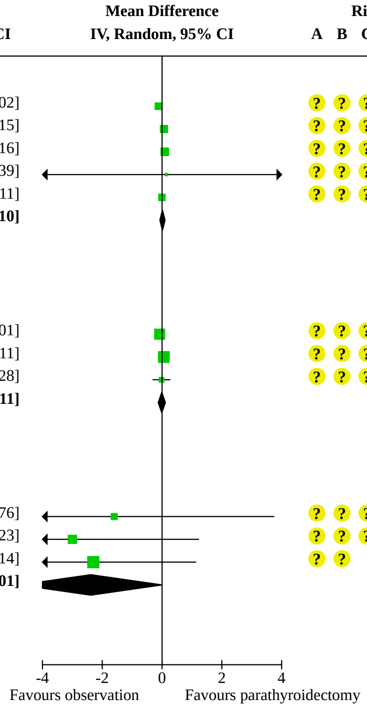
Heterogeneity: Tau² = 0.00; Chi² = 1.77, df = 7 (P = 0.97); I² = 0%
Test for overall effect: Z = 7.59 (P < 0.00001)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): Cure of primary hyperparathyroidism
(D) Blinding of outcome assessment (detection bias): Cure of primary hyperparathyroidism
(E) Incomplete outcome data (attrition bias): Cure of primary hyperparathyroidism
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.2. Comparison 1: Parathyroidectomy versus observation, Outcome 2: Morbidity related to primary hyperparathyroidism

	Parathyroidectomy			Observation				Mean Difference	Risk of Bias						
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	A	B	C	D	E	F	G
1.2.1 Bone mineral density at lumbar spine (g/cm 2)															
Almqvist 2004	0.97	0.17	23	1.09	0.2	25	23.3%	-0.12 [-0.22 , -0.02]	?	?	?	?	+	?	+
Ambrogini 2007	0.885	0.18	24	0.821	0.126	25	26.0%	0.06 [-0.02 , 0.15]	?	?	?	+	?	+	+
Bollerslev 2007 (1)	1.13	0.19	56	1.04	0.2	59	28.6%	0.09 [0.02 , 0.16]	?	?	?	?	-	?	+
Horiuchi 2002	0.83	17	13	0.68	0.148	9	0.0%	0.15 [-9.09 , 9.39]	?	?	?	?	+	?	+
Talpos 2000	1.116	0.24	25	1.121	0.17	28	22.1%	-0.00 [-0.12 , 0.11]	?	?	?	?	+	?	+
Subtotal (95% CI)			**141**			**146**	**100.0%**	**0.01 [-0.07 , 0.10]**							
Heterogeneity: Tau² = 0.01; Chi² = 11.55, df = 4 (P = 0.02); I² = 65%															
Test for overall effect: Z = 0.30 (P = 0.76)															
1.2.2 Bone mineral density at femoral neck (g/cm 2)															
Almqvist 2004	0.74	0.13	23	0.82	0.11	25	42.2%	-0.08 [-0.15 , -0.01]	?	?	?	?	+	?	+
Bollerslev 2007 (1)	0.87	0.13	56	0.81	0.12	59	45.6%	0.06 [0.01 , 0.11]	?	?	?	?	-	?	+
Talpos 2000	0.77	0.03	25	0.79	0.8	28	12.2%	-0.02 [-0.32 , 0.28]	?	?	?	?	+	?	+
Subtotal (95% CI)			**104**			**112**	**100.0%**	**-0.01 [-0.13 , 0.11]**							
Heterogeneity: Tau² = 0.01; Chi² = 11.16, df = 2 (P = 0.004); I² = 82%															
Test for overall effect: Z = 0.14 (P = 0.89)															
1.2.3 Left ventricular ejection fraction (%)															
Almqvist 2004 (2)	64.1	8.5	23	65.7	10.4	25	19.9%	-1.60 [-6.96 , 3.76]	?	?	?	?	+	?	+
Bollerslev 2007 (3)	65	7	26	68	8	23	31.9%	-3.00 [-7.23 , 1.23]	?	?	?	?	-	?	+
Pepe 2013 (4)	63.8	4.4	12	66.1	4.2	12	48.2%	-2.30 [-5.74 , 1.14]	?	?				?	+
Subtotal (95% CI)			**61**			**60**	**100.0%**	**-2.38 [-4.77 , 0.01]**							
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 2 (P = 0.92); I² = 0%															
Test for overall effect: Z = 1.95 (P = 0.05)															
Test for subgroup differences: Chi² = 3.92, df = 2 (P = 0.14), I² = 49.0%															

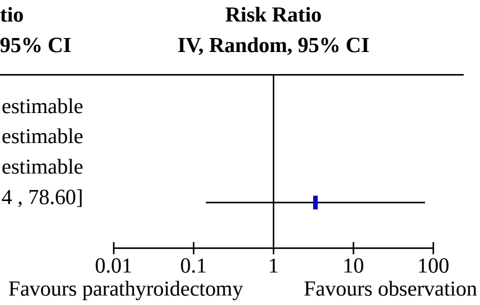


Footnotes
(1) BMD measurements at one year of follow-up were used due to the larger number of participants in comparison to two years of follow-up.
(2) Follow-up 12 months.
(3) Follow-up 24 months; data originate from only one of the three included study centres.
(4) Follow-up 6 months

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): Morbidity related to primary hyperparathyroidism
(D) Blinding of outcome assessment (detection bias): Morbidity related to primary hyperparathyroidism
(E) Incomplete outcome data (attrition bias): Morbidity related to primary hyperparathyroidism
(F) Selective reporting (reporting bias)
(G) Other bias

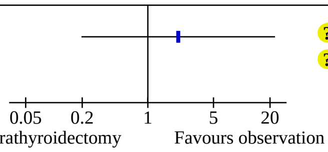
Analysis 1.3. Comparison 1: Parathyroidectomy versus observation, Outcome 3: Serious adverse events

	Parathyroidectomy		Observation		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	IV, Random, 95% CI
Almqvist 2004	0	23	0	25	Not estimable
Ambrogini 2007	0	24	0	25	Not estimable
Morris 2010	0	9	0	9	Not estimable
Talpos 2000	1	25	0	28	3.35 [0.14 , 78.60]



Analysis 1.4. Comparison 1: Parathyroidectomy versus observation, Outcome 4: All-cause mortality

Study or Subgroup	Parathyroidectomy Events	Parathyroidectomy Total	Observation Events	Observation Total	Risk Ratio IV, Random, 95% CI	A	B	C	D	E	F	G
Bollerslev 2007	2	56	1	59	2.11 [0.20 , 22.60]	?	?	+	+	−	?	+
Morris 2010	0	9	0	9	Not estimable	?	?	+	+	+	−	+

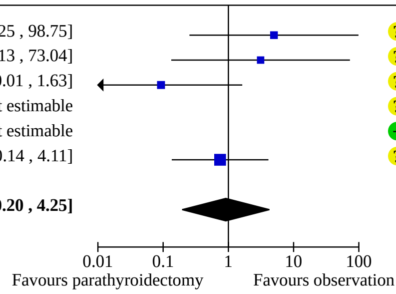


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All-cause mortality
(D) Blinding of outcome assessment (detection bias): All-cause mortality
(E) Incomplete outcome data (attrition bias): All-cause mortality
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.5. Comparison 1: Parathyroidectomy versus observation, Outcome 5: Hospitalisation for correction of hypercalcaemia

Study or Subgroup	Parathyroidectomy Events	Parathyroidectomy Total	Observation Events	Observation Total	Weight	Risk Ratio IV, Random, 95% CI	A	B	C	D	E	F	G
Almqvist 2004	2	23	0	23	20.0%	5.00 [0.25 , 98.75]	?	?				?	+
Ambrogini 2007	1	24	0	25	18.4%	3.12 [0.13 , 73.04]	?	?	+	+	+	+	+
Bollerslev 2007	0	47	5	48	21.2%	0.09 [0.01 , 1.63]	?	?	+	+	−	?	+
Morris 2010	0	9	0	9		Not estimable	?	?	+	+	+	−	+
Pepe 2018	0	13	0	13		Not estimable	+	?	+	+	+	?	+
Talpos 2000	2	25	3	28	40.4%	0.75 [0.14 , 4.11]	?	?	+	+	+	?	+
Total (95% CI)		**141**		**146**	**100.0%**	**0.91 [0.20 , 4.25]**							
Total events:	5		8										

Heterogeneity: Tau² = 0.77; Chi² = 4.32, df = 3 (P = 0.23); I² = 31%
Test for overall effect: Z = 0.12 (P = 0.91)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis
(D) Blinding of outcome assessment (detection bias): Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis
(E) Incomplete outcome data (attrition bias): Hospitalisation for hypercalcaemia, acute renal impairment or pancreatitis
(F) Selective reporting (reporting bias)
(G) Other bias

ADDITIONAL TABLES

Table 1. Overview of study populations

Study ID (study design)	Study groups	Screened/ eligible (n)	Randomised (n)	Analysed for primary outcome (n)	Randomised finishing study (n (%))	Duration of follow-up (extended follow-up)
Almqvist 2004 (parallel RCT)	Parathyroidectomy	200/50[a]	25	23	25 (100%)	12 months
	Observation		25	25	24 (96%)[b]	

Table 1. Overview of study populations *(Continued)*

	Total:		**50**	**48**	49 (98%)	
Ambrogini 2007 (parallel RCT)	Parathyroidectomy	412/50[c]	24	24 (24)	24 (100%)	6 months (12 months)
	Observation		26	25 (25)	26 (100%)	
	Total:		**50**	**49 (49)**	**50 (100%)**	
Bollerslev 2007 (parallel RCT)	Parathyroidectomy	191[a]	96	56 (47)	82 (85%)[d]	12 months (24 months)
	Observation		95	59 (48)	82 (86%)[e]	
	Total:		**191**	**115 (95)**	**164 (86%)**	
Horiuchi 2002 (parallel RCT)	Parathyroidectomy	22[a]	13	13	13 (100%)	12 months
	Etidronate therapy		9	9	9 (100%)	
	Total:		22	22	22 (100%)	
Morris 2010 (parallel RCT)	Parathyroidectomy	54/21[a]	10	9	9 (90%)[f]	6 months
	Observation		11	9	9 (82%)[f,g]	
	Total:		**21**	**18**	**18 (86%)**	
Pepe 2013 (parallel RCT)	Parathyroidectomy	37/30[a]	15	12	12 (80%)[h]	6 months
	Observation		15	12	12 (80%)[h]	
	Total:		**30**	**24**	**24 (80%)**	
Pepe 2018 (parallel RCT)	Parathyroidectomy	33/30[a]	15	13[ag]	13 (87%)[h]	6 months
	Observation		15	13[ag]	13 (87%)[h]	
	Total:		**30**	**26**	**26 (87%)**	
Talpos 2000 (parallel RCT)	Parathyroidectomy	283/53[a]	25	25	25 (100%)	24 months
	Observation		28	28	28 (100%)	
	Total:		53	53	53 (100%)	
All studies	**All interventions**		**223**		**203 (91%)**	
	All controls		**224**		**203 (91%)**	
	Interventions + controls		**447**		**406 (91%)**	

[a] Sample size calculation not performed.
[b] One participant was withdrawn from the study after one year because of progressive angina pectoris.
[c] Sample size calculation was based on a pilot study; for ≥ 5% difference between groups in mean lumbar spine bone mineral density at 1 year with 90% power and significance level of 0.05 using 2-sided t-test, each group should have ≥ 22 people. Assuming 10% dropout rate, investigators planned to include 24 people in each group.

[d] One participant died, 12 withdrew.
[e] One participant died, 12 withdrew and one was excluded because of parathyroid cancer.
[f] One participant did not receive the allocated intervention and was excluded from the study.
[g] One participant withdrew from the study.
[h] Participants who violated the protocol left the study.
RCT: randomised controlled trial.

APPENDICES

Appendix 1. Search strategies

MEDLINE (Ovid SP)
1. Hyperparathyroidism, Primary/
2. (primary adj3 hyperparathyroid*).tw.
3. Parathyroid Neoplasms/
4. (parathyroid* adj3 (adenoma? or hyperplasia? or neoplasm? or tumo?r?)).tw.
5. or/1-4
6. Parathyroidectomy/
7. parathyroidectom*.tw.
8. (parathyroid* adj6 (surger* or surgic* or resection or excision or exploration)).tw.
9. ((endoscop* or video or camera or minimally invasive or small incision or open) adj6 (surger* or surgic* or resection or excision or exploration)).tw.
10. or/6-9
11. 5 and 10
[Cochrane Handbook 2021 RCT filter - sensitivity maximizing version]
12. randomized controlled trial.pt.
13. controlled clinical trial.pt.
14. randomi?ed.ab.
15. placebo.ab.
16. drug therapy.fs.
17. randomly.ab.
18. trial.ab.
19. groups.ab.
20. or/12-19
21. exp animals/ not humans/
22. 20 not 21
23. 11 and 22

(Continued)
= 885 references

CENTRAL (via Cochrane Register of Studies Online)

1. MESH DESCRIPTOR Hyperparathyroidism, Primary

2. (primary ADJ4 hyperparathyroid*):TI,AB,KY

3. MESH DESCRIPTOR Parathyroid Neoplasms

4. (parathyroid* ADJ4 (adenoma* or hyperplasia* or neoplasm* or tumor* or tumour*)):TI,AB,KY

5. #1 OR #2 OR #3 OR #4

6. MESH DESCRIPTOR Parathyroidectomy

7. parathyroidectom*:TI,AB,KY

8. (parathyroid* ADJ7 (surgic* or resection or excision or exploration)):TI,AB,KY

9. ((endoscop* or video or camera or minimally invasive or small incision or open) ADJ7 (surgic* or resection or excision or exploration)):TI,AB,KY

10. (surger* or surgica*):TI,AB,KY

11. #6 OR #7 OR #8 OR #9 OR #10

12. #5 and #11
= 192 references

LILACS (iAHx)

(MH:"Hyperparathyroidism, Primary" OR hyperparathyroid$ OR hiperparatireoid$ OR MH:"Parathyroid Neoplasms" OR (parathyroid AND (adenoma$ or hyperplasia$ or neoplasm$ or tumor$))) AND (MH:"Parathyroidectomy" OR parathyroidectom$ OR paratiroidectom$ OR cirur$ OR surger$ or surgic$ OR resection OR excision OR exploration) + Filter "Controlled Clinical Trial"
= 7 references

WHO ICTRP (Advanced search)

hyperparathyroid* AND parathyroidectom* OR

hyperparathyroid* AND surg* OR

parathyroid AND parathyroidectom* OR

parathyroid AND surg*
= 160 references

ClinicalTrials.gov (Advanced search)

Condition or disease: hyperparathyroidism OR parathyroid

Intervention/treatment: parathyroidectomy OR surgery OR surgical OR resection OR exploration
= 137 references

Appendix 2. Baseline characteristics (I)

Study ID	Comparison	Duration of follow-up	Description of participants[a]	Study period	Country	Setting	Ethnic groups (%)
Almqvist 2004	Parathyroidectomy vs observation	24 months (comparison between parathyroidectomy and observation up to 12 months)	Adults (> 45 years) with mild PHPT	Before 2002	Sweden	Inpatients	100% white
Ambrogini 2007	Parathyroidectomy vs observation	12 months	Adults with PHPT who did not meet NIH criteria for surgery	2002–2006	Italy	Inpatients	100% white
Bollerslev 2007	Parathyroidectomy vs observation	120 months	Adults with asymptomatic PHPT	1999–2018	Norway, Sweden, Denmark	Inpatients	100% white
Horiuchi 2002	Parathyroidectomy vs treatment with etidronate	12 months	Postmenopausal women with biochemical evidence of PHPT	Before 2002	Japan	Inpatients	100% Japanese
Morris 2010	Parathyroidectomy vs observation	6 months	Adults (≥ 50 years) with biochemically confirmed PHPT that did not meet 1990 NIH criteria for parathyroidectomy	2005–2007	USA	Inpatients	Not reported
Pepe 2013	Parathyroidectomy vs observation	6 months	Postmenopausal women (45–75 years) with biochemically proven PHPT	2009–2011	Italy	Inpatients	100% white
Pepe 2018	Parathyroidectomy vs observation	6 months	Postmenopausal women (45–80 years) with biochemically proven PHPT	2015– 2016	Italy	Inpatients	100% white
Talpos 2000	Parathyroidectomy vs observation	24 months	Adults (50–75 years) with asymptomatic mild PHPT	1994– 1999	USA	Inpatients	44% Black; 56% white

[a] No studies reported duration of PHPT.
NIH: National Institutes of Health; PHPT: primary hyperparathyroidism.

Appendix 3. Baseline characteristics (II)

Study ID	Study groups	Sex (female)	Age, years (mean (SD))	Baseline Ca, mmol/L (mean (SD))	Follow-up Ca, mmol/L (mean (SD))	Cointerventions	Comorbidities
Almqvist 2004	Parathyroidectomy	100%	70.5 (8.2)	2.62 (0.11)	2.36 (0.13) at 1 year	Antihypertensives: 52%	CVD: 20% HTN: 52% DM: 8% Renal calculi: 12% Neuropsychiatric symptoms: 80 Osteoporotic fractures: 36
	Observation	84%	68.0 (9.1)	2.64 (0.11)	2.64 (0.08) at 2 years	Antihypertensives: 64%	CVD: 4 HTN:64 DM: 12 Renal calculi: 24 Neuropsychiatric symptoms: 76 Osteoporotic fractures: 24
Ambrogini 2007	Parathyroidectomy	83%	64.0 (6.0)	2.55 (0.12)	2.36 (0.16)	Not reported	Osteoporosis: 54%
	Observation	77%	65.0 (6.0)	2.55 (0.09)	2.59 (0.09)	Not reported	Osteoporosis: 62%
Bollerslev 2007	Parathyroidectomy	86%	63.8 (7.1)	2.7 (0.08)	2.4 (0.15)	Bisphosphonates: 2% Oestrogens: 15%	Not reported
	Observation	86%	64.5 (7.8)	2.69 (0.08)	2.67 (0.14)	Bisphosphonates: 3% Oestrogens: 9% Parathyroidectomy: 10.5%	Not reported

(Continued)

Horiuchi 2002	Parathyroidecto-my	100%	76.8 (10.1)	2.74 (0.12)	2.35 (0.07)	Not reported	Osteoporosis: 46%
	Treatment with etidronate	100%	76.3 (5.2)	2.69 (0.11)	2.59 (0.07)	Not reported	Osteoporosis; 33%
Morris 2010	Parathyroidecto-my	78%	63.0 (19.0)	2.62 (0.07)	2.3 (0.08)	Not reported	HTN: 67% DM: 33% CAD: 11%
	Observation	89%	63.0 (15.0)	2.55 (0.1)	2.57 (0.07)	Not reported	HTN: 56% DM: 22% CAD: 11%
Pepe 2013	Parathyroidecto-my	100%	59.8 (7.2)	2.70 (0.10)	2.30 (0.14)	Not reported	Osteoporosis: total 70% Renal stones: total 38%
	C: observation	100%	60.2 (9.0)	2.70 (0.10)	2.70 (0.10)	Not reported	
Pepe 2018	Parathyroidecto-my	100%	66.0 (6.5)	2.73 (0.13)	2.45 (0.12)	Antihypertensives (total 39%) Statins (total 67%)	Osteoporosis: total 54% Renal stones: total 33%
	Observation	100%	70.6 (8.4)	2.73 (0.15)	2.72 (0.12)		
Talpos 2000	Parathyroidecto-my	84%	67.0 (7.0)	2.59 (0.14)	2.33 (0.1)	Overnight postoperative neck drain: 5%	Not reported
	Observation	75%	63.0 (7.0)	2.56 (0.13)	Not reported	Parathyroidectomy: 11%	Not reported

Ca: calcium; CAD: coronary artery disease; CVD: cerebrovascular disease; DM: diabetes mellitus; HTN: hypertension; SD: standard deviation.

Appendix 4. Matrix of study endpoints (publications and trial documents)

Study ID	Study endpoints
Almqvist 2004	**Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]**
	No trial documents available
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): not reported **Secondary outcome measure(s)**: not reported **Other outcome measure(s)**: BMD measurement, biochemical evaluation echocardiography
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): not reported **Secondary outcome measure(s)**: not reported **Other outcome measure(s)**: BMD measurements, biochemical evaluation, echocardiography
Ambrogini 2007	**Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]**
	No trial document available
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): BMD measurement at lumbar spine **Secondary outcome measure(s)**: BMD measurements at other locations, ECG measurements, quality of life and psychosocial well-being, complications of surgery and appearance of NIH criteria for parathyroidectomy in the observational study arm. **Other outcome measure(s)**: biochemical evaluation
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): BMD measurement **Secondary outcome measure(s)**: not reported **Other outcome measure(s)**: HRQOL measures
Bollerslev 2007	**Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]**
	Source: NCT00522028 **Primary outcome measure(s)**: not reported **Secondary outcome measure(s)**: not reported **Other outcome measure(s)**: not reported **Trial results available in trial register**: no

(Continued)

	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): not reported **Secondary outcome measure(s)**: not reported **Other outcome measure(s)**: BMD measurement, biochemical analysis, HRQOL, metabolic measures, biochemical markers of bone turnover, vertebral fracture assessment, radiography of the urinary tract, body composition measurements, echocardiographic measures
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): not reported **Secondary outcome measure(s)**: not reported **Other outcome measure(s)**: BMD measurement, biochemical analysis, metabolic measures, HRQOL, biochemical markers of bone turnover, body composition measurements, vertebral fracture assessment, echocardiographic measures
Horiuchi 2002	**Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]**
	No trial document available
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): not reported **Secondary outcome measure(s)**: not reported **Other outcome measure(s)**: BMD measurement, biochemical evaluation, spine X-ray
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): not reported **Secondary outcome measure(s)**: not reported **Other outcome measure(s)**: BMD measurement, biochemical evaluation, spine X-ray
Morris 2010	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]
	Source: NCT00501215 **Primary outcome measure(s)**: total sleep time **Secondary outcome measure(s)**: overnight sleep test **Other outcome measure(s)**: effectiveness of 2 sleep-related questionnaires **Trial results available in trial register**: no
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): not reported **Secondary outcome measure(s)**: not reported

(Continued)

	Other outcome measure(s): functional testing (walking and repeated sit-to-stand test), biochemical evaluation, sleep assessment, functional MRI, neuropsychological tests
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): not reported **Secondary outcome measure(s)**: not reported **Other outcome measure(s)**: functional testing (walking and repeated sit-to-stand test), biochemical evaluation, functional MRI, sleep assessment, neuropsychological tests
Pepe 2013	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]
	No trial document available
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): not reported **Secondary outcome measure(s)**: not reported **Other outcome measure(s)**: exercise testing, mineral metabolism, echocardiography
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): not reported **Secondary outcome measure(s)**: not reported **Other outcome measure(s)**: exercise testing, echocardiography, biochemical evaluation
Pepe 2018	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]
	No trial document available
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): not reported **Secondary outcome measure(s)**: not reported **Other outcome measure(s)**: cardiovascular risk factors, mineral metabolism biochemical evaluation, BMD measurement, standard ECG, 24-hour ECG
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): not reported **Secondary outcome measure(s)**: not reported **Other outcome measure(s)**: mineral metabolism biochemical evaluation, BMD measurement, standard ECG, 24-hour ECG
Talpos 2000	**Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]**

(Continued)

	No trial document available
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): not reported **Secondary outcome measure(s)**: not reported **Other outcome measure(s)**: physical examination, biochemical evaluation, X-rays, tomograms of the abdomen, BMD measurement, ECG, food-frequency questionnaire, HRQOL, adverse events
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): not reported **Secondary outcome measure(s)**: not reported **Other outcome measure(s)**: HRQOL, BMD measurement, biochemical evaluation, psychological function

[a] Trial document(s) refers to all available information from published design papers and sources other than regular publications (e.g. FDA/EMA documents, manufacturer's websites or trial registers).

[b] Publication(s) refers to study information published in scientific journals (primary reference, duplicate publications, companion documents or multiple reports of a primary study).
[c] Primary and secondary outcomes refer to verbatim specifications in publication/records. Unspecified outcome measures refer to all outcomes not described as primary or secondary outcome measures.

BMD: bone mineral density; ECG: electrocardiography; MRI: magnetic resonance imaging; HRQOL: health-related quality of life; NIH; National Institutes of Health; PHPT: primary hyperparathyroidism.

Appendix 5. Additional information requested from study authors

Study ID	Date of request	Date of reply	Short summary of information requested	Short summary of reply
Almqvist 2004	15 January 2020	No reply	Study protocol, SF-36 full data and companion publications other than 2 published papers	No reply
Ambrogini 2007	15 January 2020	22 January 2020	Study protocol, additional data on SF-36 scores and details of any trial registration	Study protocol and SF-36 data provided; confirmation that trial was not registered in any international registries, only hospital ethics committee
Bollerslev 2007	15 January 2020	27 January 2020	Additional data on SF-36 scores	Data unavailable
Horiuchi 2002	15 January 2020	No reply	Full study results, registration details, trial protocol and companion publications	Our emails bounced back (the study authors may have retired from the institution they worked for).

(Continued)

Morris 2010	18 January 2020/28 January 2020	04 February 2020	Follow-up data at 3 years as mentioned in study protocol and specific complications of surgery	3-year outcome data were not analysed
Pepe 2013/Pepe 2018	28 January 2020	29 January 2020	Clinical trial registration details, specific complications related to parathyroid surgery and types of parathyroidectomy	Trial not registered except with local ethics committee and parathyroidectomy was BNE in all cases, without complications
Talpos 2000	15 January 2020	29 January 2020	Additional data on SF-36 scores	PI agreed to look for data, but no update received at time of writing.
EudraCT2013-005027-16 (ongoing study)	24 January 2020	No reply	Date of study completion, available data and whether any interim analysis	No reply

BNE: bilateral neck exploration; PI: principal investigator; SF-36: 36-Item Short Form Health Survey.

Appendix 6. Health-related quality of life: instruments

Instrument	Dimensions (no. of items)	Validated instrument	Answer options	Scores	Minimum score Maximum score	Weighting of scores	Direction of scales	Minimal important difference
SF-36 (G) Employed in: Ambrogini 2007 Bollerslev 2007 Talpos 2000	Physical functioning (10) Role-physical (4) Bodily pain (2) General health (5) Vitality (4) Social functioning (2) Role-emotional (3) Mental health (5) Reported health transition (1)	Yes	3, 5 and 6-point Likert-scale	Scores for dimensions: Physical component summary (PCS); Mental component summary (MCS)	Minimum scores: scores for single dimensions/PCS/ MCS: norm-based scale Maximum scores: scores for single dimensions/PCS/ MCS: norm-based scale	No	Higher values mean better assessment	PCS: 2-3 points MCS: 3 points Dimensions: physical functioning/bodily pain/vitality: 2 points, if score < 40 3 points, if score ≥ 40 Role physical: 2 points Social functioning/mental health: 3 points Role emotional: 4 points

G: generic; S: specific; SF-36: 36-Item Short Form Health Survey.

Appendix 7. High risk of outcome reporting bias according to Outcome Reporting Bias In Trials (ORBIT) classification

Study ID	Outcome	High RoB (category A)[a]	High RoB (category D)[b]	High RoB (category E)[c]	High RoB (category G)[d]
Almqvist 2004	No outcome reporting bias detected				
Ambrogini 2007	**Serious adverse events**	No	Yes	No	No
	Cure of PHPT	No	No	No	No
	HRQOL	Yes	No	No	No
	Morbidity related to PHPT	No	Yes	No	No
Bollerslev 2007	**HRQOL**	Yes	No	No	No
Horiuchi 2002	No outcome reporting bias detected				
Morris 2010	No outcome reporting bias detected				
Pepe 2013	**Serious adverse events**	No	Yes	No	No
	Cure of PHPT	No	Yes	No	No
Pepe 2018	No outcome reporting bias detected				
Talpos 2000	**Serious adverse events**	No	Yes	No	No
	Cure of PHPT	No	Yes	No	No
	HRQOL	Yes	No	No	No
	Morbidity related to PHPT	No	Yes	No	No

[a] Clear that outcome was measured and analysed; study report states that outcome was analysed but reports only that result was not significant (Classification 'A', table 2, Kirkham 2010).
[b] Clear that outcome was measured and analysed;study report states that outcome was analysed but report no results (Classification 'D', table 2, Kirkham 2010).
[c] Clear that outcome was measured but was not necessarily analysed; judgement says likely to have been analysed but not reported due to non-significant results (Classification 'E', table 2, Kirkham 2010).
[d] Unclear whether outcome was measured; not mentioned, but clinical judgement says likely to have been measured and analysed but not reported on the basis of non-significant results (Classification 'G', table 2, Kirkham 2010).

HRQOL: health-related quality of life; PHPT: primary hyperparathyroidism; RoB: risk of bias.

Appendix 8. Adverse events

Study ID	Intervention and control	Participants included in analysis (n)	Deaths (n (%))	Participants with AEs (n (%))	Dropouts due to AEs (n (%))	Participants with SAEs (n (%))	Participants with ≥ 1 hospitalisation (n (%))	Participants with specific AEs (description; n (%))
Almqvist 2004	Parathyroidectomy	23	NR	NR	0 (0)	0 (0)	2 (9)	NR
	Observation	25	NR	NR	1 (4)	0 (0)	0 (0)	Angina pectoris; 1 (4)
Ambrogini 2007	Parathyroidectomy	24	NR	NR	0 (0)	0 (0)	1 (4)	NR
	Observation	25	NR	NR	1 (4)	0 (0)	0 (0)	Renal stone; 1 (4) Vertebral fracture; 1 (4)
Bollerslev 2007	Parathyroidectomy	65	2 (3)	NR	NR	NR	0 (0)	Parathyroid cancer; 1 (2)
	Observation	59	1 (2)	NR	NR	NR	5 (8)	Hypercalcaemia; 4 (7) Paget´s disease; 1 (2)
Horiuchi 2002	Parathyroidectomy	13	NR	NR	0 (0)	NR	NR	NR
	Treatment with etidronate	9	NR	NR	0 (0)	NR	NR	NR
Morris 2010	Parathyroidectomy	9	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NR
	Observation	9	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NR
Pepe 2013	Parathyroidectomy	12	NR	NR	0 (0)	NR	NR	NR
	Observation	12	NR	NR	0 (0)	NR	NR	NR
Pepe 2018	Parathyroidectomy	13	NR	NR	0 (0)	NR	0 (0)	NR
	Observation	13	NR	NR	0 (0)	NR	0 (0)	NR
Talpos 2000	Parathyroidectomy	25	NR	0 (0)	0 (0)	1 (4)	2 (8)	Recurrent hyperparathyroidism; 3 (12)

(Continued)

	Observation	28	NR	0 (0)	0 (0)	0 (0)	3 (11)	Pancreatitis; 1 (4) Renal stone; 1 (4) Vertebral fracture; 1 (4)

AE: adverse event; NR: not reported; SAE: serious/severe adverse event.

HISTORY

Protocol first published: Issue 5, 2018

CONTRIBUTIONS OF AUTHORS

JMP: protocol draft, search strategy development, acquisition of study reports, study selection, data extraction, data interpretation, review of the draft and review updates
IML: protocol draft, search strategy development, acquisition of study reports, data analysis, review of the draft and review updates
AKV: protocol draft, search strategy development, study selection, data interpretation, review of the draft and review updates
FB: acquisition of study reports, study selection, data extraction, review of the draft and review updates
RS: protocol draft, search strategy development, study selection, review of the draft and review updates
MIM: search strategy development, data interpretation, review of the draft and review updates
BB: data extraction, data analysis, data interpretation, review of the draft and review updates

DECLARATIONS OF INTEREST

JMP: none known
IML: none known
AKV: received speakers fees for providing diabetes educational meetings for GPS/Primary care colleagues. These events were supported by various pharmaceutical companies. Received support from pharmaceutical companies to attend international diabetes conferences.
FB: none known
RS: received speakers fees for providing biochemistry educational meetings for GPS/Primary care colleagues.
MIM: none known
BB: none known. She is the Co-ordinating Editor of the CMED Group. Nevertheless, she was excluded from the editorial processing of this protocol, and an independent editor acted as Sign-off Editor.

SOURCES OF SUPPORT

Internal sources

- Department of Endocrinology & Metabolism, Lancashire Teaching Hospitals NHS Trust, Preston, UK

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

See Pappachan 2018 (review protocol).

- We simplified the objective to: "To evaluate the benefits and harms of parathyroidectomy for adults with PHPT compared to simple observation or medical therapy."
- We deleted "We will define any follow-up period going beyond the original time frame for the primary outcome measure as specified in the power calculation of the trial's protocol as an extended follow-up period (also called open-label extension study) (Buch 2011; Megan 2012)." as it did not apply to our review.
- We deleted the outcome 'Socioeconomic effects' because MECIR guidance indicates that additional methods are needed to include them.
- We changed the outcome 'Adverse events of surgery' to 'Serious adverse events', considering that the formulation would be better suited for both arms of the main comparison (where one arm did not undergo surgery)
- We specified that we would use risk ratio as a measure of treatment effect.
- We added more specifications to the section on risk of bias, assessment of heterogeneity, data synthesis and GRADE based on the updated *Cochrane Handbook for Systematic Reviews of Interventions*, and we corrected the references (Higgins 2022). We restricted sensitivity analysis to considerations of the risk of bias.

We planned to investigate the effects of parathyroidectomy on PHPT-related morbidities such as osteoporosis, osteopenia or acute kidney injury. However, the included RCTs did not report these parameters directly, so we were unable to meta-analyse these outcomes. We performed a post-hoc analysis to examine BMD outcomes as a surrogate marker for these morbidities (we downgraded the certainty of the evidence due to indirectness).

We also planned to compare the effects of different types of parathyroidectomy, such as minimally invasive parathyroidectomy and bilateral neck exploration; however, no studies provided the necessary data for this subgroup analysis. There was also insufficient data to perform sensitivity analysis.

INDEX TERMS

Medical Subject Headings (MeSH)

*Cardiovascular Diseases; *Hypercalcemia [etiology]; *Hyperparathyroidism, Primary [complications] [surgery]; *Osteoporosis; Parathyroid Hormone; Parathyroidectomy [adverse effects]; Randomized Controlled Trials as Topic

MeSH check words

Aged; Female; Humans; Male