Biomolecules and Biomedicine
ISSN: 2831-0896 (Print) | ISSN: 2831-090X (Online)
Journal Impact Factor® (2024): 2.2
CiteScore® (2024): 5.2
www.biomolbiomed.com | blog.bjbms.org

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META-ANALYSIS

Shen et al: Prediabetes and thyroid cancer risk

Association between prediabetes and thyroid cancer risk: A meta-analysis

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DOI: https://doi.org/10.17305/bb.2025.12744

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ABSTRACT

Prediabetes, characterized by intermediate hyperglycemia, is increasingly prevalent worldwide. While diabetes has been associated with a heightened risk of various cancers, the relationship between prediabetes and thyroid cancer remains ambiguous. This meta-analysis sought to assess whether prediabetes correlates with an elevated incidence of thyroid cancer. A systematic literature search was conducted across PubMed, Embase, Web of Science, Wanfang, and CNKI to identify longitudinal studies that compared the incidence of thyroid cancer in individuals with prediabetes to those with normoglycemia. Risk ratios (RRs) with 95% confidence intervals (CIs) were aggregated using a random-effects model. Subgroup and sensitivity analyses were performed to identify potential effect modifiers. Six prospective cohort studies, encompassing 5,743,849 participants, were included in the analysis. Overall, prediabetes was not significantly correlated with thyroid cancer incidence (RR = 1.04; 95% CI: 0.98–1.11; $p = 0.23$; $I^2 = 53\%$). Subgroup analyses revealed no significant variations based on age, sex, region, follow-up duration, or definition of prediabetes. Notably, a significant association was identified in studies utilizing cancer registries or validated clinical diagnoses (RR = 1.29; 95% CI: 1.04–1.60), in contrast to studies relying solely on ICD-10 codes (RR = 1.01; 95% CI: 0.98–1.05; p for subgroup difference = 0.03). In conclusion, prediabetes was not linked to a significantly increased risk of thyroid cancer overall. However, a potential association was noted in studies employing clinically validated cancer diagnoses. These findings, derived from observational cohorts, should be interpreted cautiously, and further prospective research is necessary to elucidate any causal relationship.

Keywords: Prediabetes, hyperglycemia, thyroid cancer, incidence, meta-analysis.

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INTRODUCTION

Thyroid cancer is the most common malignancy of the endocrine system, with a steadily increasing global incidence over the past few decades (1-3). It is estimated that thyroid cancer accounts for approximately 3% of all new cancer diagnoses worldwide, with a higher prevalence among women and in high-income countries (4, 5). While most differentiated thyroid cancers have a favorable prognosis with a 5-year survival rate exceeding 90%, the risk of recurrence and progression remains substantial in certain subgroups, particularly those with aggressive histological subtypes or distant metastases (6, 7). Treatment primarily involves surgical resection, often followed by radioactive iodine therapy and thyroid hormone suppression(8). However, despite advances in management, challenges remain in predicting which individuals are at greater risk of developing thyroid cancer (9, 10). Identifying modifiable risk factors and at-risk populations is crucial for effective early detection and primary prevention strategies.

Metabolic disturbances such as hyperglycemia, insulin resistance, and chronic low-grade inflammation are increasingly recognized as contributors to carcinogenesis (11, 12). Emerging evidence also suggests that glucose metabolism may play a role in thyroid tumorigenesis (13, 14). Mechanistically, insulin resistance and elevated insulin-like growth factor levels may stimulate thyroid cell proliferation and inhibit apoptosis, potentially promoting malignant transformation (15, 16). Prediabetes, defined as a state of intermediate hyperglycemia that does not meet the diagnostic threshold for diabetes, is commonly diagnosed through impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or elevated glycated hemoglobin (HbA1c) levels (typically 5.7–6.4%) (17, 18). With an estimated global prevalence affecting over 7% to 10% of adults, prediabetes represents an important stage for intervention to prevent not only diabetes but also possibly associated comorbidities, including cancer (19).

Several observational studies have investigated the association between prediabetes and the incidence of various site-specific cancers (20), with some reporting increased risks for colorectal (21), liver (22), pancreatic (23), gastric (24), and lung cancers (25). Accumulating evidence suggests that diabetes is related to a higher incidence of thyroid cancer (26-29). However, the relationship between prediabetes and thyroid cancer remains unclear. Individual studies have yielded inconsistent findings,

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potentially due to differences in study design, population characteristics, definitions of prediabetes, and methods for validating cancer outcomes (30-35). To date, no comprehensive meta-analysis has been conducted to quantitatively assess whether individuals with prediabetes are at increased risk of developing thyroid cancer. Given the rising global burden of prediabetes and the increasing incidence of thyroid cancer, understanding this potential association has significant public health implications. Therefore, we conducted a systematic review and meta-analysis of longitudinal studies to evaluate the association between prediabetes and the incidence of thyroid cancer and to explore the potential influence of study-level characteristics on this relationship.

MATERIAL AND METHODS

This meta-analysis was conducted in accordance with the PRISMA 2020 statement (36, 37) and the Cochrane Handbook for Systematic Reviews (38), which guided the development of the protocol, data collection, statistical synthesis, and reporting. The protocol has been prospectively registered in the PROSPERO database under the identifier CRD420251059664.

Database search

To retrieve studies according to the aim of this meta-analysis, we searched PubMed, Embase, Web of Science, Wanfang, and Chinese National Knowledge Infrastructure (CNKI) databases using an extensive array of search terms, which included: (1) "prediabetes" OR "pre-diabetes" OR "prediabetic" OR "pre-diabetic" OR "prediabetic state" OR "borderline diabetes" OR "impaired fasting glucose" OR "impaired glucose tolerance" OR "IFG" OR "IGT" OR "fasting glucose" OR "HbA1c"; (2) "thyroid"; and (3) "cancer" OR "neoplasm" OR "carcinoma" OR "malignancy" OR "tumor" OR "malignant". The literature search was limited to studies involving human participants and included only full-length, peer-reviewed articles published in English or Chinese. To ensure comprehensive coverage, the reference lists of relevant original and review articles were also manually screened for additional eligible studies. The search spanned from the inception of each database through April 12, 2025, with the full search strategies detailed in **Supplemental File 1**.

Study selection

The inclusion criteria were structured according to the PICOS framework.

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Population (P): Adults aged 18 years or older without a prior history of thyroid cancer.

Exposure (I): Participants with prediabetes, defined by recognized criteria such as IFG, IGT, or mildly elevated HbA1c levels below the diagnostic threshold for diabetes. Differences in prediabetes definitions across studies—such as IFG (typically 100–125 mg/dL), IGT (2-hour glucose 140–199 mg/dL), and HbA1c (5.7–6.4%)—were noted and addressed using subgroup analyses to evaluate whether diagnostic approach influenced the association with thyroid cancer risk.

Comparison (C): Participants with normoglycemia.

Outcome (O): Incidence of thyroid cancer during follow-up, compared between subjects with prediabetes and those with normoglycemia.

Study design (S): Longitudinal observational studies, including cohort studies, nested case-control designs, and post-hoc analyses of clinical trials.

Exclusion criteria included reviews, editorials, meta-analyses, and studies that included children, lacked evaluation of prediabetes as exposure, or did not report the outcome of thyroid cancer incidence. In cases of overlapping populations, the study with the largest and most complete dataset was included.

Study quality evaluation and data collection

The literature search, study selection, quality assessment, and data extraction were conducted independently by two reviewers, with any disagreements resolved through discussion with the corresponding author. Study quality was evaluated using the Newcastle–Ottawa Scale (NOS), which assesses three domains: participant selection, control for confounding, and outcome assessment (39). The NOS assigns scores from 1 to 9, with higher scores indicating better quality; studies scoring 7 or above were classified as high quality. Extracted data included study-level information (first author, publication year, country, and study design), participant characteristics (source of the population, sample size, mean age, and sex distribution), details on the diagnostic criteria of prediabetes and number of participants with prediabetes at baseline, mean follow-up durations, number of participants who developed thyroid cancer during follow-up, methods for validation the diagnosis of thyroid cancer, and the covariates adjusted for in the association analyses.

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Statistical analyses

The association between prediabetes and the incidence of thyroid cancer was evaluated by pooling risk ratios (RRs) and their corresponding 95% confidence intervals (CIs), comparing individuals with prediabetes and normoglycemia. When necessary, RRs and their standard errors were calculated from reported 95% CIs or p-values and then log-transformed to stabilize variance and normalize the distribution (38). Between-study heterogeneity was assessed using the Cochrane Q test and the I^2 statistic, with thresholds of < 25%, 25–75%, and > 75% interpreted as low, moderate, and high heterogeneity, respectively (40). A random-effects model was applied to account for between-study variability (38). Specifically, we used the DerSimonian–Laird estimator with an inverse-variance (IV) weighting approach to pool the results. Sensitivity analysis was conducted by sequentially omitting each study to examine the stability of the pooled estimate. Subgroup analyses were also performed to explore the influence of study-level characteristics, such as study country (Asian vs. Western countries), mean ages, sex, definition of prediabetes, mean follow-up durations, and methods to validate the diagnosis of thyroid cancer. Median values of continuous variables were used to define subgroup cutoffs. Publication bias was evaluated through visual inspection of funnel plots and formally tested using Egger's regression test (41). A p value < 0.05 indicates statistical significance. All statistical analyses were performed using RevMan (version 5.1; Cochrane Collaboration, Oxford, UK) and Stata (version 12.0; Stata Corporation, College Station, TX, USA). The certainty of evidence for the main outcome was assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) framework, which evaluates five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias (42). Based on these criteria, the evidence was rated as high, moderate, low, or very low certainty.

RESULTS

Study retrieval

The study selection process is illustrated in **Figure 1**. An initial total of 698 potentially relevant records were identified through database searches and citation screening. After removing 268 duplicates, 430 records remained for title and abstract screening, which resulted in the exclusion of 414 articles that did not align with the

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meta-analysis objectives. The full texts of the remaining 16 articles were then independently assessed by two reviewers, leading to the exclusion of 10 studies for reasons outlined in **Figure 1**. Ultimately, six studies met the inclusion criteria and were included in the quantitative synthesis (30-35).

Overview of the study characteristics

Table 1 summarizes the characteristics of the six studies included in this meta-analysis. Overall, six studies (30-35), published between 2006 and 2023 and conducted in Austria, the United Kingdom, Korea, China, and the United States, were included. All studies were prospective cohort designs, with most involving adults from the general population (30-34), while one study focused on women who had a sister with breast cancer (35). A total of 5,743,849 adults were included. The mean age of participants varied from 43 to 67.2 years, and the percentage of women ranged from 47% to 100%. Prediabetes was defined using IFG in three studies (30, 33, 34), as mildly elevated HbA1c levels in one study (31), and used combined criteria, such as IFG and/or IGT (32), as well IFG, IGT or mildly elevated HbA1c levels (35) in another two studies. The number of individuals with prediabetes ranged from approximately 6,754 to over 1.5 million, and follow-up durations ranged from 4.4 to 12.5 years. Thyroid cancer diagnosis was confirmed using population-based cancer registries (30, 32), self-reported clinically validated diagnosis (33, 35), or International Classification of Disease (ICD) codes (31, 34), each methods for two studies respectively. All studies reported multivariate-adjusted data, including covariates such as age, sex, BMI, smoking status, physical activity, and socioeconomic factors to a varying extent. The methodological quality of the included studies, as assessed by the NOS, was generally high, with total scores ranging from 7 to 9 (**Table 2**). All studies received full points for representativeness, exposure ascertainment, and control for age and sex. However, variation was noted in the "Assessment of outcome" domain. Specifically, studies that used cancer registries or clinically validated diagnoses were awarded full scores, while those relying on ICD-10 codes were downgraded due to potential for outcome misclassification. This aligns with our subgroup findings and underscores the importance of rigorous outcome validation in epidemiologic studies.

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Association between prediabetes and the incidence of thyroid cancer

Because four studies reported the association between prediabetes and the incidence of thyroid cancer in men and women separately (30, 32-34), these datasets were independently included in the meta-analysis, making a total of 10 datasets available for the meta-analysis. These strata were mutually exclusive and each provided risk estimates adjusted for relevant confounders. Statistically, treating independently adjusted, non-overlapping strata as separate units is a valid approach in meta-analysis and does not underestimate variance. As some studies did not report combined estimates across sexes, a sensitivity analysis based on pooled study-level estimates could not be performed. The pooled analysis showed that prediabetes was not significantly associated with thyroid cancer incidence compared to normoglycemia (RR: 1.04; 95% CI: 0.98–1.11; $p = 0.23$; $I^2 = 53\%$; **Figure 2**). A sensitivity analysis by excluding one dataset at a time showed similar results, with pooled RRs ranging from 1.03 to 1.15, all with $p > 0.05$. Subsequently, subgroup analyses suggested that the results were not significantly affected by study country (p for subgroup difference = 0.13; **Figure 3A**), mean ages of the participants (p for subgroup difference = 0.13; **Figure 3B**), sex of the participants (p for subgroup difference = 0.81; **Figure 4A**), definitions of prediabetes (p for subgroup difference = 0.09; **Figure 4B**), or follow-up durations (p for subgroup difference = 0.25; **Figure 5A**). Interestingly, prediabetes was associated with a significantly increased risk of thyroid cancer as evidenced by cancer registry or self-reported clinical diagnosis (RR: 1.29, 95% CI: 1.04–1.60; $p = 0.02$; $I^2 = 28\%$), but not in studies with thyroid cancer diagnosis by ICD-10 codes (RR: 1.01, 95% CI: 0.98–1.05; $p = 0.52$; $I^2 = 46\%$; p for subgroup difference = 0.03; **Figure 5B**).

Publication bias

The funnel plots assessing the association between prediabetes and thyroid cancer are presented in **Figure 6.** Visual inspection of the plots suggests a symmetrical distribution, indicating a low likelihood of publication bias. This observation is further supported by Egger's regression test, which yielded a non-significant result ($p = 0.58$).

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Certainty of evidence

The overall certainty of evidence was rated as low based on GRADE criteria (**Supplemental File 2**), primarily due to inconsistency and unexplained heterogeneity despite of the sensitivity and subgroup analyses.

DISCUSSION

In this meta-analysis of six prospective cohort studies involving over 5.7 million participants, we found that prediabetes was not significantly associated with an increased incidence of thyroid cancer in the overall analysis. Subgroup analyses further demonstrated that the null association was consistent regardless of geographic region, age group, sex, follow-up duration, or the specific criteria used to define prediabetes. These findings suggest that prediabetes, as a broad diagnostic category, may not independently confer a significantly elevated risk for thyroid cancer in the general adult population.

Importantly, our subgroup analysis revealed that the method of thyroid cancer ascertainment significantly influenced the observed associations. Studies that relied on population-based cancer registries or self-reported diagnoses validated through medical records or pathology reports showed a significantly increased risk of thyroid cancer among individuals with prediabetes (RR: 1.29; 95% CI: 1.04–1.60), with low residual heterogeneity ($I^2 = 28\%$). In contrast, studies relying solely on administrative ICD-10 codes reported no significant association. This discrepancy may reflect differential misclassification: cancer registries and validated clinical records generally apply stringent diagnostic criteria and require histopathological confirmation, reducing the likelihood of false positives and ensuring more accurate case identification (43). Similarly, self-reported cancer diagnoses that are clinically validated through pathology or medical records tend to have high specificity (44).Conversely, administrative data using ICD codes may be prone to inaccuracies from miscoding, inclusion of rule-out diagnoses, or over-diagnosis, potentially biasing the results toward the null (45). Surveillance bias could also contribute—individuals with prediabetes may undergo more frequent health monitoring, increasing the chance of cancer detection in validated settings, whereas such effects may be diluted in large-scale administrative databases (45). These methodological differences underscore the critical importance of outcome validation in epidemiological research on cancer risk.

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The attenuation of associations in these studies may thus reflect non-differential misclassification of the outcome, potentially biasing the results toward the null.

The findings of this study are consistent with some previous literature examining the relationship between metabolic dysregulation and cancer risk. While diabetes has been associated with a modest increase in the risk of thyroid (46) and other cancers (47), the evidence linking prediabetes to thyroid cancer has been limited and inconsistent. Mechanistic studies suggest that insulin resistance, a hallmark of prediabetes, may promote tumorigenesis through hyperinsulinemia and activation of insulin-like growth factor signaling pathways (48, 49). A similar uncertainty about disease associations and the influence of outcome ascertainment has been noted in studies on non-malignant conditions; for example, a recent meta-analysis by Jin et al. (50) found a potential link between prediabetes and Parkinson's disease but emphasized the impact of diagnostic approaches on risk estimates. These parallels reinforce the importance of accurate outcome classification in prediabetes-related research. However, it is possible that the degree of metabolic disturbance in prediabetes may be insufficient to exert a measurable effect on thyroid cancer risk, especially in population-level analyses. Alternatively, the null association observed in most studies may reflect the influence of unmeasured or residual confounders, such as iodine intake, radiation exposure, or thyroid autoimmunity (51-53), which are known to influence thyroid cancer risk but were not consistently adjusted for across studies. Similar observation has also been found in other cancers. For example, diabetes has been related to a higher risk of breast cancer (54), but a recent meta-analysis did not support a significant association between prediabetes and increased risk of breast cancer (55).

This meta-analysis has several notable strengths. It is the first comprehensive quantitative synthesis of longitudinal studies assessing the association between prediabetes and thyroid cancer risk. The inclusion of over 5.7 million participants provides substantial statistical power to detect modest associations. All included studies were prospective in design, reducing the likelihood of recall bias and temporal ambiguity. In addition, we conducted a series of prespecified subgroup and sensitivity analyses to explore potential sources of heterogeneity, and the risk of publication bias appeared to be low based on both funnel plot symmetry and Egger's test. Nonetheless, several limitations should be acknowledged. First, the definition of prediabetes varied across studies, with some using IFG, others using HbA1c, and some applying

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combined criteria. Although this was addressed in subgroup analysis, it may still contribute to underlying heterogeneity. Second, the number of included studies was relatively small, and not all studies reported sex-specific or subgroup data, limiting the ability to explore effect modification in greater depth. Third, potential confounding cannot be completely excluded, despite multivariable adjustment in all studies. Important variables such as dietary patterns, family history of thyroid disease, or environmental exposures were not uniformly accounted for. Fourth, the observed difference in associations by cancer diagnosis method raises the concern of differential misclassification bias, which may have influenced the pooled estimates. In addition, a subgroup according to the histological type of thyroid cancer could not be performed because these stratified data were not reported in the included studies. Moreover, none of the included studies accounted for the presence of chronic autoimmune thyroiditis, which has been proposed as a risk factor for thyroid cancer (56). The lack of data on baseline thyroid inflammation may have introduced residual confounding and limited the ability to assess effect modification by underlying thyroid conditions. Finally, while Egger's regression test did not suggest significant publication bias ($p = 0.58$), it is important to note that the test has limited statistical power when applied to fewer than 10 to 15 studies. Therefore, the symmetrical appearance of the funnel plot and the negative result should be interpreted with caution.

Clinically, our findings suggest that prediabetes alone may not warrant targeted thyroid cancer screening beyond current population-based recommendations. However, in settings where cancer is ascertained through robust and validated methods, a modest increase in thyroid cancer risk associated with prediabetes cannot be entirely ruled out. These findings reinforce the importance of accurate case identification in epidemiological research and highlight the potential for misclassification to obscure real associations. Future studies should strive to use validated cancer outcomes and consider stratifying analyses by underlying metabolic profiles, such as insulin levels, inflammatory markers, or duration of prediabetes, to better characterize the at-risk subgroups. Additionally, studies in populations with different ethnic backgrounds and iodine intake patterns would help improve the generalizability of the findings.

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CONCLUSION

In conclusion, this meta-analysis found no significant overall association between prediabetes and the incidence of thyroid cancer. However, a possible association was observed in studies with clinically validated cancer diagnoses, suggesting that outcome ascertainment methods may influence observed relationships. As all included studies were observational in design, the findings should be interpreted with caution, and prospective comparative studies are needed to confirm any potential causal link between prediabetes and thyroid cancer risk.

Conflicts of interest: Authors declare no conflicts of interest.

Funding: Authors received no specific funding for this work.

Data availability: All data generated or analyzed during this study are included in this published article.

Submitted: June 4, 2025

Accepted: July 16, 2025

Published online: September 2, 2025

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TABLES AND FIGURES WITH LEGENDS

Table 1. Characteristics of the included studies

Study	Country	Design	Population characteristics	No. of participants	Mean age (years)	Women (%)	Diagnosis of PreD	No. of subjects with PreD	Mean follow-up (years)	No. of patients with TC	Methods for TC validation	Variables adjusted
Rapp 2006	Austria	PC	Adults >19 years from the general population	140,813	43	54.8	IFG	6754	8.4	70	Population-based cancer registry, histologically confirmed	Age, sex, smoking status, occupational group, BMI
Peila 2020	UK	PC	Adults aged 40–69 years from the general population	476,517	56.2	54	Mildly elevated HbA1c (5.7-6.5%)	64,167	7.1	269	ICD-10 code	Age, sex, education, non-white race, smoking status, pack-years, alcohol intake, physical

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												activity, BMI
Park 2022	Korea	PC	Adults aged 40–70 years from the general population	4,658,473	51.5	47	IFG	1,570,425	6	47,325	ICD-10 code	Age, sex, and BMI
Nguyen 2022	Korea	PC	Adults aged 40-79 years from general population	160,650	65.6	54.5	IFG	40,929	7.4	471	Self-reported physician-diagnosed TC validated by medical records/pathology reports	Age, sex, smoking, alcohol, physical activity, education; for women, also adjusted for menopausal status and hormone therapy
Miao 2022	China	PC	Adults >20 years from the general	259,657	67.2	65.3	IFG and/or IGT	31,568	4.4	78	Population-based cancer	Age and sex

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			population								registry	
Pasqual 2023	USA	PC	Women aged 35–74 years with a sister who had breast cancer	47,739	55.4	100	Self-reported borderline diabetes (IFG, IGT, and/or mildly elevated HbA1c	NR [a]	12.5	249	Self-report confirmed by medical records/pathology reports	Age and BMI

Note: Summary of six prospective cohort studies included in this meta-analysis, detailing study design, populations, definitions of prediabetes, follow-up duration, thyroid cancer validation methods, and adjusted variables. a, Not reported in the original publication. This value was not required for meta-analysis, which pooled adjusted risk estimates and 95% CIs. Abbreviations: PC, prospective cohort;

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PreD, prediabetes; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; HbA1c, glycated hemoglobin; TC, thyroid cancer; BMI, body mass index; ICD-10, International Classification of Diseases, 10th Revision; NR, not reported.

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Table 2. Study quality evaluation via the Newcastle-Ottawa scale

Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at baseline	Control for age and sex	Control for other confounding factors	Assessment of outcome	Enough long follow-up duration	Adequacy of follow-up of cohorts	Total
Rapp 2006	1	1	1	1	1	1	1	1	1	9
Peila 2020	1	1	1	1	1	1	0	1	1	8
Park 2022	1	1	1	1	1	1	0	1	1	8
Nguyen 2022	1	1	1	1	1	1	0	1	1	8
Miao 2022	1	1	1	1	1	0	1	0	1	7
Pasqual 2023	1	1	0	1	1	1	0	1	1	7

Note: Overview of methodological quality assessment of the included studies using the Newcastle-Ottawa scale, covering domains of selection, comparability, and outcome.

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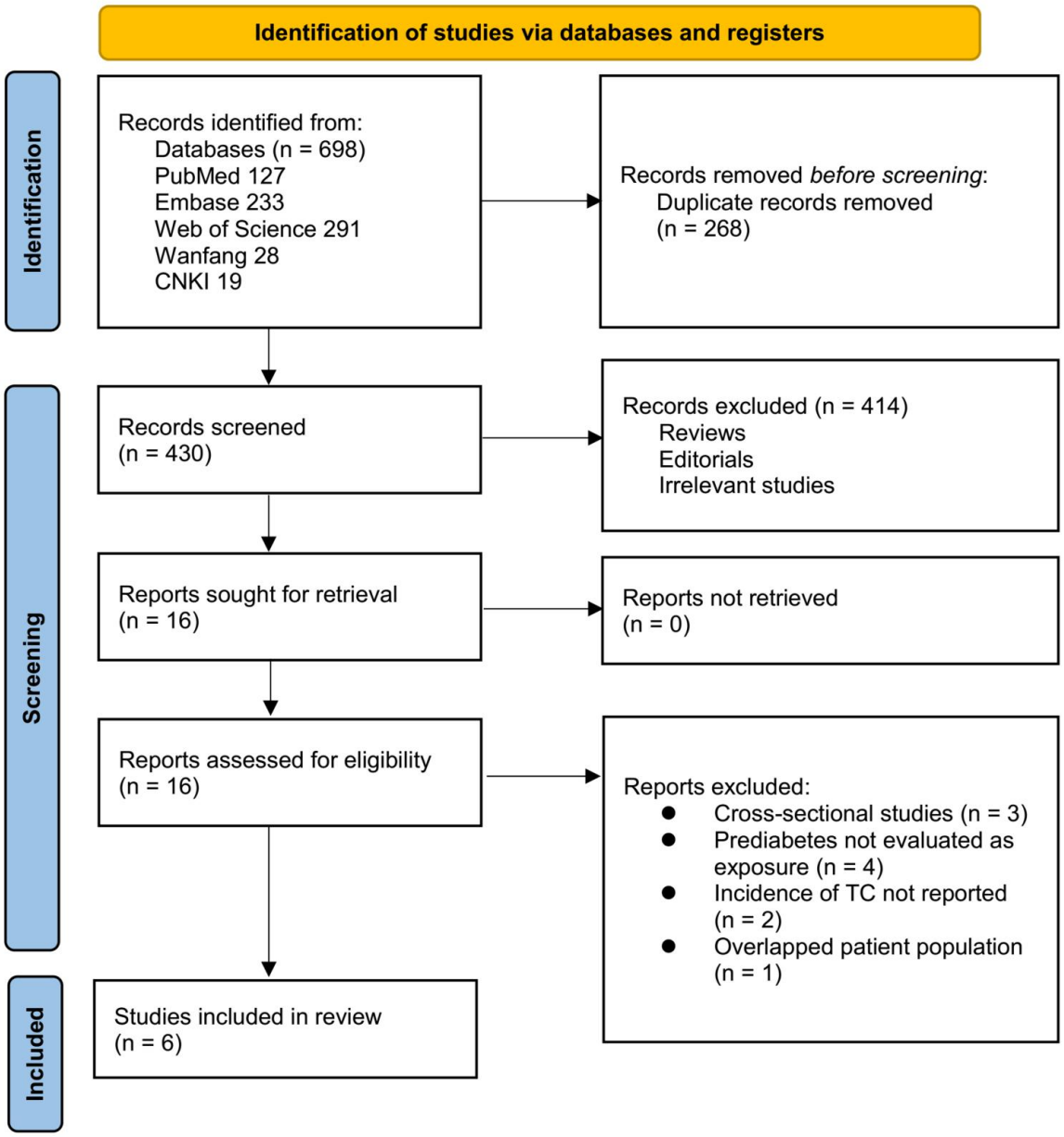

Figure 1. Flow diagram of study selection.

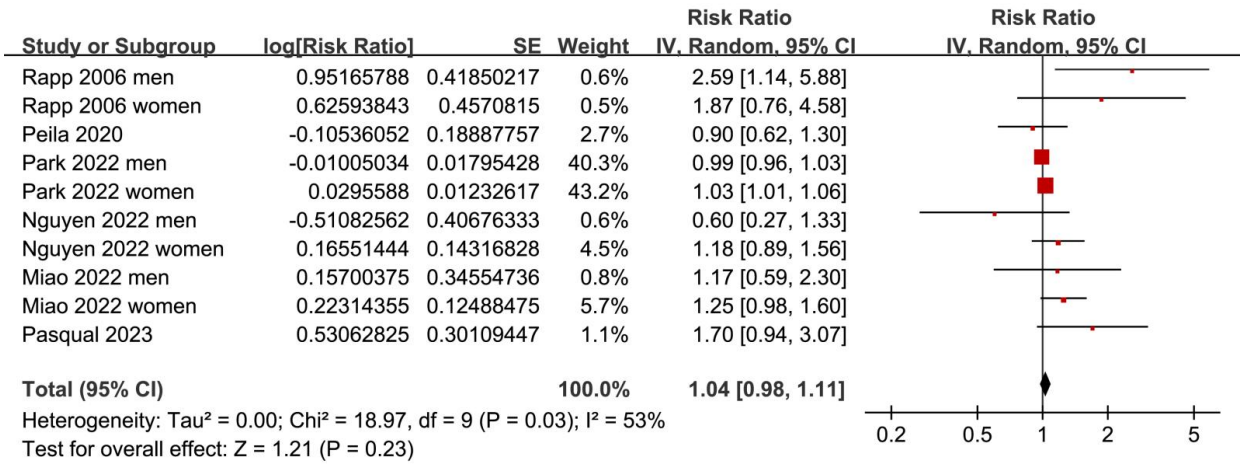

Figure 2. Association between prediabetes and the incidence of thyroid cancer.

Forest plot showing RRs and 95% CIs for the association between prediabetes and thyroid cancer incidence across 10 datasets from six prospective cohort studies. Separate risk estimates were included for men and women where available. Abbreviations: RR, risk ratio; CI, confidence interval; SE, standard error; IV, inverse variance.

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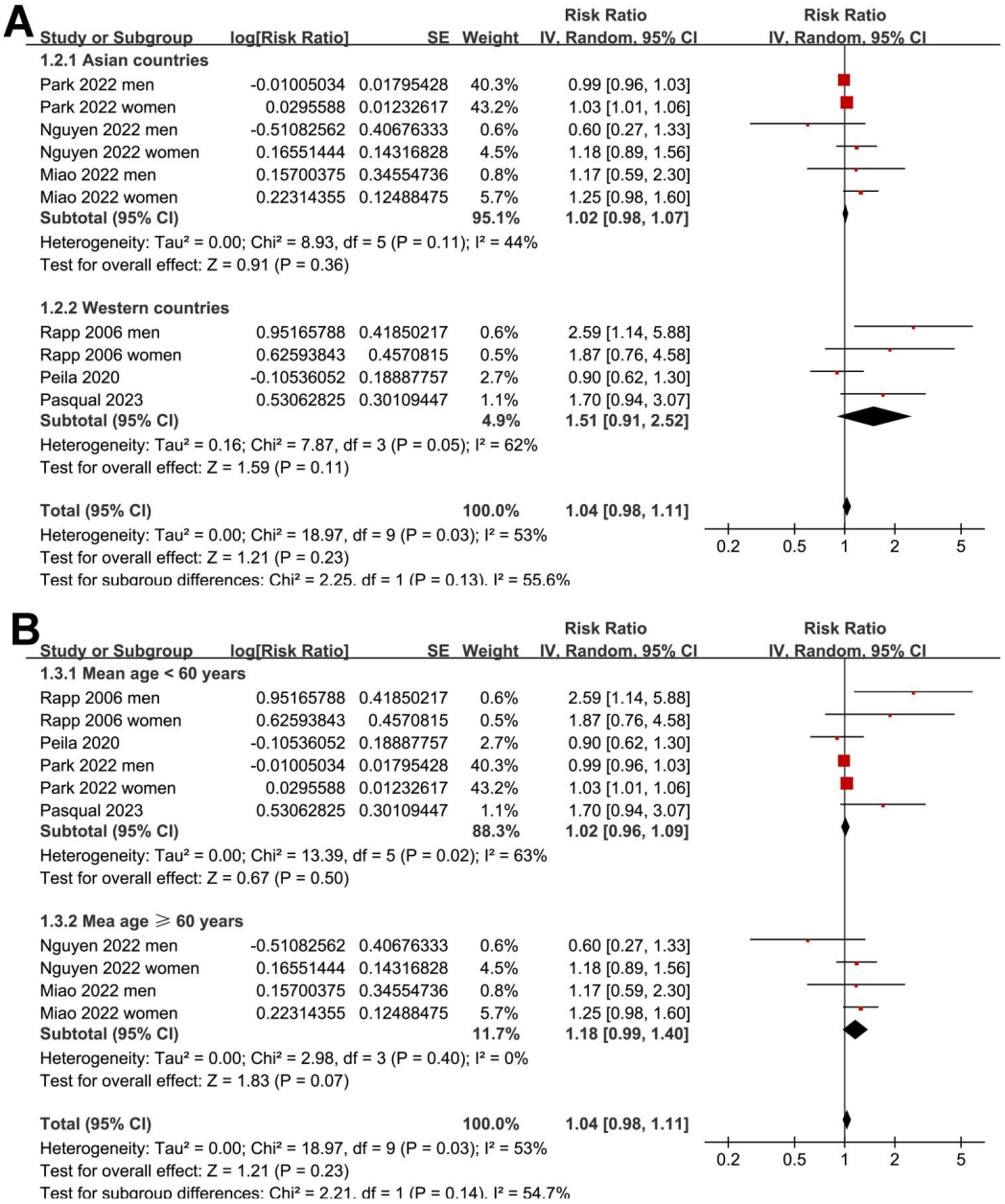

Figure 3. Subgroup analyses of the association between prediabetes and thyroid cancer incidence by (A) study country and (B) mean age of participants. Forest plots show pooled RRs and 95% CIs for thyroid cancer incidence in individuals with prediabetes compared to normoglycemia. Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error; RR, risk ratio.

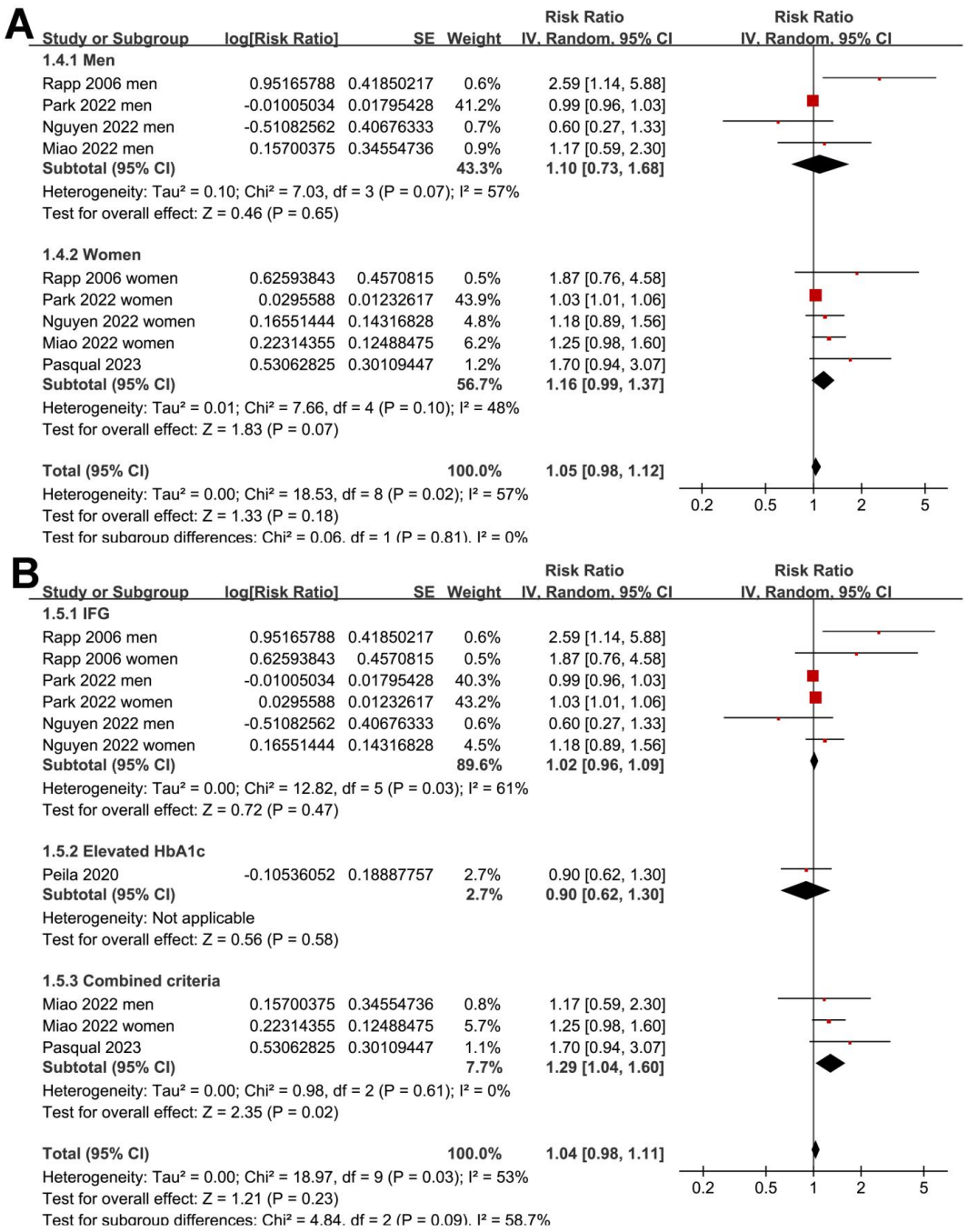

Figure 4. Subgroup analyses of the association between prediabetes and thyroid cancer incidence by (A) sex of participants and (B) definitions of prediabetes. Forest plots show pooled RRs and 95% CIs for thyroid cancer incidence in individuals with prediabetes compared to normoglycemia. Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin A1c; IFG, impaired fasting glucose; IV, inverse variance; SE, standard error; RR, risk ratio.

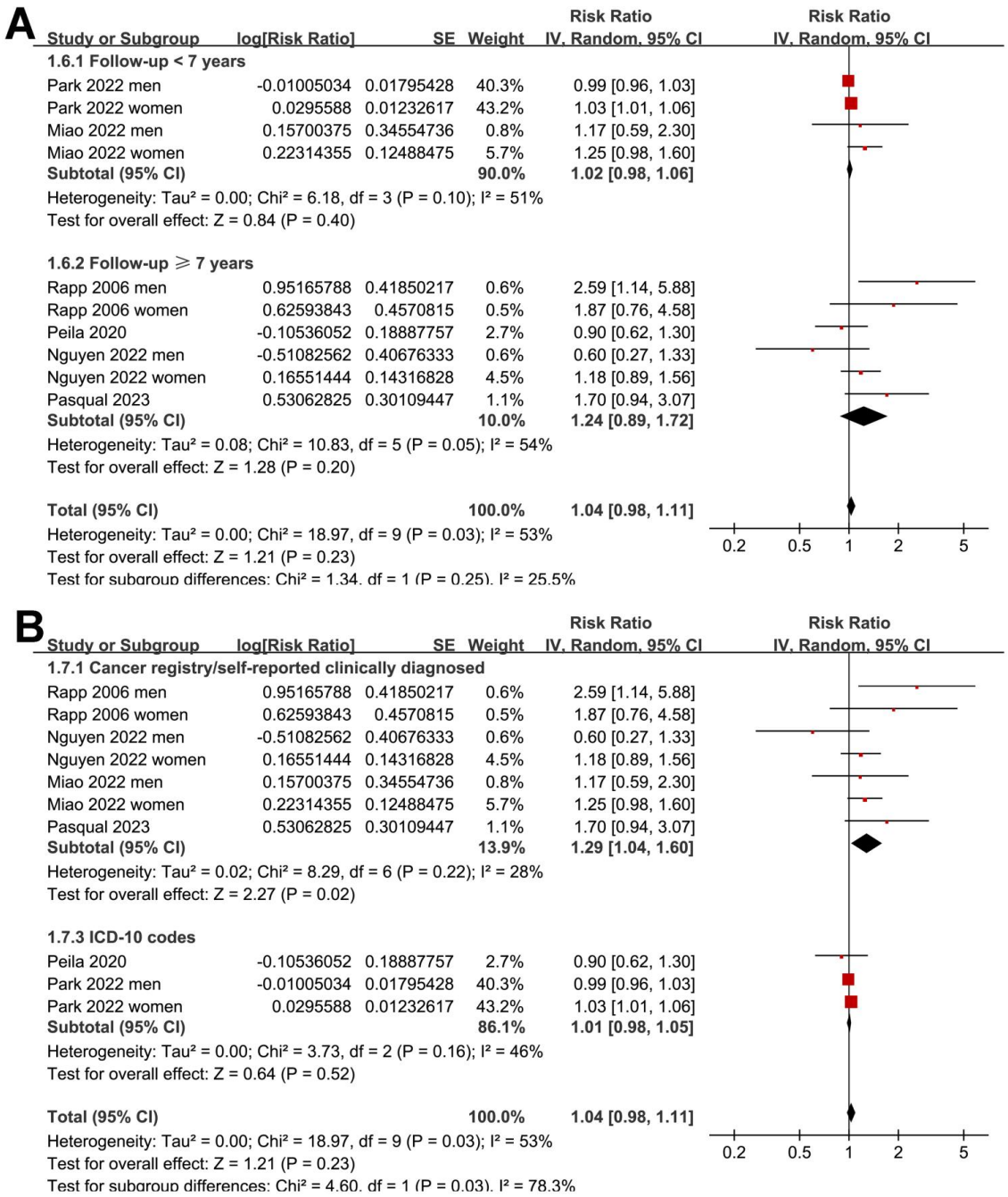

Figure 5. Subgroup analyses of the association between prediabetes and thyroid cancer incidence by (A) follow-up duration and (B) method of thyroid cancer diagnosis. Forest plots show pooled RRs and 95% CIs for thyroid cancer incidence in individuals with prediabetes compared to normoglycemia. Abbreviations: CI, confidence interval; ICD-10, International Classification of Diseases, 10th Revision; IV, inverse variance; SE, standard error; RR, risk ratio.

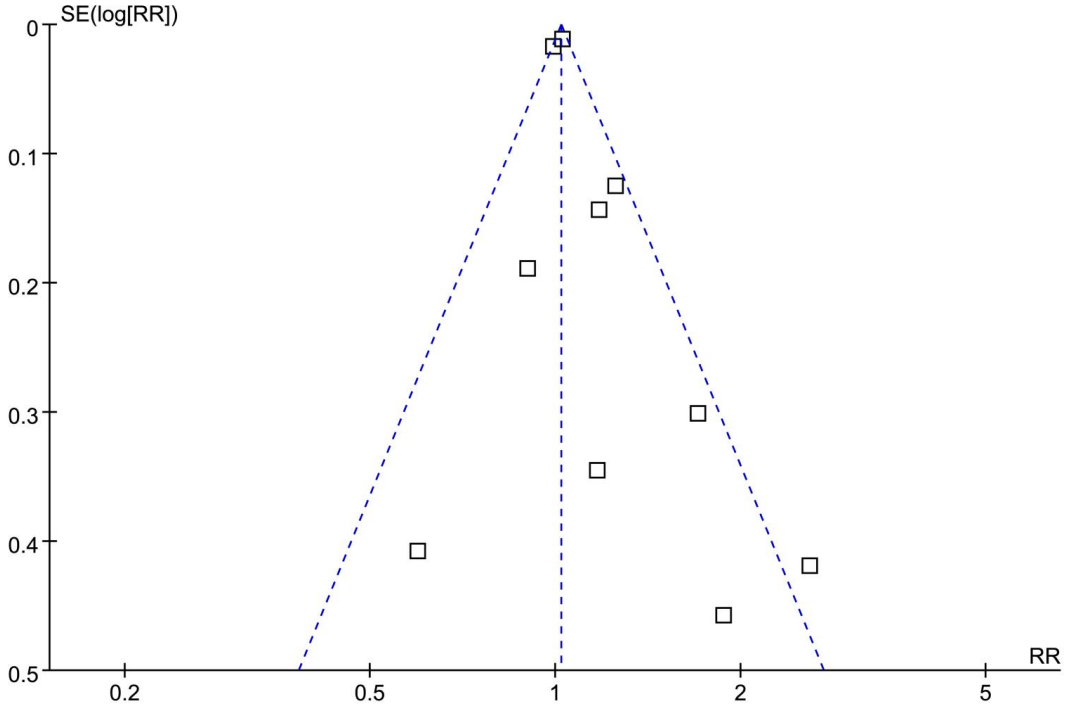

Figure 6. Funnel plot assessing publication bias underlying the meta-analysis of association between prediabetes and the incidence of thyroid cancer. The dotted line indicates the expected log[RR] under the assumption of symmetry.

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SUPPLEMENTAL DATA

Supplemental file 1.

Detailed search strategy for each database

PubMed

("Prediabetic State"[Mesh] OR "prediabetes"[tiab] OR "pre-diabetes"[tiab] OR "prediabetic"[tiab] OR "pre-diabetic"[tiab] OR "prediabetic state"[tiab] OR "borderline diabetes"[tiab] OR "impaired fasting glucose"[tiab] OR "impaired glucose tolerance"[tiab] OR "IFG"[tiab] OR "IGT"[tiab] OR "fasting glucose"[tiab] OR "HbA1c"[tiab]) AND ("Thyroid Neoplasms"[Mesh] OR "thyroid cancer"[tiab] OR "thyroid carcinoma"[tiab] OR "thyroid neoplasm"[tiab] OR "thyroid malignancy"[tiab] OR "thyroid tumor"[tiab])
Limits: Humans, English or Chinese, full-length articles
Date range: Inception to April 12, 2025

Embase

('prediabetic state'/exp OR 'prediabetes':ti,ab OR 'pre-diabetes':ti,ab OR 'prediabetic':ti,ab OR 'pre-diabetic':ti,ab OR 'prediabetic state':ti,ab OR 'borderline diabetes':ti,ab OR 'impaired fasting glucose':ti,ab OR 'impaired glucose tolerance':ti,ab OR IFG:ti,ab OR IGT:ti,ab OR 'fasting glucose':ti,ab OR HbA1c:ti,ab) AND ('thyroid tumor'/exp OR 'thyroid cancer':ti,ab OR 'thyroid carcinoma':ti,ab OR 'thyroid neoplasm':ti,ab OR 'thyroid malignancy':ti,ab OR 'thyroid tumor':ti,ab)
Limits: Humans, English or Chinese, full-length articles
Date range: Inception to April 12, 2025

Web of Science

TS=("prediabetes" OR "pre-diabetes" OR "prediabetic" OR "pre-diabetic" OR "prediabetic state" OR "borderline diabetes" OR "impaired fasting glucose" OR "impaired glucose tolerance" OR "IFG" OR "IGT" OR "fasting glucose" OR "HbA1c") AND TS=("thyroid cancer" OR "thyroid neoplasm" OR "thyroid carcinoma" OR "thyroid malignancy" OR "thyroid tumor")
Date range: Inception to April 12, 2025

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Wanfang

主题=("糖尿病前期" OR "糖耐量受损" OR "空腹血糖受损" OR "边缘性糖尿病" OR "糖化血红蛋白") AND 主题=("甲状腺癌" OR "甲状腺恶性肿瘤" OR "甲状腺肿瘤" OR "甲状腺癌瘤")

English translation: Topic = ("prediabetes" OR "impaired glucose tolerance" OR "impaired fasting glucose" OR "borderline diabetes" OR "glycated hemoglobin") AND Topic = ("thyroid cancer" OR "malignant thyroid neoplasm" OR "thyroid neoplasm" OR "thyroid carcinoma")
Limits: Human studies, Chinese language, full-length articles
Date range: Inception to April 12, 2025

CNKI

主题=("糖耐量受损" OR "空腹血糖受损" OR "糖尿病前期" OR "边缘性糖尿病" OR "糖化血红蛋白") AND 主题=("甲状腺癌" OR "甲状腺肿瘤" OR "甲状腺恶性肿瘤" OR "甲状腺癌瘤")

English translation: Topic = ("impaired glucose tolerance" OR "impaired fasting glucose" OR "prediabetes" OR "borderline diabetes" OR "glycated hemoglobin") AND Topic = ("thyroid cancer" OR "thyroid neoplasm" OR "malignant thyroid neoplasm" OR "thyroid carcinoma")

Limits: Human studies, Chinese language, full-length articles
Date range: Inception to April 12, 2025

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Supplemental file 2. GRADE summary of findings

Outcome	No. of Studies (datasets)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Prediabetes and incidence of thyroid cancer	6 (10)	Observational (cohort)	Not serious – most studies high quality; lower scores in ICD-based studies considered in subgroup analysis	Serious – moderate heterogeneity (I^2 = 53%) only partially explained by subgroup analysis	Not serious – population, exposure, and outcome directly applicable to research question	Not serious – confidence intervals were narrow and excluded clinically large effects	None detected – symmetrical funnel plot and non-significant Egger's test (p = 0.58)	Low

Note: The certainty of evidence was downgraded one level due to inconsistency. Despite low risk of bias and precise estimates, moderate unexplained heterogeneity in the overall analysis warranted downgrading. Subgroup analysis revealed more consistent findings in studies using validated outcomes. Abbreviations: GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; ICD, International Classification of Diseases.

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