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

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**Journal Name:** Pituitary

**Keywords:** Acromegaly; Meta-Analysis; Thyroid Cancer; Goiter; Growth Hormone-Secreting Pituitary Adenoma; Thyroid.

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**Appendix A: Sample additional information**

| Study (year) | Original information | Used information |
|---|---|---|
| Barzilay et al. (1991) | Two differentiated thyroid carcinomas, one explicitly described as papillary carcinoma, other described as “papillary follicular carcinoma”. | Both cases were included in the overall thyroid cancer analysis, but only the explicit case of papillary carcinoma was included in the histology-specific analysis. |
| Herrmann et al. (2004) | Thyroid nodules reported in 33.1% of 199 controls. | 33.1% of 199 was considered as 66 patients, using the nearest-integer rounding. |
| Reverter et al. (2014) | Thyroid nodules reported in 55.7% of 123 patients with acromegaly, of wich 25.5% was solitary and 30.2% were multiple. | 25.5% of 123 was considered as 31 and 30.2% of 123 was considered as 37 using the nearest-integer rounding rather than 55.7% of 123. |
| Can et al. (2021) | Table 1 uses mg/dL, but Materials and Methods section uses ng/dL for serum free T4 | Serum free T4 unit of measure was considered as ng/dL since it is clinically compatible |
| Cankurtaran et al. (2023) | Uses IU/mL for sreum TSH | Serum TSH measure was considered as mIU/L due to it being clinically plausible |

**Supplementary Table 1:** Adaptation of information provided by original articles regarding the histological type of thyroid cancer, absolute numbers derived from percentages and units of measurement

**Appendix B: Search Strategy**

| Database | String |
|---|---|
| PubMed | (acromegaly OR "Growth Hormone-Secreting Pituitary Adenoma"[mh])<br>AND<br>(thyroid OR "thyroid cancer" OR "thyroid nodules" OR goiter OR "Thyroid Neoplasms"[mh] OR "thyroid carcinoma") |
| Embase | (acromegaly)<br>AND<br>(thyroid OR "thyroid cancer" OR "thyroid nodules" OR goiter OR "thyroid carcinoma") |
| Cochrane | (acromegaly)<br>AND<br>(thyroid OR "thyroid cancer" OR "thyroid nodules" OR goiter OR "thyroid carcinoma") |

**Supplementary Table 2:** Search string for literature systematic review and study selection for each database used

## Appendix C: PRISMA Checklist

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review. | Main manuscript, title page ("Systematic Review and Meta-Analysis"). |
| **ABSTRACT** | | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | Main manuscript, Abstract (Purpose, Methods, Results, Conclusion). |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | Main manuscript, Section 1 (Introduction: clinical context, mechanisms and prior systematic reviews). |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | Main manuscript, Section 1 (final paragraph); Abstract (Purpose). |
| **METHODS** | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | Main manuscript, Sections 2.1 (Eligibility Criteria), 2.4 (Outcomes) and 2.5 (Subgroup Analyses); Section 3.3 (outcome-specific syntheses). |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | Main manuscript, Section 2.2 (PubMed, Embase, Cochrane Library, reference screening; inception–March 2026); Online Resource 1, Appendix B (p. 4). |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Online Resource 1, Appendix B, Supplementary Table 2 (p. 4: search strings for PubMed, Embase and Cochrane); main manuscript, Section 2.2. |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | Main manuscript, Section 2.2 (two independent reviewers; Rayyan; discussion and third reviewer for disagreements). |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | Main manuscript, Section 2.3 (three independent data extractors; extracted variables and reconciliation of overlapping samples). |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | Main manuscript, Sections 2.1, 2.3, 2.4 and 2.5 (primary/secondary outcomes and eligible reports). |
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | Main manuscript, Section 2.3 and Table 1; Online Resource 1, Appendix A, Supplementary Table 1 (p. 3: event-count reconstruction, thyroid histology decisions and unit conversions). |

| | | | |
|---|---|---|---|
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | Main manuscript, Section 2.6 (independent JBI/ROBINS-E assessments, consensus and robvis); Online Resource 1, Appendix E, Supplementary Table 5 (p. 10: study–tool assignments); Appendix H, Supplementary Figures 3–6 (pp. 14–15). |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | Main manuscript, Sections 2.4 and 2.7 (ORs and MDs with 95% CIs); Section 3.3.1–3.3.6; Online Resource 1, Appendix F (p. 11: descriptive single-arm GH/IGF-1 estimates). |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | Main manuscript, Sections 2.1, 2.4 and 2.5 (thyroid-cancer eligibility; secondary outcomes; histological and comparator subgroups); Section 3.3.1–3.3.6. |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | Main manuscript, Sections 2.3 and 2.7 (event reconstruction, units, zero-event correction and log GH analysis); Online Resource 1, Appendix A, Supplementary Table 1 (p. 3) and Appendix F (p. 11). |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | Main manuscript, Table 1 and Figures 1–8; Online Resource 1, Appendices F (Supplementary Figures 1–2, p. 11), G (Supplementary Table 6, pp. 12–13), H (Figures 3–6, pp. 14–15) and I (Figures 7–13, pp. 16–22). |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | Main manuscript, Section 2.7 (R/meta; random effects, REML, Paule–Mandel, Hartung–Knapp, Cochran Q and $I^2$); Online Resource 1, Appendix F (p. 11). |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | Main manuscript, Sections 2.5, 3.3.2, 3.3.3 and 4; Figures 3–4 (histological and comparator subgroup analyses, interpreted as exploratory). |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | Main manuscript, Sections 2.7 and 3.4; Online Resource 1, Appendix I, Supplementary Figures 7–11 (pp. 16–20: leave-one-out, TACC and sensitivity excluding Can et al.). |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | Main manuscript, Section 2.7 (funnel plot inspection and Egger regression for thyroid cancer); Section 3.5; Online Resource 1, Appendix I, Supplementary Figures 12–13 (pp. 21–22). |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | Main manuscript, Section 2.6 (GRADE/GRADEpro, independent assessors, consensus); Section 3.5; Online Resource 1, Appendix G, Supplementary Table 6 (pp. 12–13: five outcomes and footnote justifications). |

| | | | |
|---|---|---|---|
| **RESULTS** | | | |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | Main manuscript, Section 3.1 (2,623 records, 711 duplicates, 28 full texts, 15 exclusions, 13 included studies); Figure 1 (PRISMA flow diagram). |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | Main manuscript, Section 3.1 (reasons for 15 full-text exclusions); Online Resource 1, Appendix D, Supplementary Table 4 (pp. 8–9: study-by-study exclusions and reasons). |
| Study characteristics | 17 | Cite each included study and present its characteristics. | Main manuscript, Section 3.2 and Table 1 (all 13 included studies, design, participants, comparator and demographics); study citations in Section 3.1. |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | Main manuscript, Section 3.5 (distribution and main concerns); Online Resource 1, Appendix E, Supplementary Table 5 (p. 10) and Appendix H, Supplementary Figures 3–6 (pp. 14–15: individual-study assessments). |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Main manuscript, Figures 2–8 (individual-study effects and 95% CIs for comparative outcomes); Online Resource 1, Appendix F, Supplementary Figures 1–2 (p. 11: GH/IGF-1). |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | Main manuscript, Sections 3.2 and 3.5; Online Resource 1, Appendix G, Supplementary Table 6 (pp. 12–13: GRADE by outcome) and Appendix H (pp. 14–15: study-level risk of bias). |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | Main manuscript, Sections 3.3.1–3.3.6 and Figures 2–8 (OR/MD, CIs, P values, $I^2$); Online Resource 1, Appendix F (p. 11: GH and IGF-1 analyses). |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | Main manuscript, Sections 3.3.2–3.3.3, Figures 3–4 (histology/comparator subgroups), and Section 4 (interpretation of heterogeneity). |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | Main manuscript, Section 3.4; Online Resource 1, Appendix I, Supplementary Figures 7–11 (pp. 16–20: leave-one-out, TACC and exclusion of Can et al.). |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | Main manuscript, Section 3.5 (funnel-plot asymmetry and Egger result); Online Resource 1, Appendix I, Supplementary Figures 12–13 (pp. 21–22: funnel plot and Egger test). |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | Main manuscript, Section 3.5 (very-low certainty for five outcomes); Online Resource 1, Appendix G, Supplementary Table 6 and explanations (pp. 12–13). |
| **DISCUSSION** | | | |

| | | | |
|---|---|---|---|
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | Main manuscript, Section 4 (comparison with previous reviews, mechanisms, cancer subtypes, structural and hormonal outcomes). |
| | 23b | Discuss any limitations of the evidence included in the review. | Main manuscript, Section 4 (observational designs, unadjusted comparisons, sparse events, control selection, surveillance and heterogeneous outcome ascertainment). |
| | 23c | Discuss any limitations of the review processes used. | Main manuscript, Section 4, final paragraph (secondary analyses restricted by primary thyroid-cancer eligibility); Section 2.3 (data conversion assumptions). |
| | 23d | Discuss implications of the results for practice, policy, and future research. | Main manuscript, Section 4 (clinical screening implications and future study requirements) and Section 5 (Conclusion). |
| **OTHER INFORMATION** | | | |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | Main manuscript, Section 2, opening paragraph (PROSPERO CRD420251266153). |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | Main manuscript, Section 2, opening paragraph (registration number). |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | Main manuscript, Section 2, opening paragraph. Online Resource 1, Appendix J (p. 24: Deviations from the Registered PROSPERO Protocol). |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | Main manuscript, Section 8 (Funding: no funding) and Section 6 (Acknowledgments: contributions). |
| Competing interests | 26 | Declare any competing interests of review authors. | Main manuscript, title-page Disclosures and Section 10 (Conflict of interest). |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | Main manuscript, Section 9 (Data availability: data on reasonable request); Online Resource 1, Appendix A (p. 3: reconstructed values). |

*From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

**Supplementary Table 3:** PRISMA Checklist demanded by PRISMA guidelines with location of where each topic is reported

**Appendix D: Selection Justification and Excluded Studies**

| Author | DOI or Link | Reason for exclusion |
|---|---|---|
| Broder et al. | https://doi.org/10.1210/endo-meetings.2016.np.12.sun-541 | Conference abstract |
| Cheung et al. | https://doi.org/10.1046/j.1365-2265.1997.1680985.x | No thyroid cancer data |
| Chiloiro et al. | https://doi.org/10.1007/s12020-022-03261-y | No thyroid cancer data |
| Colao et al. | https://doi.org/10.1007/bf03346334 | No thyroid cancer data |
| Danilowicz et al. | https://doi.org/10.1186/s40842-020-00113-4 | Wrong population |
| Delibasi et al. | https://www.embase.com/search/results?subaction=viewrecord&id=L70834114&from=export%20%20%20%20%20U2%20%20-%20L70834114 | Conference abstract |
| Ishibashi et al. | https://doi.org/10.1507/endocrj1954.38.517 | No thyroid cancer data |
| Roelfsema et al. | https://doi.org/10.1210/jc.2009-0174 | No thyroid cancer data |
| Sierra et al. | https://www.embase.com/search/results?subaction=viewrecord&id=L70165755&from=export%20%20%20%20%20U2%20%20-%20L70165755 | Conference abstract |
| Sobrinho et al. | https://doi.org/10.1007/s11102-011-0324-1 | No thyroid cancer data |
| Urbani et al. | https://doi.org/10.1159/000339890 | Conference abstract |
| Vargas-Ortega et al. | https://doi.org/10.1016/j.ghir.2021.101431 | Wrong control group (patients with acromegaly from cohort, who to date had not developed thyroid |

| | | |
|---|---|---|
| | | nodular disease) |
| Wolinski et al. | https://doi.org/10.1007/s40618-016-0565-y | Overlapping populations |
| Wuster et al. | https://doi.org/10.1055/s-2007-1003632 | No thyroid cancer data |
| Xiao et al. | https://doi.org/10.1007/s12020-023-03447-y | Wrong control group |

**Supplementary Table 4:** Reasons for individual study exclusion after full paper screening of all reports assessed for eligibility

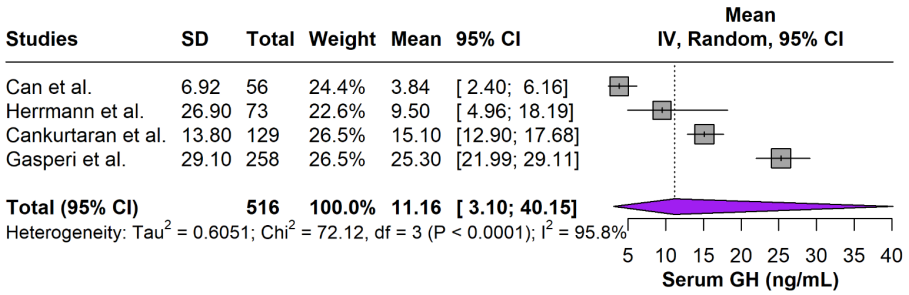
**Appendix E: Risk of Bias Assessment Tool Used for Each Study**

| Author | Risk of bias assessment tool used |
|---|---|
| Barzilay et al. | ROBINS-E |
| Can et al. | JBI Analytical Cross-Sectional Checklist |
| Cankurtaran et al. | JBI Analytical Cross-Sectional Checklist |
| dos Santos et al. | JBI Analytical Cross-Sectional Checklist |
| Gasperi et al. | JBI Analytical Cross-Sectional Checklist |
| Herrmann et al. | JBI Analytical Cross-Sectional Checklist |
| Iglesias et al. | JBI Analytical Cross-Sectional Checklist |
| Park et al. | ROBINS-E |
| Popovic et al. | ROBINS-E |
| Reverter et al. | JBI Analytical Cross-Sectional Checklist |
| Selman et al. | JBI Analytical Cross-Sectional Checklist |
| Wolinski et al. | JBI Analytical Cross-Sectional Checklist |
| Xu et al. | JBI Analytical Cross-Sectional Checklist |

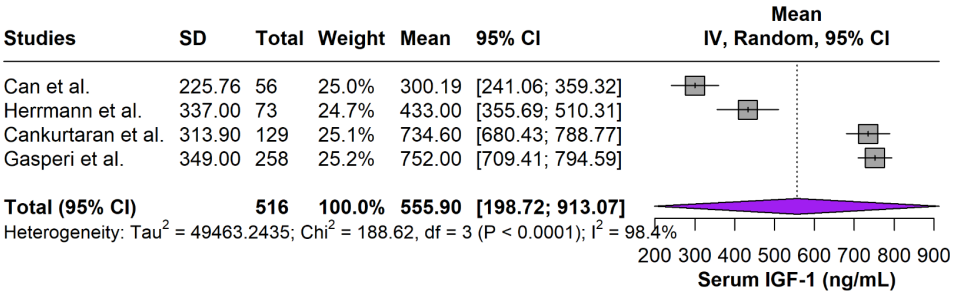
**Supplementary Table 5:** Which risk of bias assessment tool was used for each study included in the final analysis according to individual study design

## Appendix F: Serum GH and IGF-1 levels single-arm analysis

The single-arm analysis of serum GH concentrations yielded a back-transformed pooled estimate of 11.16 ng/mL (95% CI 3.10–40.14; $I^2$ = 95.7%; ***Supplementary Figure 1***). The pooled mean serum IGF-1 concentration was 555.82 ng/mL (95% CI 198.64–913.00; $I^2$ = 98.4%; ***Supplementary Figure 2***). Both outcomes exhibited considerable heterogeneity.




**Supplementary Figure 1:** Single arm analysis forest plot showing individual and pooled means for Serum GH Levels outcome with 95% confidence intervals among acromegaly patients




**Supplementary Figure 2:** Single arm analysis forest plot showing individual and pooled means for Serum IGF-1 Levels outcome with 95% confidence intervals among acromegaly patients

# Appendix G: Quality Assessment

**Author(s):** Ana Luiza Potiguara de Sousa, Miray Kurtca, Pedro Diniz Rocha Guimarães, et al.

**Question:** In adults with acromegaly, compared with adults without acromegaly, what are the associations with thyroid cancer, ultrasonography-detected thyroid nodular disease, thyroid volume, TSH, and free T4?

**Setting:** Specialized endocrinology clinics, hospital-based cohorts, and population-based or administrative healthcare databases, with healthy, pituitary adenoma, other endocrine disease, and population-based comparator groups.

**Bibliography:** Sousa ALP, Kurtca M, Guimarães PDR, et al. Thyroid Cancer and Structural Thyroid Disease in Patients with Acromegaly: a Systematic Review and Meta-Analysis.

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Acromegaly | Individuals without acromegaly | Relative (95% CI) | Absolute (95% CI) | | |
| **Thyroid cancer** | | | | | | | | | | | | |
| 13 | non-randomised studies | serious[a] | not serious[b] | not serious | not serious | none | 90/2674 (3.4%) | 0.3% | **OR 4.00** (2.21 to 7.24) | **8 more per 1.000** (from 3 more to 17 more) | ⨁◯◯◯ Very low[a,b] | CRITICAL |
| **Thyroid nodular disease** | | | | | | | | | | | | |
| 6 | non-randomised studies | serious[c] | not serious[d] | not serious | not serious[e] | none | 333/572 (58.2%) | 318/882 (36.1%) | **OR 2.60** (1.80 to 3.76) | **234 more per 1.000** (from 143 more to 319 more) | ⨁◯◯◯ Very low[c,d,e] | IMPORTANT |
| **Thyroid volume** | | | | | | | | | | | | |
| 6 | non-randomised studies | serious[f] | serious[g] | not serious | not serious | none | 740 | 873 | - | MD **12.57 mL higher** (5.27 higher to 19.86 higher) | ⨁◯◯◯ Very low[f,g] | IMPORTANT |
| **TSH level** | | | | | | | | | | | | |
| 3 | non-randomised studies | serious[h] | serious[i] | not serious | serious[j] | none | 407 | 453 | - | MD **0.72 mU/L lower** (2.71 lower to 1.27 higher) | ⨁◯◯◯ Very low[h,i,j] | IMPORTANT |
| **Free T4 levels** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | non-randomised studies | serious[h] | serious[k] | not serious | serious[l] | none | 407 | 453 | - | MD **0.01 ng/dL higher** (0.39 lower to 0.42 higher) | ⨁◯◯◯ Very low[h,k,l] | IMPORTANT |

**CI:** confidence interval; **MD:** mean difference; **OR:** odds ratio

## Explanations

a. Downgraded one level for serious risk of bias because several contributing studies used non-equivalent comparator groups, reported unadjusted effect estimates, or had limited control for confounding factors. Potential differences in thyroid cancer surveillance and diagnostic ascertainment may have influenced the observed association.

b. Not downgraded for inconsistency. Moderate statistical heterogeneity was observed ($I^2 = 47.4\%$). Most studies reported an association in the same direction; however, the magnitude of the estimates varied. The judgment should be interpreted in conjunction with the distribution of individual study estimates and their clinical relevance.

c. Downgraded one level for serious risk of bias. The evidence was derived from non-randomized observational studies with potential residual confounding, particularly due to differences in age, clinical settings, and comparator-group selection. Although thyroid ultrasonography was performed in both groups, differences in ultrasound protocols and operational definitions of nodular thyroid disease may have influenced outcome ascertainment. Limited adjustment for relevant confounders further reduced confidence in the estimated association.

d. Not downgraded for inconsistency. Moderate statistical heterogeneity was observed ($I^2 = 30.8\%$; Cochran's Q test, $P = 0.2100$). All six studies reported associations in the same direction, with study-specific odds ratios ranging from 1.98 to 5.15. Although the magnitude of the associations varied, the consistency in direction and the limited extent of statistical heterogeneity did not warrant downgrading.

e. Not downgraded for imprecision. Six studies involving 1,454 participants yielded a pooled odds ratio of 2.60 (95% CI 1.80–3.76). Using the observed control-group prevalence of 36.1% as the assumed baseline, the confidence interval corresponded to approximately 143 to 319 additional individuals with thyroid nodular disease per 1,000. The entire interval was considered compatible with an appreciable increase in nodular disease occurrence. Although no minimally important effect threshold was prespecified, the available precision was judged sufficient for the review's objective of estimating the association.

f. Downgraded one level for serious risk of bias because differences in participant selection, prior thyroid treatment, acromegaly activity, and ultrasound measurement procedures may have affected the comparisons. Adjustment for potential confounding factors was limited.

g. Downgraded one level for serious inconsistency. Considerable heterogeneity was observed ($I^2 = 92.5\%$), with substantial variation in the magnitude of thyroid volume differences across studies.

h. Downgraded one level for serious risk of bias because differences in thyroid comorbidities, medication use, acromegaly treatment status, laboratory methods, and comparator selection may have affected biochemical measurements. These concerns require confirmation against outcome-specific risk-of-bias assessments.

i. Downgraded one level for serious inconsistency. Substantial heterogeneity was present in the TSH analysis ($I^2=83.7\%$), indicating important variation in the magnitude of the effect across the three contributing studies. However, the estimates generally indicated lower TSH levels in patients with acromegaly, supporting a one-level rather than a two-level downgrade.

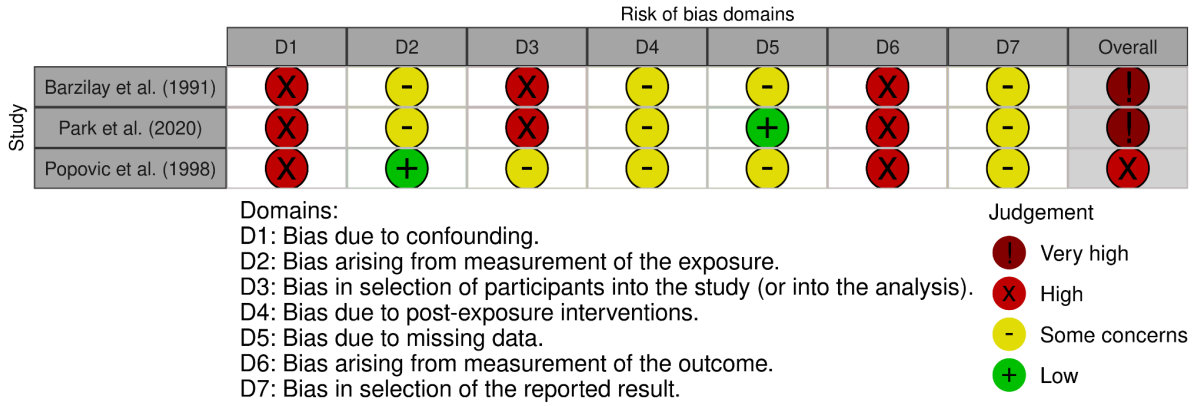
j. Downgraded one level for serious imprecision. The pooled TSH confidence interval crossed the null value (MD −0.72, 95% CI −2.71 to 1.27) and included both a potentially relevant reduction and a possible increase in TSH levels. Besides that, only three studies contributed to this analysis.

k. Downgraded one level for serious inconsistency. Substantial heterogeneity was observed across the three contributing studies ($I^2=72.2\%$), with differences in both the direction and magnitude of study-specific estimates. This variability reduced confidence in the pooled free T4 estimate.

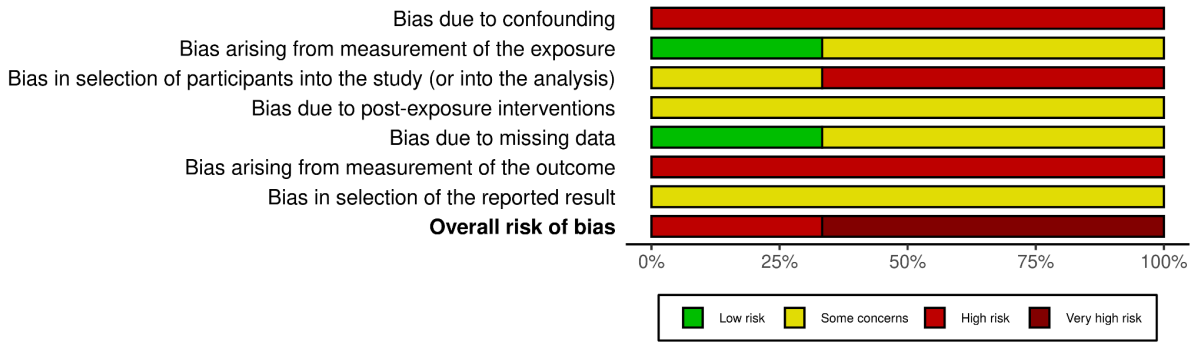
l. Downgraded one level for serious imprecision. The pooled confidence interval crossed the null value (MD 0.01 ng/dL, 95% CI −0.39 to 0.42), encompassing potentially relevant decreases and increases in free T4 concentrations. The limited number of contributing studies further reduced confidence in the estimate.

**Supplementary Table 6:** GRADE analysis for quality of evidence for Thyroid Cancer, Thyroid Nodular Disease Thyroid Volume, TSH Levels and Free T4 Levels outcomes.

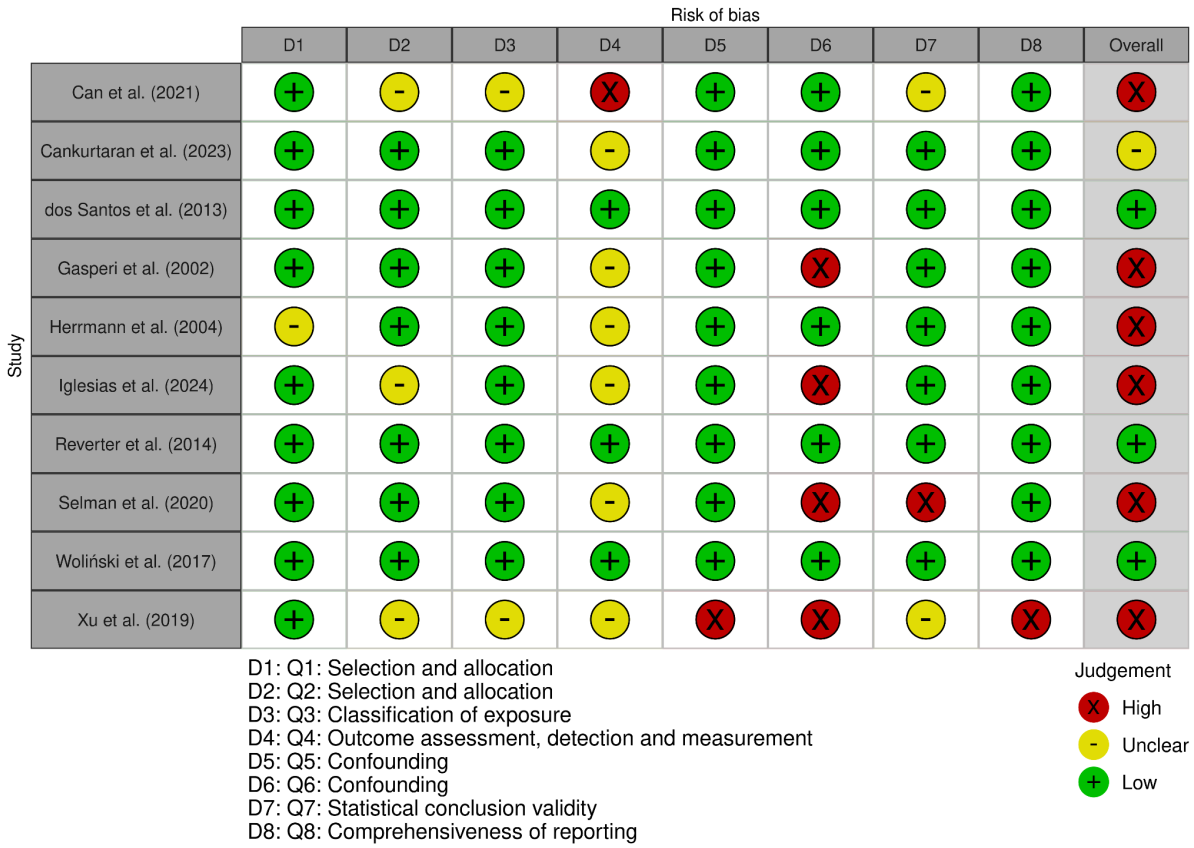
## Appendix H: Risk of Bias Assessment



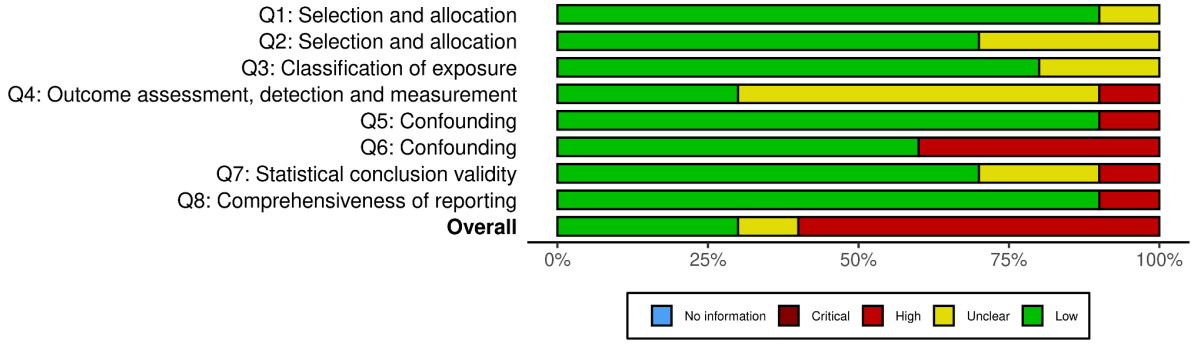

**Supplementary Figure 3:** ROBINS-E Traffic-Light Plot analysis showing individual domains and overall risk of bias for three studies




**Supplementary Figure 4:** ROBINS-E Summary Plot analysis showing individual domains and overall risk of bias for three studies

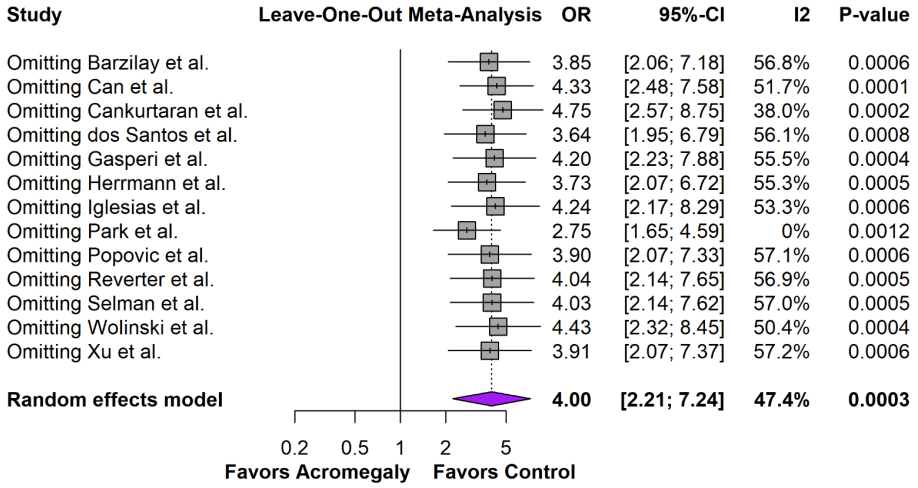



**Supplementary Figure 5:** JBI Traffic-Light Plot analysis showing individual domains and overall risk of bias for ten studies

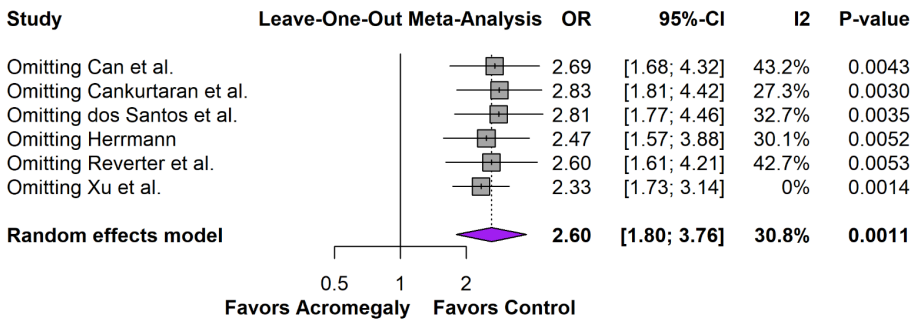



**Supplementary Figure 6:** JBI Summary Plot analysis showing individual domains and overall risk of bias for ten studies

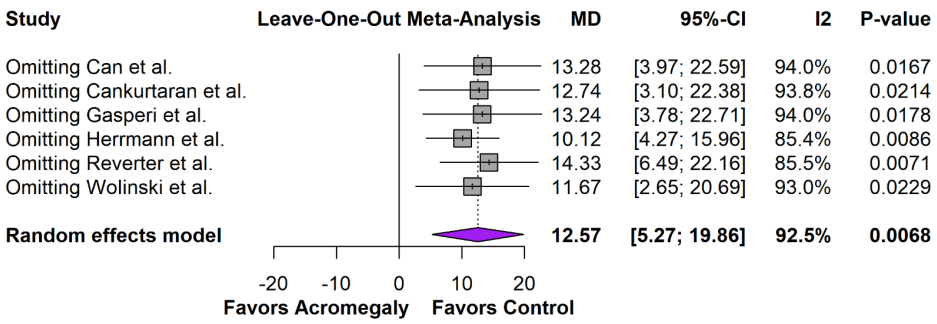
## Appendix I: Sensitivity Analysis



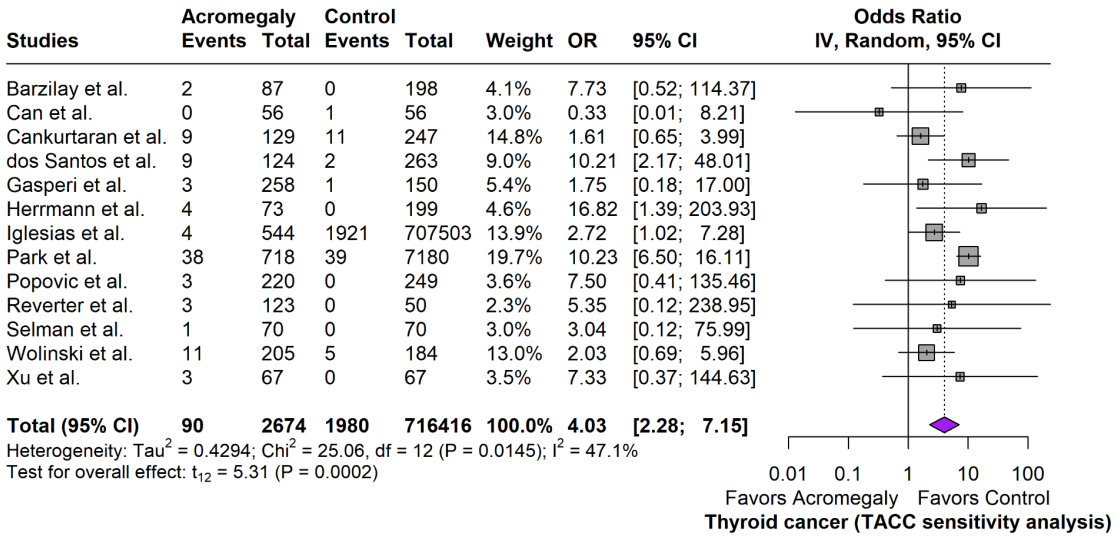

**Supplementary Figure 7:** Leave-One-Out analysis forest plot showing individual and pooled ORs after omitting each study included for Thyroid Cancer outcome



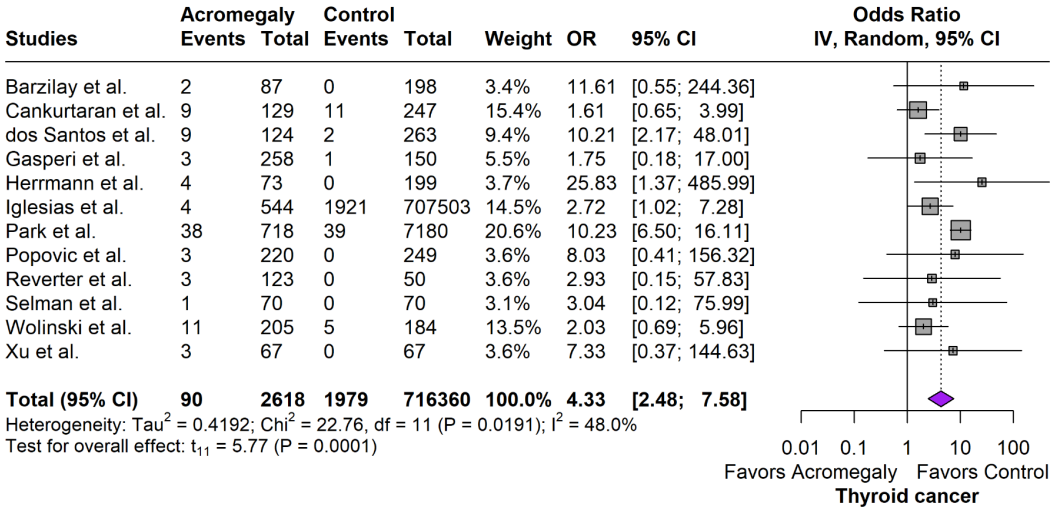

**Supplementary Figure 8:** Leave-One-Out analysis forest plot showing individual and pooled ORs after omitting each study included for Thyroid Nodular Disease outcome



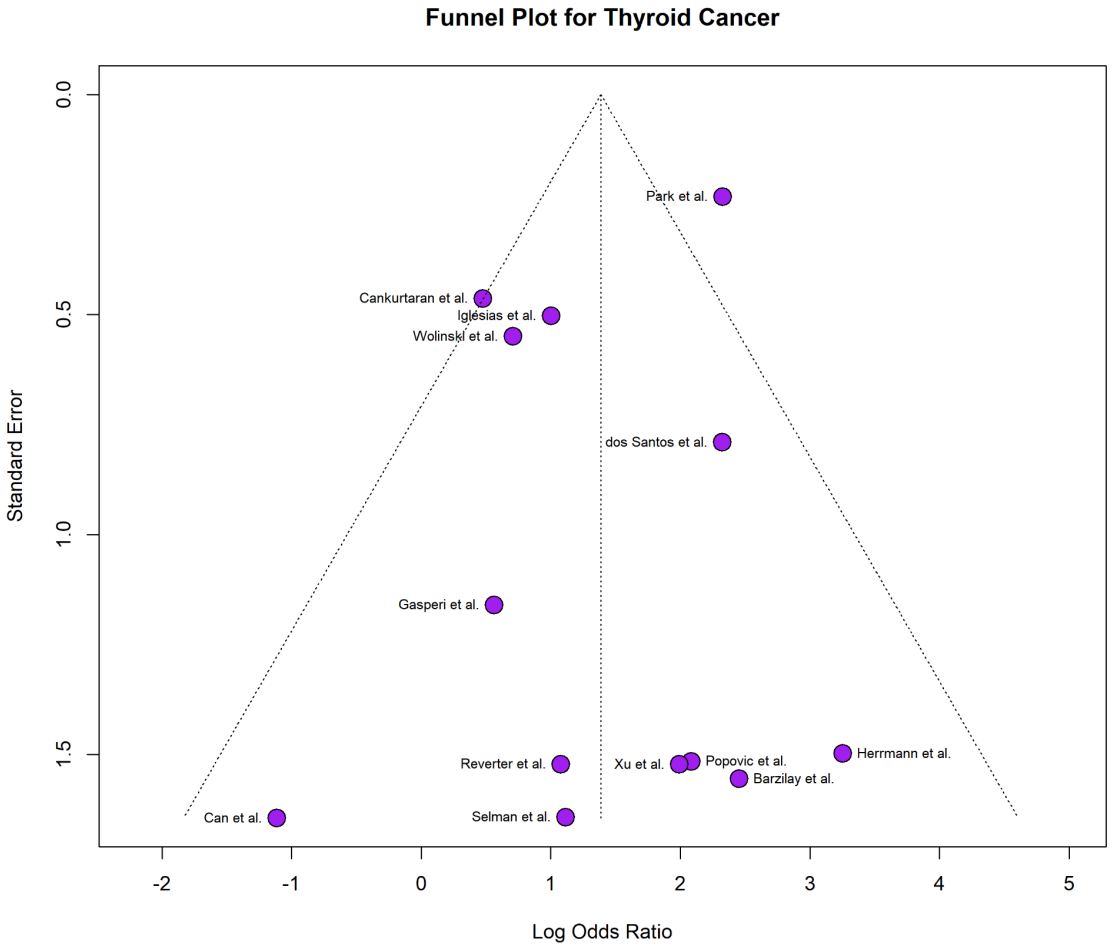

**Supplementary Figure 9:** Leave-One-Out analysis forest plot showing individual and pooled MDs after omitting each study included for Thyroid Volume outcome



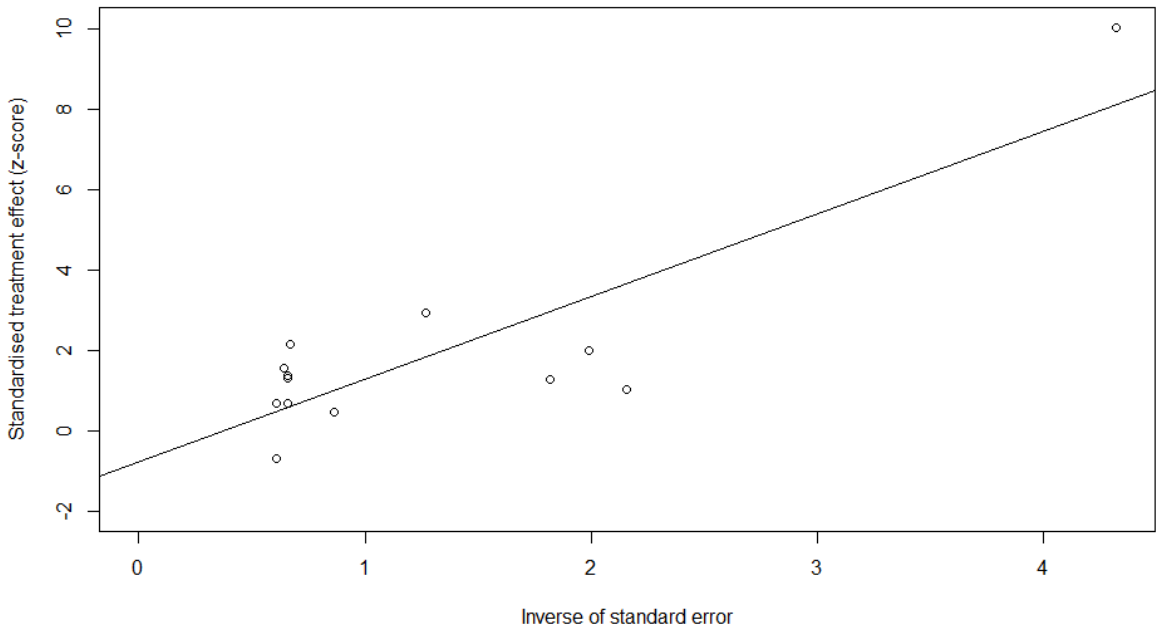

**Supplementary Figure 10:** Sensitivity analysis forest plot showing individual and pooled ORs for thyroid cancer using treatment-arm continuity correction (TACC) for studies with zero-event cells.




**Supplementary Figure 11:** Sensitivity analysis of thyroid cancer odds in patients with acromegaly compared with controls after excluding Can et al. (2021). Individual and pooled odds ratios are presented with 95% confidence intervals using a random-effects model




**Supplementary Figure 12:** Funnel Plot analysis showing individual Log of ORs for Thyroid Cancer outcome with 95% pseudo-confidence intervals around the summary effect




**Supplementary Figure 13:** Egger's linear regression test for Thyroid Cancer outcome displaying the standardized effect size against standard error for the included studies

## Appendix J: Deviations from the Registered PROSPERO Protocol

| Aspect | Original PROSPERO protocol | Final review |
|---|---|---|
| Comparators | Controls without acromegaly, matched by age, sex and race. | Healthy, endocrine, hospital and population controls; matching was not mandatory. |
| Primary outcome | Thyroid cancer and nodular disease as co-primary outcomes. | Thyroid cancer only; nodular disease became secondary. Eligibility required comparative cancer data. |
| Other outcomes | Goiter subtypes, metastasis, other endocrine diseases and mortality; hormonal outcomes planned. | Cancer histology, nodular disease, thyroid volume, TSH and free T4 analyzed; GH/IGF-1 summarized descriptively. Other planned outcomes were not synthesized. |
| Risk of bias | ROBINS-E for included observational studies. | ROBINS-E for three longitudinal studies; revised JBI 2026 tool for ten cross-sectional studies. |
| Effect measure | Risk ratios (RRs) for binary outcomes. | Unadjusted odds ratios (ORs) for binary outcomes. |
| Meta-analysis model | DerSimonian–Laird random-effects model. | REML for thyroid cancer; Paule–Mandel for other comparative outcomes; Hartung–Knapp confidence intervals for main analyses. |
| Additional analyses | No specific sensitivity analyses stated. | Leave-one-out, treatment-arm continuity correction and exclusion of Can et al. (2021); the latter two were reported as post hoc. |

**Supplementary Table 7:** Comparison of the originally registered PROSPERO protocol (CRD420251266153) with the methods implemented in the final systematic review and meta-analysis, including methodological amendments and reporting clarifications