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Author Affiliation:The First Norman Bethune Clinical
Medical College of Jilin University.**Does ascertainment intensity modify the association between Hashimoto's thyroiditis and papillary thyroid carcinoma? A retrospectively registered protocol for a systematic review and meta-regression**

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ADMINISTRATIVE INFORMATION**Support** - Jilin Provincial Medical and Health Talent Special Project.**Review Stage at time of this submission** - Completed but not published.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2026100001**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 1 October 2026 and was last updated on 1 October 2026.**INTRODUCTION**

Review question / Objective Does the magnitude of the association between Hashimoto's thyroiditis and papillary thyroid carcinoma differ according to the intensity and pathway of PTC ascertainment, and can these ascertainment differences explain between-study heterogeneity in the reported association?

Condition being studied The condition of interest is the association between Hashimoto's thyroiditis and papillary thyroid carcinoma, with emphasis on the potential influence of differential cancer ascertainment, including surgical pathology, fine-needle aspiration/nodule-based evaluation, and registry-based detection.

METHODS

Participant or population Patients or participants evaluated for thyroid disease, including individuals with thyroid nodules, patients undergoing fine-needle aspiration, and patients undergoing

thyroidectomy with subsequent histopathological examination. Population- or registry-based cohorts will also be considered where appropriate. Studies of both adults and children will be eligible if they provide comparative data on Hashimoto's thyroiditis and papillary thyroid carcinoma.

Intervention Exposure: Hashimoto's thyroiditis, diagnosed by histopathology, serology with compatible clinical/ultrasonographic findings, or other clearly defined criteria. Isolated thyroid autoantibody positivity without a diagnosis of HT will be considered exploratory rather than part of the primary analysis.

Comparator The comparator will consist of participants without Hashimoto's thyroiditis (non-HT controls), as defined by the corresponding primary study. Comparator groups may include individuals evaluated for thyroid nodules, patients undergoing thyroidectomy, or participants from clinical or registry-based populations, provided that they do not meet the study-specific diagnostic criteria for HT and that the comparison allows

estimation of the association between HT and papillary thyroid carcinoma.

Study designs to be included Observational studies, including cohort, case-control, cross-sectional, thyroidectomy/pathology-based comparative studies, and thyroid nodule/FNA-based studies, will be included if they provide comparative data on HT and PTC sufficient for effect estimation. Reviews, meta-analyses, case reports, non-comparative case series, and non-human studies will be excluded.

Eligibility criteria Eligible studies must evaluate HT as the exposure, include a non-HT comparator, report PTC as a specific outcome, and provide an effect estimate or sufficient data to reconstruct a 2×2 table. Observational cohort, case-control, cross-sectional, thyroidectomy/pathology-based, and FNA/nodule-based comparative studies will be included. Studies reporting only broader thyroid cancer outcomes, using non-specific thyroiditis definitions, evaluating isolated autoantibody positivity, lacking an appropriate comparator, or providing insufficient quantitative data will be excluded from the primary meta-analysis. Reviews, meta-analyses, case reports, non-comparative case series, and non-human studies will also be excluded.

Information sources Electronic literature searches were conducted in PubMed/MEDLINE, Embase, Web of Science, and Scopus from database inception to August 11, 2026. The reference lists of eligible studies and relevant systematic reviews were also manually screened to identify additional potentially eligible studies.

Main outcome(s) The main outcome is the association between Hashimoto's thyroiditis and papillary thyroid carcinoma, measured primarily by odds ratios (ORs) with 95% confidence intervals. Crude ORs will be calculated from 2×2 data when available, and adjusted estimates will be analyzed separately where appropriate.

Quality assessment / Risk of bias analysis Cohort and case-control studies will be assessed using the Newcastle–Ottawa Scale, and cross-sectional studies using the appropriate JBI critical appraisal checklist. Two reviewers will assess risk of bias independently, with disagreements resolved by consensus or a third reviewer. PTC ascertainment pathway will be evaluated separately from overall study quality and classified as a study-level proxy for susceptibility to detection, selection, and verification biases.

Strategy of data synthesis Crude ORs with 95% CIs will be calculated from 2×2 data and analyzed on the log scale. A random-effects model with REML estimation of τ^2 and Hartung–Knapp inference will be used. Heterogeneity will be assessed using Cochran's Q , I^2 , τ^2 , and 95% prediction intervals. Subgroup analyses will compare PTC ascertainment pathways, particularly thyroidectomy/pathology-based versus FNA/nodule-based studies, and random-effects meta-regression will assess effect modification, reported as ratios of odds ratios (RORs). Adjusted estimates will be analyzed separately. Sensitivity analyses, leave-one-out analysis, funnel plots, and Egger's test will be performed where appropriate.

Subgroup analysis The primary subgroup analysis will compare thyroidectomy/pathology-based studies with FNA/nodule-based studies according to PTC ascertainment intensity. Population/registry-based studies will be considered separately where appropriate. Exploratory subgroup analyses may include HT diagnostic method, PTC ascertainment method, geographic region, study design, PTMC/incidental PTC status, age group, and risk of bias. Between-subgroup differences will be assessed using formal interaction tests or random-effects meta-regression.

Sensitivity analysis Sensitivity analyses will assess the robustness of the primary results by excluding studies with nodule-level analyses, atypical comparator groups, pediatric populations, incidental PTC/PTMC-focused designs, higher methodological risk, or selective histological verification. Adjusted estimates will be analyzed separately where appropriate. Leave-one-out analysis will also be performed by sequentially excluding each study to evaluate the influence of individual studies on the pooled effect and heterogeneity.

Country(ies) involved China.

Keywords Hashimoto's thyroiditis; papillary thyroid carcinoma; thyroid cancer; ascertainment bias; detection bias; meta-analysis; meta-regression; papillary thyroid microcarcinoma.

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