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Thyroid Cancer and Structural Thyroid Disease in Patients with Acromegaly: A Systematic Review and Meta-Analysis

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Abstract

Purpose: Acromegaly causes chronic growth hormone and insulin-like growth factor-1 excess, which may promote thyroid proliferation. Whether acromegaly increases thyroid cancer and structural thyroid disease odds remains uncertain. So we aim to determine whether patients with acromegaly have higher odds of thyroid cancer and structural thyroid abnormalities than individuals without acromegaly.

Methods: PubMed, Embase, and Cochrane Library were searched from inception to March 2026. Observational comparative studies of patients with acromegaly and non-acromegaly comparators reporting thyroid outcomes were eligible. Case reports, case series, reviews, abstracts, overlapping populations and studies without comparative thyroid cancer data were excluded. Two reviewers independently screened records; 13 of 2,623 were included. Three reviewers independently extracted study characteristics, participant data, acromegaly criteria, thyroid cancer subtypes, nodular disease, volume, and biochemical outcomes. Risk of bias was assessed using ROBINS-E or JBI, and certainty was evaluated using GRADE.

Results: Thirteen studies included 719,090 participants; 2,674 had acromegaly. Acromegaly was associated with higher odds of overall thyroid cancer (OR 4.00, 95% CI 2.21 – 7.24), papillary carcinoma (OR 2.81, 95% CI 1.60 – 4.91) and thyroid nodular disease (OR 2.60, 95% CI 1.80 – 3.76). Thyroid volume was greater in acromegaly (MD 12.57 mL, 95% CI 5.27 – 19.86). Follicular thyroid carcinoma, free thyroxine and thyroid-stimulating hormone did not differ significantly.

Conclusion: Acromegaly was associated with thyroid cancer and structural thyroid disease, but not with significant differences in routine thyroid function markers.

Abbreviations

CI, Confidence Interval

EHR, Electronic Health Record

FT4, Free Thyroxine

GH, Growth Hormone

GRADE, Grading of Recommendations Assessment, Development, and Evaluation

IGF-1, Insulin-Like Growth Factor Type 1

JBI, Joanna Briggs Institute

MD, Mean Difference

OGTT, Oral Glucose Tolerance Test

OR, Odds Ratio

PRISMA, Preferred Reporting Items For Systematic Reviews And Meta-Analyses

PROSPERO, International Prospective Register of Systematic Reviews

REML, Restricted Maximum Likelihood

ROBINS-E, Risk Of Bias In Nonrandomized Studies Of Exposure

ROBVIS, Risk-Of-Bias VISualization

SIR, Standard Incidence Ratio

T3, Triiodothyronine

T4, Thyroxine

TACC, Treatment-arm continuity correction

TRH, Thyrotropin-releasing hormone

TSH, Thyroid-Stimulating Hormone

1. Introduction

Acromegaly is a chronic and systemic disease caused by the hypersecretion of growth hormone (GH), and consequent overproduction of insulin-like growth factor 1 (IGF-1) [1]. This hormonal dysregulation primarily stems from benign pituitary adenomas (somatotropinoma) in approximately 98% of cases [2]. The presentation of acromegaly is often insidious, and the prolonged period of undiagnosed disease contributes to the manifestation of various multisystem morbidities, including thyroid cancer [3–6].

The relationship between GH/IGF-1 excess and thyroid alterations is partly explained by upregulation of type 2 deiodinase activity, which increases thyroxine (T4) to triiodothyronine (T3) conversion, and by direct IGF-1-mediated trophic stimulation of thyroid tissue [5, 6]. However, the pathophysiology likely extends beyond these mechanisms, as altered sympathetic tone, leptin, somatostatin, and dopamine signaling have also been associated with thyroid dysfunction in acromegaly [7, 8], pointing to a complex, multifactorial process. The extent to which these pathways translate into clinically significant thyroid abnormalities, and which specific alterations are most prevalent, remains unclear.

Previous systematic reviews have suggested that acromegaly may be associated with increased odds of several neoplastic outcomes, including thyroid cancer [7–10]. However, this paper includes more recent studies [11–16] and enhances the relationship between acromegaly and thyroid abnormalities by including subgroups not yet analyzed, such as the type of thyroid cancer and thyroid volume. In light of this, we aim to conduct an updated systematic review and meta-analysis to evaluate the odds of thyroid cancer occurrence in patients with acromegaly compared with those without it, with a particular focus on control group differences, nodular thyroid disease, thyroid volume, and selected thyroid- and acromegaly-related biochemical parameters.

2. Materials and Methods

This review was prospectively registered in PROSPERO (CRD420251266153) and reported according to PRISMA 2020 [17, 18]. Post-registration deviations included broadening comparators beyond demographically matched groups, prioritizing thyroid cancer over nodular disease, using odds ratios instead of risk ratios, replacing DerSimonian–Laird with REML/Paule–Mandel, and applying design-specific ROBINS-E/JBI assessments. Additional secondary outcomes were examined; some originally planned outcomes were not synthesized. Changes and justifications are detailed in ***Online Resource 1***.

2.1 Eligibility Criteria

Eligible studies were comparative observational investigations, including cohort, case-control, and cross-sectional designs, reporting thyroid cancer in patients with clinically, biochemically, and/or radiologically diagnosed acromegaly and controls without acromegaly. Biochemical criteria could include elevated GH or IGF-1 and failure of GH suppression during an oral glucose tolerance test. Comparators could be healthy individuals, patients with other endocrine disorders, or hospital- or population-based controls. Thyroid cancer was identified using the original studies' reported histopathology, malignant cytology, or clinical/administrative diagnoses. Indeterminate cytology or suspicious ultrasound findings alone were not regarded as cancer. Studies reporting only benign thyroid outcomes were ineligible because inclusion was determined by the primary thyroid cancer outcome. Studies with incident or prevalent thyroid cancer were eligible when comparative data were available. We excluded case reports, non-comparative case series, reviews, editorials, letters, experimental studies, conference abstracts, reports without comparative thyroid cancer data, and overlapping populations when a more informative dataset was available. Secondary outcomes were extracted only from studies eligible for the primary outcome.

2.2 Search Strategy and Study Selection

PubMed, Embase, and the Cochrane Library were searched from inception through March 2026. Reference lists of included studies and relevant reviews were screened; database-specific search strategies are provided in ***Online Resource 1***. After deduplication, two reviewers (A.L. and M.K.) independently screened titles, abstracts, and eligible full texts using Rayyan. Studies were not selected based on the direction or statistical significance of their findings. Disagreements were resolved by discussion or consultation with a third reviewer (P.D.). Full-text exclusions are documented in ***Online Resource 1***.

2.3 Data Extraction

Three reviewers (A.L.; R.P. and S.H.) independently extracted baseline characteristics, such as: (1) study design; (2) country; (3) study setting; (4) comparator type; (5) sample size; (6) participant characteristics; (7) diagnostic criteria for acromegaly; (8) thyroid outcome definitions; (9) thyroid cancer subtype; (10) nodular thyroid disease; (11) thyroid volume, and (12) biochemical outcomes of interest. When overlapping populations were identified, the study with the larger or more informative dataset was retained for quantitative synthesis.

Hormonal measurements were standardized to mIU/L for TSH, ng/dL for free T4, and ng/mL for GH and IGF-1 before quantitative synthesis.

When raw event counts were not explicitly reported, but percentages and denominators were available, event counts were back-calculated and rounded to the nearest whole number. Medians and subgroup-specific descriptive data were retained as reported for baseline characterization and were not converted to means for quantitative synthesis. For continuous outcomes, studies were included only when mean, standard deviation, and sample size were

available. When studies reported composite or overlapping thyroid findings or ambiguous histological terminology, outcomes were classified conservatively, and any reconstructed values or classification decisions were documented in ***Online Resource 1***.

2.4 Outcomes

The primary outcome was the odds of thyroid cancer in patients with acromegaly compared with controls. Secondary outcomes included (1) thyroid nodular disease detected by ultrasonography; (2) thyroid cancer subtype; (3) thyroid volume in mL; (4) serum thyroid-stimulating hormone (TSH), and (5) free T4 (fT4).

2.5 Subgroup Analyses

Subgroup analyses were performed according to thyroid cancer histological subtype and comparator-group characteristics. Control-group subgroup analyses were considered exploratory.

2.6 Risk of Bias, Quality of Evidence and Reporting Bias Assessment

We assessed the risk of bias according to study design. Risk of bias in nonrandomized studies of exposure (ROBINS-E) [17, 19] was applied to follow-up observational exposure studies [15, 20, 21]. The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies [17, 22] was applied to the remaining comparative observational studies [11–14, 16, 23–26]. The exact risk of bias assessment tool used for each study available in ***Online Resource 1***. Two reviewers (A.L. and A.D.) independently performed all assessments, and disagreements were resolved by consensus. Graphical summaries of the risk-of-bias assessments were produced with the Robvis (Risk-of-Bias VISualization) tool [27].

The overall quality of evidence was evaluated with the grading of recommendations assessment, development, and evaluation (GRADE) [17, 28] approach, implemented through GRADEpro GDT [17, 29]. Two authors (A.L. and A.D.) independently performed risk-of-bias and GRADE assessments, with disagreements resolved through consensus.

2.7 Statistical Analysis

All statistical analyses were performed using R version 4.5.2 and the *meta* package. Binary outcomes were based on non-adjusted estimates from original studies results and pooled as odds ratios (ORs), and continuous outcomes as mean differences (MDs), using inverse-variance random-effects models [30, 31]. Between-study variance (τ^2) was estimated using restricted maximum likelihood for overall thyroid cancer and Paule–Mandel for the remaining comparative outcomes. Hartung–Knapp confidence intervals were used for the main pooled analyses, whereas conventional random-effects confidence intervals were used for exploratory control-group subgroup analyses. For binary outcomes, a continuity correction of 0.5 was applied to studies with zero-event cells . A post hoc sensitivity analysis using treatment-arm continuity correction (TACC) assessed the robustness of the overall thyroid cancer estimate and post hoc sensitivity analysis excluded Can et al. [14], because thyroid malignancy was reported only by cytology and patients with previously diagnosed thyroid cancer had been excluded from the acromegaly group. All statistical settings were maintained.

Single-arm GH and IGF-1 concentrations were pooled descriptively using random-effects models with Paule–Mandel estimation and Hartung–Knapp confidence intervals. GH means were analyzed on a logarithmic scale and subsequently back-transformed to ng/mL for presentation, while IGF-1 means were analyzed on their original scale [32–35] **(*Online Resource 1)***. Heterogeneity was assessed using Cochran's Q and I^2 statistics. Leave-one-out analyses assessed the influence of individual studies. Funnel plot asymmetry was assessed

visually for the primary thyroid cancer outcome and investigated using Egger's regression test [17].

3. Results

3.1 Study Selection

The database search identified 2,623 records. After duplicate removal and title/abstract screening, 28 reports were assessed in full text. Fifteen reports were excluded for predefined reasons, including conference abstract only (n = 4), no thyroid cancer data (n = 7), overlapping populations (n = 1), wrong population (n = 1), and inappropriate control group (n = 2). Thirteen studies were ultimately included in the systematic review and meta-analysis, comprising 719,090 patients, of whom 2,674 (0.37%) were diagnosed with acromegaly [8, 11–16, 20, 21, 23–26] (***Fig. 1***).

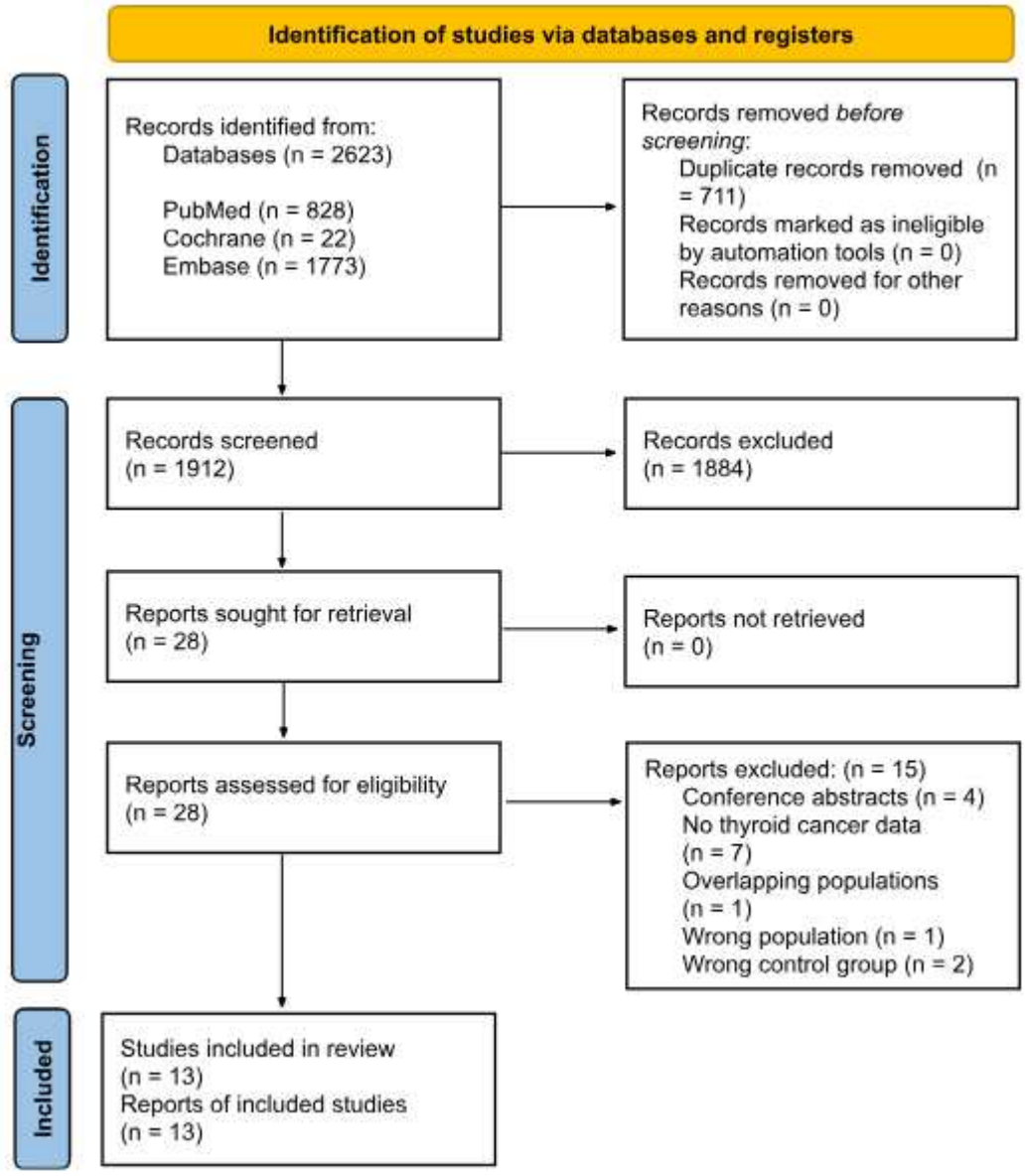


Fig. 1 PRISMA flowchart detailing a four-stage systematic review process: Identification, Screening, Eligibility, and Inclusion. The process begins with 2623 articles identified, then 711 duplicates are removed, resulting in 1912 articles available for abstract screening. After that, 1884 studies were excluded, leaving 28 full texts for full-text screening. At the end, 15 articles are excluded and 13 articles are ultimately included in the final review

3.2 Baseline Population Characteristics

Baseline characteristics were variably reported across the 13 included studies. Study sample sizes ranged from 56 to 718 patients in the acromegaly groups and from 50 to 707,503 participants in the control groups. Across studies, the overall study-level mean age was 49.5 years, with mean ages of 49.4 years in acromegaly cohorts and 49.5 years in control cohorts.

The mean proportion of women was 56.2% in the acromegaly group and 60.6% in the control group.

Acromegaly-specific variables were less consistently available. Reported mean disease duration from diagnosis ranged from 6.7 to 8.0 years, while reported symptom duration before diagnosis ranged from 5.4 to 8.0 years. Among studies reporting disease activity, the proportion of patients with active acromegaly ranged from 51.4% to 100%. Macroadenomas accounted for 73.4% to 88.5% of cases and microadenomas for 11.5% to 16.6% among studies reporting adenoma size. Prior acromegaly treatment was inconsistently reported: when available, surgery or hypophysectomy ranged from 51.4% to 97.0%, radiotherapy from 7.7% to 36.6%, and somatostatin analogue use from 32.9% to 100%. Comparator groups and thyroid evaluation methods varied across studies and are summarized in ***Table 1*** and ***Online Resource 1***.

Table 1: Study design, population, comparator, and demographic characteristics

Study (year)	Country / period	Design and data source	Comparator / control group	N (acromegaly / control)	Age (mean +/- SD)	Sex
Barzilay et al. (1991)	USA; 1957-1988.	Retrospective record review / comparative cohort. Malignancy rates were compared with pituitary tumor controls and with Connecticut Tumor Registry rates.	Patients with non-GH-secreting pituitary tumors; Cushing disease excluded. Registry comparator also used for standardized malignancy rates.	87 / 198	Median age at diagnosis: 37.0 y (range 16-70) / 44.0 y (range 11-82).	M/F: 44/43 / 93/105; women: 49.4% / 53.0%.
Can et al. (2021)	Turkey; July-December 2020.	Comparative cross-sectional thyroid ultrasound study.	Healthy volunteers matched by age, sex, and BMI; controls with known thyroid disease were excluded.	56 / 56	47.41 +/- 11.73 y / 44.70 +/- 7.07 y.	Female: 34/56 (60.7%) / 35/56 (62.5%).
Cankurtaran et al. (2023)	Turkey; 2006-2018.	Retrospective comparative study using medical records.	Patients who underwent thyroid ultrasonography for dysphagia and/or neck swelling; 280 sampled from database, 33 excluded for missing data.	129 / 247	40.7 +/- 12.5 y / 48.4 +/- 15.5 y.	Female: 78/129 (60.5%) / 151/247 (61.1%).
dos Santos et al. (2013)	Brazil.	Cross-sectional study with control group.	Volunteers older than 18 years matched by age and sex; 39 controls had microadenoma (prolactinoma or nonfunctioning adenoma) with normal GH and IGF-1.	124 / 263	45.1 +/- 13.4 y (range 18-77) / 44.7 +/- 13.4 y (range 19-81).	Female: 76/124 (61.3%) / 156/263 (59.3%).
Gasperi et al. (2002)	Italy.	Italian multicenter comparative cross-sectional study.	Pituitary adenoma controls: 44 non-functioning pituitary adenomas and 106 prolactin-secreting pituitary adenomas.	258 / 150	50 +/- 13 y (range 17-80) / 48 +/- 15 y (range 13-85).	Female: 147/258 (57.0%) / 122/150 (81.3%).
Herrmann et al. (2004)	Germany.	Retrospective comparative basal evaluation with longitudinal follow-up subgroup.	199 thyroid-screening volunteers from the same clinic; age/sex comparable; 14% had thyroid disease history and received iodide and/or levothyroxine.	73 / 199	55 +/- 13 y (range 32-82) / 54 +/- 5 y (range 32-72).	M/F: 34/39 / 88/111; women: 53.4% / 55.8%.
Iglesias et al. (2024)	Spain; 2008- 2023.	Retrospective observational real-world EHR / NLP / big-data study using Savana Manager 4.0.	All hospital patients without acromegaly in the same EHR database.	544 / 707,503	64.2 +/- 16.0 y / 60.0 +/- 19.9 y; mean age at acromegaly	Female: 330/544 (60.7%) / 387,182/707,503 (54.7%).

Study (year)	Country / period	Design and data source	Comparator / control group	N (acromegaly / control)	Age (mean +/- SD)	Sex
					diagnosis: 53.0 +/- 15.8 y.	
Park et al. (2020)	South Korea; 2010-2017.	Nationwide population-based cohort / longitudinal case-control study using claims data.	Ten age- and sex-matched controls per acromegaly patient, randomly selected among patients who had undergone appendectomy and had no acromegaly diagnosis.	718 / 7,180	Acromegaly: 46.0 +/- 12.9 y overall; 43.5 +/- 12.6 y in males; 47.9 +/- 12.8 y in females. Controls were age-matched; exact mean NR.	Acromegaly: male 311 (43.3%), female 407 (56.7%); controls: male 3,110, female 4,070.
Popovic et al. (1998)	Yugoslavia (present-day Serbia).	Retrospective clinical-record review comparing neoplasia rates in pituitary adenoma groups.	Non-functioning pituitary tumors (n = 151), prolactinomas (n = 98), and cancer registry expected rates. Aditiona group ofl 163 patients with Grave's disease not included in our analysis.	220 / 249 (151 NFPA and 98 prolactinoma)	Mean +/- SE age at diagnosis: acromegaly 49.5 +/- 0.9 y; NFPA 47.6 +/- 1.0 y; prolactinoma 39.9 +/- 1.4 y.	M/F: acromegaly 83/137; NFPA 65/86; prolactinoma 31/67.
Reverter et al. (2014)	Spain.	Multicenter cross-sectional study with control group.	Otherwise healthy adult controls older than 18 years.	123 / 50	59 +/- 13 y / 58 +/- 15 y.	Acromegaly: 50% male; controls: 51% male. Absolute counts NR.
Selman et al. (2020)	Iraq; January-December 2017.	Case-control / comparative cross-sectional study.	Healthy controls reported as age- and sex-matched in methods.	70 / 70	46 +/- 11 y (table: 46.2 +/- 10.9) / 42.9 +/- 14.3 y.	Female: 29/70 (41.5%) / 47/70 (67.0%); male: 41/70 (58.5%) / 23/70 (33.0%).
Wolinski et al. (2017)	Poland; 2003-2013.	Retrospective case-control study plus updated meta-analysis.	Patients with small, benign, hormonally inactive adrenal incidentalomas; lesions >4 cm, hormonal activity, or malignant character were excluded.	205 / 184	52.6 +/- 12.3 y / 53.9 +/- 12.7 y.	Female: 124/205 (60.5%) / 120/184 (65.2%).
Xu et al. (2019)	China; 2015-2017.	Retrospective comparative study with 1-year postoperative follow-up subgroup.	Patients with non-functioning pituitary adenoma.	67 / 67	NR.	NR.

Abbreviations: ACR TI-RADS, American College of Radiology Thyroid Imaging Reporting and Data System; AUS/FLUS, atypia/follicular lesion of undetermined significance; BMI, body mass index; CT, computed tomography; DTC, differentiated thyroid cancer; EHR, electronic health record; FNA/FNAB/FNAC, fine-needle aspiration/biopsy/cytology; FTC, follicular thyroid carcinoma; GH, growth hormone; HIRA, Health Insurance Review and Assessment; IGF-1, insulin-like growth factor 1; IQR, interquartile range; LT4, levothyroxine; MNG, multinodular goiter; MRI, magnetic resonance imaging; NFPA, non-functioning pituitary adenoma; NLP, natural language processing; NR, not reported; OGTT, oral glucose tolerance test; PRL, prolactin; PTC, papillary thyroid carcinoma; SSA, somatostatin analogue; TNG, toxic nodular goiter; TSA, transsphenoidal approach; TSH, thyroid-stimulating hormone; US, ultrasonography; SD, standard deviation; SE, standard error

3.3 Pooled Outcomes

3.3.1 Thyroid cancer

Our results showed that patients with acromegaly were significantly associated with increased odds of thyroid cancer compared with controls (OR 4.00, 95% CI 2.21 – 7.24; P = 0.0003; I^2 = 47.4%; ***Fig. 2***).

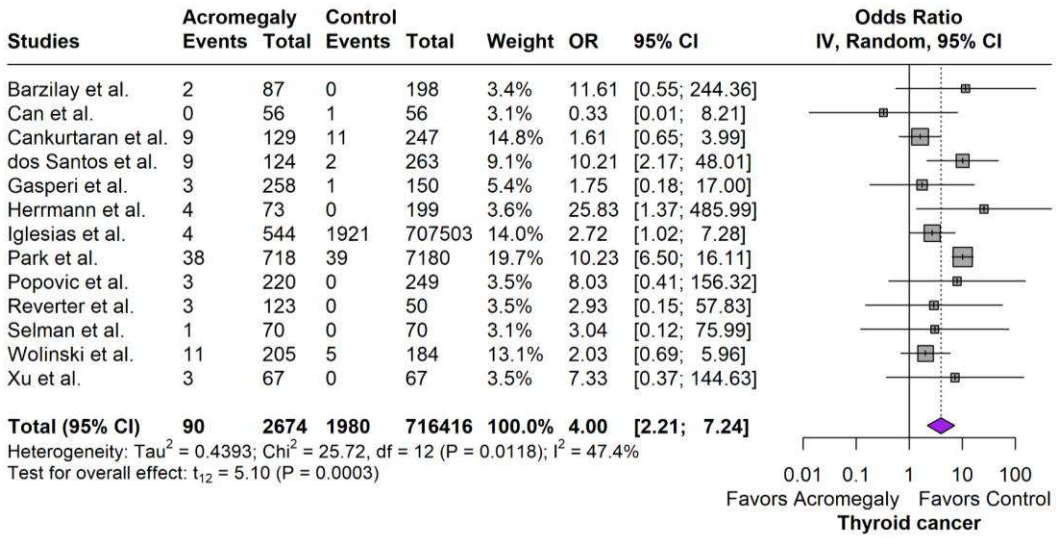


Fig. 2 Forest plot showing individual and pooled ORs for Thyroid Cancer outcome with 95% confidence intervals and p-values among acromegaly patients and control groups. Acromegaly was significantly associated with thyroid cancer when compared with control group

3.3.2 Thyroid cancer subtypes

In thyroid cancer subtypes subgroup analyses, acromegaly was associated with increased odds of papillary thyroid cancer compared with the control group (OR 2.81, 95% CI 1.60 – 4.91; P = 0.0003; I^2 = 0%; ***Fig. 3***). While follicular thyroid cancer odds were not statistically significant (OR 5.05, 95% CI 0.79 – 32.21; P = 0.0866; I^2 = 0%; ***Fig. 3***). However, no statistically significant difference was detected between histological subgroups (P = 0.5520; ***Fig. 3***).

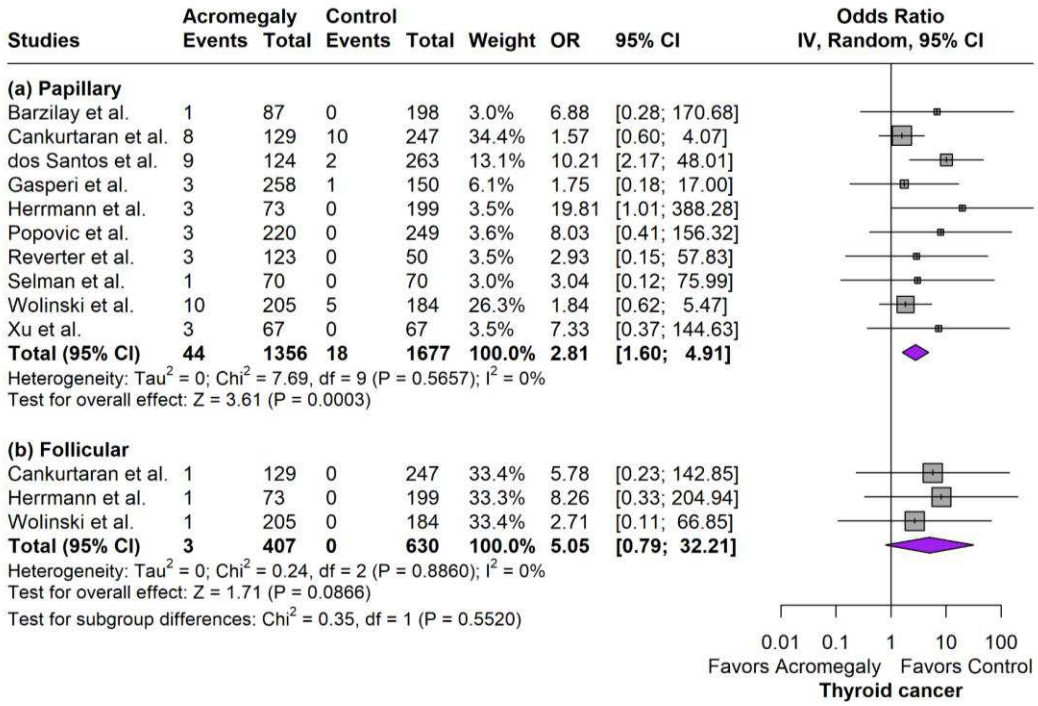


Fig. 3 Forest plot showing individual and pooled ORs for Thyroid Cancer Subtypes: (a) Papillary and (b) Follicular carcinomas outcome with 95% confidence intervals and p-values among acromegaly patients and control groups. Acromegaly was significantly associated with (a) papillary thyroid cancer when compared with control group

3.3.3 Thyroid cancer control group subtypes exploratory analysis

Exploratory analyses stratified by comparator type yielded ORs of 4.85 (95% CI 1.22 – 19.24; P = 0.0246; I^2 = 0%; ***Fig. 4***) for non-GH-secreting pituitary adenomas, 4.48 (95% CI 0.32 – 61.76; P = 0.2631; I^2 = 68.1%; ***Fig. 4***) for thyroid disease screening populations, and 1.49 (95% CI 0.24 – 9.08; P = 0.6678; I^2 = 0%; ***Fig. 4***) for healthy controls. Although the association reached statistical significance only in the non-GH-secreting pituitary adenoma subgroup, no statistically significant difference was detected between subgroups (P = 0.5770; ***Fig. 4***).

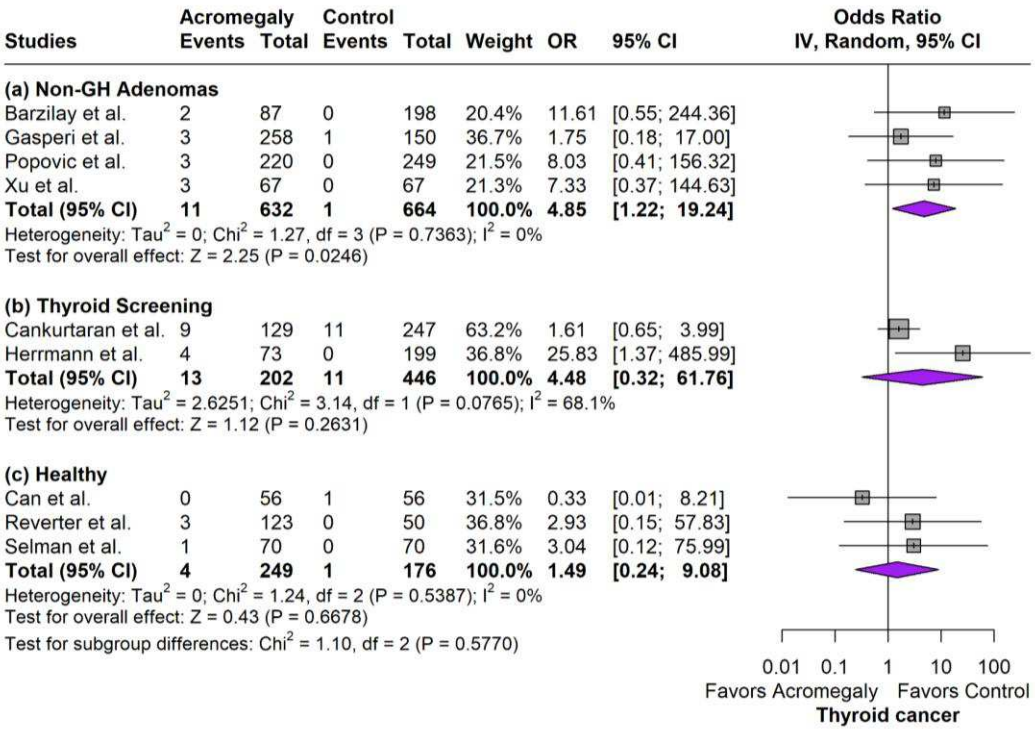


Fig. 4 Forest plot for control group subgroup analysis showing individual and pooled ORs for thyroid cancer according to control group subtypes: (a) non-GH-secreting pituitary adenomas, (b) patients undergoing thyroid disease screening, and (c) healthy controls, with 95% confidence intervals and p-values. No statistically significant differences were detected between subgroups (P = 0.5770).

3.3.4 Thyroid nodular disease

Our results showed that acromegaly was significantly associated with increased odds of ultrasonography-detected thyroid nodular disease when compared with the control group (OR 2.60, 95% CI 1.80 – 3.76; P = 0.0011; I^2 = 30.8%; ***Fig. 5***).

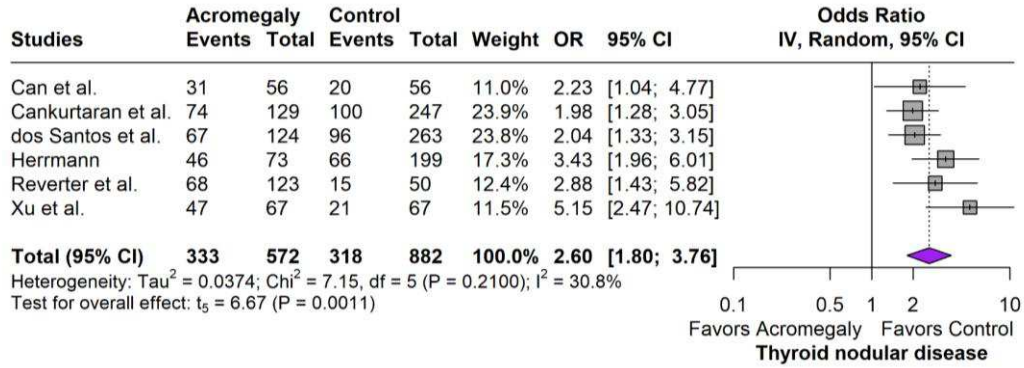


Fig. 5 Forest plot showing individual and pooled ORs for Thyroid Nodular Disease outcome with 95% confidence intervals and p-values among acromegaly patients and control groups. Acromegaly was significantly associated with thyroid nodular disease when compared with control group

3.3.5 Thyroid volume

Thyroid volume was significantly higher in patients with acromegaly (MD 12.57 mL, 95% CI 5.27 – 19.86; P = 0.0068; I^2 = 92.5%; ***Fig. 6***) compared with the control group.

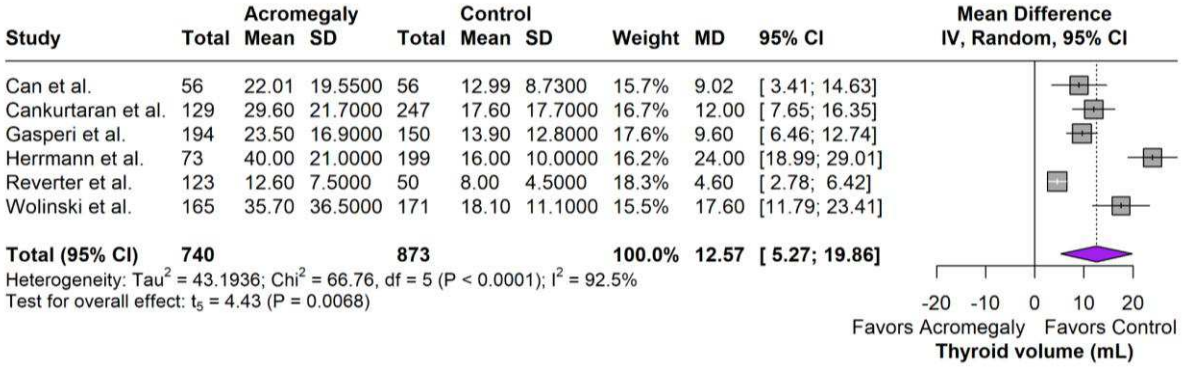


Fig. 6 Forest plot showing individual and pooled MDs for Thyroid Volume outcome with 95% confidence intervals and p-values among acromegaly patients and control groups. Thyroid volume was significantly increased in patients with acromegaly compared with control group

3.3.6 Serum Free T4 and TSH levels

There were no significant differences between groups in serum fT4 (MD 0.01 ng/dL, 95% CI -0.39 to 0.42; P = 0.9095; I^2 = 72.8%; ***Fig. 7***) and TSH levels (MD -0.72 mIU/L, 95% CI -2.71 – 1.27; P = 0.2591; I^2 = 83.8%; ***Fig. 8***).

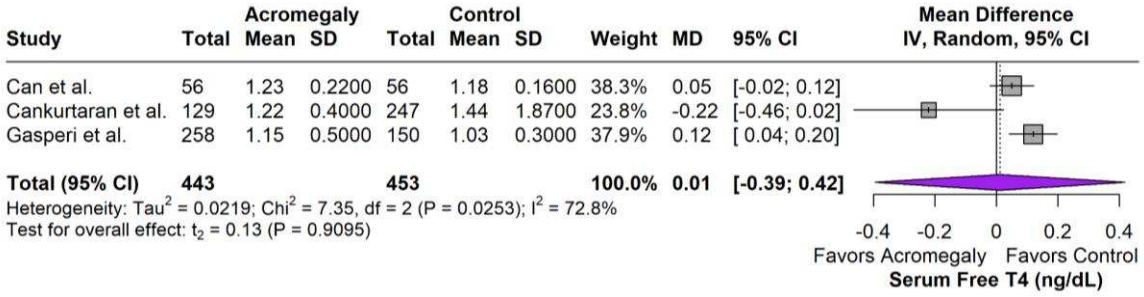


Fig. 7 Forest plot showing individual and pooled MDs for Serum fT4 Levels outcome with 95% confidence intervals and p-values among acromegaly patients and control groups. No statistically significant difference was detected in the pooled analysis for serum fT4 in patients with acromegaly compared with control group

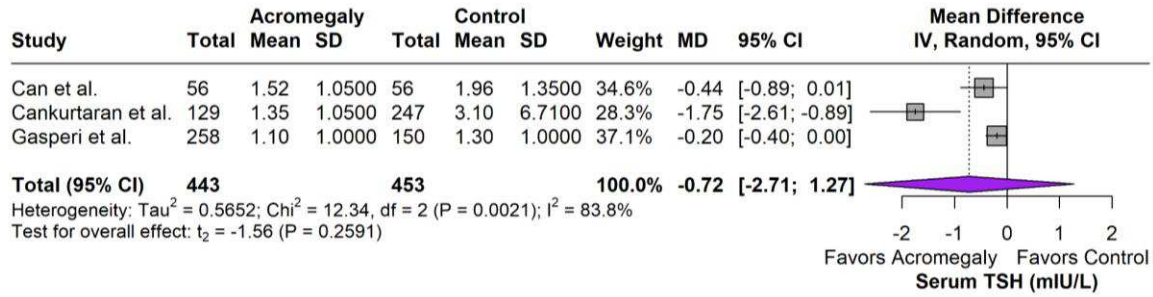


Fig. 8 Forest plot showing individual and pooled MDs for Serum TSH Levels outcome with 95% confidence intervals and p-values among acromegaly patients and control groups. No statistically significant difference was detected in the pooled analysis for serum TSH in patients with acromegaly compared with control group

3.4 Sensitivity analysis

Leave-one-out analyses showed that the pooled associations for thyroid cancer, nodular disease, and thyroid volume remained statistically significant after omitting each study in turn. Nevertheless, substantial heterogeneity persisted for thyroid volume, so statistical stability did not establish methodological comparability. Treatment-arm continuity correction yielded OR 4.03 (95% CI 2.28–7.15; $I^2 = 47.1\%$) for thyroid cancer. Excluding Can et al. [14] produced a similar result (OR 4.33, 95% CI 2.48–7.58; $I^2 = 48.0\%$; ***Online Resource 1***).

3.5 Publication Bias, Risk of Bias and Certainty of Evidence

The thyroid cancer funnel plot suggested possible asymmetry, but Egger's test was not statistically significant ($t = -1.25$, $df = 11$, $P = 0.2360$; ***Online Resource 1***). ROBINS-E classified one longitudinal study at high and two at very high risk of bias. Among ten JBI-assessed studies, reviewer-defined overall categories were low for three, moderate for one, and high for six; JBI does not prescribe these overall categories. Major concerns included limited adjustment for confounding, selection of non-equivalent comparator groups, and differences in thyroid imaging, follow-up, or cancer ascertainment. The three studies rated low using the reviewer-defined JBI summary were dos Santos et al. [23], Reverter et al. [26], and Woliński et al. [8].

GRADE certainty was very low for all five comparative outcomes: thyroid cancer, nodular disease, thyroid volume, TSH, and free T4. Thyroid cancer and nodular disease were downgraded for serious risk of bias; thyroid volume additionally for inconsistency; and TSH and free T4 for inconsistency and imprecision. The Summary of Findings and individual risk-of-bias judgments appear in ***Online Resource 1***.

4. Discussion

This synthesis of 13 observational studies (719,090 participants; 2,674 with acromegaly) found higher odds of thyroid cancer, papillary carcinoma, and nodular disease, alongside greater thyroid volume. Follicular carcinoma, TSH, and free T4 estimates were inconclusive. The thyroid cancer association persisted in sensitivity analyses, although GRADE certainty was very low.

Our findings are consistent with previous meta-analyses reporting higher thyroid cancer occurrence in acromegaly [7–10]. GH/IGF-1 signaling may stimulate thyrocyte proliferation and inhibit apoptosis, providing biological plausibility for thyroid growth and neoplasia [5, 8]. Nevertheless, biological plausibility does not establish causation. Several individual studies reported nonsignificant associations [8, 11, 12, 14, 16, 21, 24, 26], potentially reflecting small samples, infrequent cancer events, or differences in disease activity and treatment. The pooled OR of 4.00 derives from unadjusted observational comparisons and should not be interpreted as a fourfold increase in incident cancer risk. Only 90 thyroid cancer events occurred among participants with acromegaly, while the large control sample was dominated by an administrative database [13]. These characteristics limit the precision and generalizability of causal interpretation despite statistical significance.

For histological subtypes, the association was evident mainly for papillary carcinoma; the follicular estimate was imprecise and included the null. The nonsignificant interaction test does not establish equivalent associations between histological subtypes. Given the sparse events and wide confidence intervals, these subtype findings should be interpreted as exploratory rather than definitive.

Comparator selection and surveillance intensity were major concerns. Included studies compared patients with acromegaly against healthy volunteers, other pituitary or endocrine disease groups, thyroid-screening populations, and hospital or administrative controls. These populations may differ in baseline thyroid cancer risk, age, comorbidities, and access to diagnostic investigations. Patients with acromegaly may undergo more intensive thyroid ultrasonography and biopsy, increasing the detection of otherwise unrecognized cancers. Exploratory analyses yielded different estimates by comparator type, but no statistically significant subgroup interaction. Given the small number of studies and wide confidence intervals, this finding does not demonstrate equivalent associations across comparator populations.

Thyroid nodular disease was more frequent, and thyroid volume greater, in patients with acromegaly, consistent with previous reports [8, 10, 12, 14, 24–26]. Prolonged exposure to GH and IGF-1 may contribute to diffuse or nodular thyroid enlargement [5, 6]. However, thyroid volume estimates were highly heterogeneous ($I^2 = 92.5\%$), possibly reflecting differences in clinical characteristics, acromegaly control, previous thyroid treatment, and ultrasound methods. The direction of the association was consistent, but the magnitude varied. Thus, the pooled mean difference should be interpreted as an overall association rather than an expected change for an individual patient.

The pooled TSH and free T4 analyses were inconclusive, consistent with the limited evidence reported previously [12, 14, 24]. Both analyses included only three studies and showed substantial heterogeneity. Differences in hormone assays, thyroid comorbidities, medication use, and acromegaly treatment may explain some variability. Importantly, nonsignificant pooled estimates do not demonstrate equivalent thyroid function between patients with and without acromegaly.

Compared with previous reviews focusing predominantly on cancer or thyroid nodules [7–10], this synthesis additionally considered histological subtypes, thyroid volume, thyroid function markers, and comparator characteristics. Its sensitivity analyses showed that the primary cancer association was not driven by any single study or by the choice of zero-cell correction. Specifically, excluding Can et al. [14] did not materially alter the pooled estimate, despite the exclusion of patients with prior papillary cancer and the use of malignant cytology to identify the control-group event. Nevertheless, stability under sensitivity analyses cannot exclude shared biases across studies.

Clinically, our results justify awareness of structural thyroid abnormalities in patients with acromegaly but do not establish the benefit of intensified cancer screening. Although thyroid cancer and nodules were more frequently detected, the available studies did not assess whether routine ultrasound surveillance improves patient-important outcomes. Previous research and contemporary guidance have not established a benefit of dedicated universal thyroid screening in this population [36–38]. Thyroid investigation should therefore follow clinical indications, relevant guidance, and individualized assessment rather than the pooled OR alone.

Important limitations include the observational designs, residual confounding, heterogeneous controls, and possible differential thyroid surveillance. Thyroid cancer was ascertained using histopathology, malignant cytology, or clinical and administrative records;

studies also varied in their treatment of prevalent and incident diagnoses. The availability of disease-duration, biochemical control, and treatment data was inconsistent. Furthermore, eligibility required comparative thyroid cancer data, so the secondary syntheses cannot represent all published studies of nodular disease, thyroid volume, or thyroid function. Future prospective investigations should use comparable controls, standardized ultrasound and biopsy criteria, separate incident from prevalent cancer, and evaluate how acromegaly activity and treatment influence thyroid outcomes. These priorities are essential for determining whether the observed associations warrant changes in clinical practice.

5. Conclusion

Acromegaly was associated with higher odds of thyroid cancer and nodular disease and with greater thyroid volume. Evidence for follicular carcinoma and differences in TSH or free T4 remained inconclusive. Given the observational designs, potential surveillance bias, and very low certainty of evidence, these findings do not establish causality or support intensified thyroid screening by themselves. Prospective studies with comparable control groups, standardized ultrasound and biopsy pathways, and separate reporting of prevalent and incident cancer are needed to clarify these associations and their clinical implications.

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7. Author contributions

ALPS: conception, data collection, data analysis, manuscript writing, manuscript revision. MK: data collection and data analysis. PDRG: data collection and data analysis. RP: data collection and data analysis. SWH: manuscript writing, manuscript revision. AFD: manuscript writing, manuscript revision. OSN: manuscript writing, manuscript revision. CMC: manuscript writing, manuscript revision. TFS: manuscript writing, manuscript revision. PHPS: data analysis, manuscript writing, manuscript revision. MCRP: data analysis, manuscript writing, manuscript revision. NLAF: supervision, data analysis, manuscript writing, manuscript revision. All authors read and approved the final manuscript.

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9. Data availability

Original data generated and analyzed during this study are available under reasonable request.

10. Conflict of interest

All authors report no relationships that could be construed as a conflict of interest. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

11. Ethics Approval

Not applicable since all data analysed was from already published studies.

12. AI declaration

ChatGPT-6 (OpenAI) was used to assist with language editing, data verification, and statistical interpretation. All AI-assisted outputs were reviewed under human supervision, and the authors retain full responsibility for the manuscript.

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