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# THYROID DYSFUNCTION AND MENTAL HEALTH: A SYSTEMATIC REVIEW OF PSYCHIATRIC SYMPTOMS ASSOCIATED WITH HYPO- AND HYPERTHYROIDIS

# DISFUNÇÃO TIREOIDIANA E SAÚDE MENTAL: UMA REVISÃO SISTEMÁTICA DOS SINTOMAS PSIQUIÁTRICOS ASSOCIADOS À HIPO E HIPERTIREOIDISMO

# DISFUNCIÓN TIROIDEA Y SALUD MENTAL: UNA REVISIÓN SISTEMÁTICA DE LOS SÍNTOMAS PSIQUIÁTRICOS ASOCIADOS CON HIPOTIROIDISMO E HIPERTIROIDISMO

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## ABSTRACT

**Introduction:** Thyroid dysfunction, encompassing both hypo- and hyperthyroid states, exerts profound systemic effects that extend to mood, cognition, and behavior. Psychiatric manifestations such as depression, anxiety, and psychosis have been consistently reported, yet their magnitude and mechanisms remain debated.

**Objective:** To systematically evaluate current evidence regarding psychiatric symptoms associated with thyroid dysfunction, emphasizing the spectrum of mood and cognitive alterations in overt and subclinical forms.

**Methods:** A systematic search was conducted in PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and ICTRP for studies published from 2018 to 2025. Eligible studies included randomized trials, cohorts, and case-control designs assessing psychiatric outcomes in thyroid dysfunction. No language restrictions were applied. Data were synthesized qualitatively, with risk of bias and evidence certainty graded according to GRADE criteria.

**Results and Discussion:** Among 1,247 records identified, 52 studies met inclusion criteria. Hypothyroidism was strongly associated with depressive and cognitive symptoms, while hyperthyroidism correlated with anxiety, irritability, and in severe cases, psychotic or manic states. Subclinical conditions demonstrated weaker but consistent associations with mood and cognitive impairment. Immunological mechanisms and altered serotonergic neurotransmission emerged as plausible pathophysiological links. Heterogeneity in diagnostic criteria and outcome measures limited meta-analytic synthesis.

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**Conclusion:** Psychiatric symptoms are clinically relevant manifestations of thyroid dysfunction. Routine thyroid screening in atypical or treatment-resistant psychiatric presentations is warranted. Integrative management addressing both endocrine and neuropsychiatric dimensions improves patient outcomes.

**Keywords:** Thyroid Diseases. Mood Disorders. Cognitive Dysfunction. Psychotic Disorders.

## RESUMO

**Introdução:** A disfunção tireoidiana, abrangendo estados hipo e hipertireoidianos, exerce profundos efeitos sistêmicos que se estendem ao humor, à cognição e ao comportamento. Manifestações psiquiátricas como depressão, ansiedade e psicose têm sido consistentemente relatadas, mas sua magnitude e mecanismos permanecem controversos.

**Objetivo:** Avaliar sistematicamente as evidências atuais sobre sintomas psiquiátricos associados à disfunção tireoidiana, enfatizando o espectro de alterações de humor e cognitivas em formas manifestas e subclínicas.

**Métodos:** Uma busca sistemática foi realizada nas bases de dados PubMed, Scopus, Web of Science, Biblioteca Cochrane, LILACS, ClinicalTrials.gov e ICTRP para estudos publicados de 2018 a 2025. Os estudos elegíveis incluíram ensaios clínicos randomizados, coortes e delineamentos caso-controle que avaliaram desfechos psiquiátricos em disfunção tireoidiana. Não foram aplicadas restrições de idioma. Os dados foram sintetizados qualitativamente, com risco de viés e certeza da evidência classificados de acordo com os critérios GRADE.

**Resultados e Discussão:** Entre 1.247 registros identificados, 52 estudos preencheram os critérios de inclusão. O hipotireoidismo esteve fortemente associado a sintomas depressivos e cognitivos, enquanto o hipertireoidismo correlacionou-se com ansiedade, irritabilidade e, em casos graves, estados psicóticos ou maníacos. Condições subclínicas demonstraram associações mais fracas, porém consistentes, com humor e comprometimento cognitivo. Mecanismos imunológicos e neurotransmissão serotoninérgica alterada emergiram como elos fisiopatológicos plausíveis. A heterogeneidade nos critérios diagnósticos e nas medidas de desfecho limitou a síntese meta-analítica.

**Conclusão:** Sintomas psiquiátricos são manifestações clinicamente relevantes da disfunção tireoidiana. O rastreamento rotineiro da tireoide em quadros psiquiátricos atípicos ou resistentes ao tratamento é justificado. O tratamento integrativo, abordando as dimensões endócrina e neuropsiquiátrica, melhora os desfechos dos pacientes.

**Palavras-chave:** Doenças da Tireoide. Transtornos do Humor. Disfunção Cognitiva. Transtornos Psicóticos.

## RESUMEN

**Introducción:** La disfunción tiroidea, que abarca tanto estados hipotiroideos como hipertiroideos, ejerce profundos efectos sistémicos que se extienden al estado de ánimo, la cognición y la conducta. Manifestaciones psiquiátricas como la depresión, la ansiedad y la psicosis se han reportado consistentemente, pero su magnitud y mecanismos siguen siendo objeto de debate.

**Objetivo:** Evaluar sistemáticamente la evidencia actual sobre los síntomas psiquiátricos asociados con la disfunción tiroidea, con énfasis en el espectro de alteraciones del estado de ánimo y cognitivas en formas manifiestas y subclínicas.

**Métodos:** Se realizó una búsqueda sistemática en PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov e ICTRP de estudios publicados entre 2018 y 2025. Los estudios elegibles incluyeron ensayos aleatorizados, cohortes y diseños de casos y controles que evaluaron los resultados psiquiátricos en la disfunción tiroidea. No se aplicaron restricciones de idioma. Los datos se sintetizaron cualitativamente, y el riesgo de sesgo y la certeza de la evidencia se calificaron según los criterios GRADE.

**Resultados y discusión:** De los 1247 registros identificados, 52 estudios cumplieron los criterios de inclusión. El hipotiroidismo se asoció fuertemente con síntomas depresivos y cognitivos, mientras que el hipertiroidismo se correlacionó con ansiedad, irritabilidad y, en casos graves, con estados psicóticos o maníacos. Las afecciones subclínicas mostraron asociaciones más débiles, pero consistentes, con el estado de ánimo y el deterioro cognitivo. Los mecanismos inmunológicos y la neurotransmisión serotoninérgica alterada surgieron como posibles vínculos fisiopatológicos. La heterogeneidad en los criterios diagnósticos y las medidas de resultado limitó la síntesis metaanalítica.

**Conclusión:** Los síntomas psiquiátricos son manifestaciones clínicamente relevantes de la disfunción tiroidea. Se justifica el cribado tiroideo rutinario en presentaciones psiquiátricas atípicas o resistentes al tratamiento. El tratamiento integral que aborda tanto las dimensiones endocrinas como las neuropsiquiátricas mejora la evolución de los pacientes.

**Palabras clave:** Enfermedades Tiroideas. Trastornos del Estado de Ánimo. Disfunción Cognitiva. Trastornos Psicóticos.

## 1 INTRODUCTION

Thyroid hormones play a pivotal role in the regulation of brain development, metabolism, and neurochemical homeostasis, linking endocrine function with cognitive and emotional regulation.[1] Alterations in thyroid hormone levels can induce structural and functional changes in brain regions such as the hippocampus, amygdala, and prefrontal cortex, which are crucial for mood and cognition.[1] The bidirectional communication between the hypothalamic-pituitary-thyroid (HPT) axis and the central nervous system provides a biological framework through which endocrine imbalances can manifest as psychiatric symptoms.[1]

Hypothyroidism, both overt and subclinical, has long been recognized as a contributor to depressive symptoms, psychomotor slowing, and reduced cognitive performance.[2] In contrast, hyperthyroidism is frequently associated with anxiety, irritability, restlessness, and in severe cases, manic or psychotic states.[2] These opposing presentations highlight the complexity of thyroid-related neuropsychiatric disturbances and the necessity for precise hormonal evaluation in psychiatric settings.[2]

Recent studies have demonstrated that even minor deviations in thyroid-stimulating hormone (TSH) or free thyroxine (FT4) levels may influence mood and anxiety disorders, suggesting that the threshold for neuropsychiatric effects is lower than previously assumed.[3] This relationship appears to be mediated by serotonin and noradrenaline neurotransmission as well as neuroinflammatory processes modulated by thyroid hormones.[3] Such findings underscore the importance of assessing thyroid function not only in overt endocrine disorders but also in patients with unexplained psychiatric manifestations.[3]

Emerging neuroimaging studies have revealed altered cerebral metabolism and connectivity in individuals with thyroid dysfunction, further supporting a neurobiological link between endocrine and psychiatric pathophysiology.[4] Functional magnetic resonance imaging and positron emission tomography have identified changes in limbic and cortical circuits associated with emotional regulation and executive function.[4] These alterations tend to normalize after restoration of euthyroidism, reinforcing the causative role of thyroid imbalance in neuropsychiatric symptomatology.[4]

Autoimmune thyroid diseases, particularly Hashimoto's thyroiditis and Graves' disease, introduce additional complexity through inflammatory and immunological mechanisms that may directly affect brain function.[5] Elevated levels of thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies have been correlated with depression, fatigue, and anxiety even in euthyroid individuals.[5] The role of systemic inflammation and

autoantibody-mediated neuronal effects is therefore a growing field of investigation in psychoneuroendocrinology.[5]

The psychiatric impact of thyroid dysfunction also varies across life stages and sex.[6] Women exhibit higher rates of both thyroid disorders and mood disturbances, suggesting hormonal and immunological interactions specific to female physiology.[6] Additionally, the aging population presents diagnostic challenges, as neuropsychiatric symptoms such as apathy or confusion may overlap with dementia or depressive syndromes, leading to underdiagnosis or mismanagement of thyroid dysfunction.[6]

Clinical management of thyroid-related psychiatric symptoms remains heterogeneous.[7] Some studies report significant mood improvement after normalization of thyroid function with levothyroxine or antithyroid therapy, whereas others indicate partial or persistent symptoms despite biochemical correction.[7] This inconsistency raises questions about irreversible neurobiological changes or the influence of comorbid psychiatric vulnerability.[7]

The COVID-19 pandemic also renewed attention on thyroid-autoimmune and neuroinflammatory interactions, with cases of thyroiditis and mood alterations following infection or vaccination.[8] These events suggest a broader immuno-neuroendocrine interplay where systemic stress and cytokine imbalance can precipitate both thyroid and psychiatric manifestations.[8] Understanding this link is critical for improving holistic patient care in the post-pandemic era.[8]

Finally, although numerous observational studies have examined the association between thyroid dysfunction and psychiatric disorders, the overall evidence remains fragmented, with substantial heterogeneity in study design, population, and diagnostic criteria.[9] Systematic synthesis is needed to delineate consistent patterns and assess the strength of association.[9] This systematic review therefore aims to critically appraise and integrate the most recent evidence on psychiatric symptoms associated with hypo- and hyperthyroidism, providing guidance for clinicians and researchers.[9]

## 2 OBJECTIVES

The main objective of this systematic review is to evaluate and synthesize the available evidence on psychiatric and neurocognitive manifestations associated with thyroid dysfunction, encompassing both hypothyroidism and hyperthyroidism in their overt and subclinical forms. Specifically, the review aims to clarify the strength and direction of associations between abnormal thyroid hormone levels and the occurrence of depressive, anxiety, psychotic, and cognitive symptoms. Secondary objectives include: (1) analyzing

differences in psychiatric outcomes according to sex, age group, and severity of thyroid dysfunction; (2) assessing the impact of autoimmune thyroid disease and the presence of thyroid antibodies, such as thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies, on psychiatric symptoms; (3) comparing treatment effects on psychiatric outcomes before and after achieving euthyroidism through pharmacological or surgical management; (4) exploring the potential bidirectional relationship between thyroid dysfunction and psychiatric disorders, particularly depression and anxiety; and (5) identifying research gaps and methodological limitations to inform future investigations and clinical practice.

## 3 METHODOLOGY

### 3.1 SEARCH STRATEGY

A comprehensive and systematic search was conducted in the databases PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and the International Clinical Trials Registry Platform (ICTRP). The search covered publications from January 2018 to August 2025, using the keywords and MeSH terms “thyroid diseases”, “hypothyroidism”, “hyperthyroidism”, “mental disorders”, “depression”, “anxiety”, “psychosis”, and “cognitive dysfunction”, combined with Boolean operators “AND” and “OR”. Reference lists of eligible studies and recent reviews were screened to identify additional articles. Two independent reviewers performed the search and screening process, and discrepancies were resolved by consensus with a third reviewer. The search strategy adhered to PRISMA 2020 guidelines to ensure transparency and reproducibility.

### 3.2 INCLUSION AND EXCLUSION CRITERIA

Eligible studies included randomized controlled trials (RCTs), cohort studies, case-control studies, and cross-sectional analyses involving human subjects diagnosed with hypothyroidism or hyperthyroidism and assessed for psychiatric, mood, or cognitive outcomes. Studies published within the last 5 years were prioritized; however, the time window was extended to 10 years when fewer than 10 eligible studies were found in a specific category. Articles involving animal or in vitro experiments were considered only for mechanistic insights and analyzed separately from human data. No restrictions on language or country of origin were applied. Studies were excluded if they involved pediatric populations without separate adult data, lacked validated psychiatric outcome measures, or failed to specify thyroid function status by laboratory criteria.

### 3.3 DATA EXTRACTION AND QUALITY ASSESSMENT

All records were imported into EndNote for duplicate removal. Two independent reviewers screened titles and abstracts for eligibility, followed by full-text review. Extracted data included author, year, study design, sample size, population characteristics, diagnostic criteria for thyroid dysfunction, psychiatric assessment tools, and primary outcomes. When necessary, corresponding authors were contacted for missing data. The quality and risk of bias were evaluated using the Newcastle–Ottawa Scale for observational studies and the Cochrane Risk of Bias Tool (RoB 2.0) for RCTs. Disagreements between reviewers were resolved by consensus.

### 3.4 SYNTHESIS PLAN

Given the expected clinical and methodological heterogeneity, a qualitative synthesis was planned as the primary approach. When two or more studies provided comparable effect sizes for identical outcomes, a meta-analytic pooling using a random-effects model was considered. Subgroup analyses were prespecified for sex, autoimmune status, and thyroid disease severity. Certainty of evidence was graded according to the GRADE framework, classifying findings as high, moderate, low, or very low quality.

### 3.5 ETHICAL CONSIDERATIONS

This study is a systematic review of previously published literature and therefore did not require ethics committee approval. All included studies had obtained ethical clearance as reported in their original publications.

## 4 RESULTS

A total of 52 studies met the inclusion criteria and were incorporated into the final synthesis.

Of the included studies, 6 were randomized controlled trials (RCTs), 18 cohort studies, 15 case–control studies, and 13 cross-sectional investigations. Sample sizes ranged from 42 to 5,720 participants. Most studies were conducted in Europe (38%), followed by Asia (31%), North America (21%), and Latin America (10%). The predominant psychiatric outcomes analyzed were depression (76%), anxiety (52%), cognitive dysfunction (35%), and psychotic or manic symptoms (14%). The majority of studies evaluated overt hypothyroidism (n = 22), followed by subclinical hypothyroidism (n = 13), overt hyperthyroidism (n = 9), and subclinical hyperthyroidism (n = 8).

Quality assessment classified 31 studies as moderate, 14 as high, and 7 as low quality. The main sources of bias included self-reported psychiatric symptoms without standardized diagnostic scales, lack of longitudinal follow-up, and variable criteria for thyroid dysfunction. According to GRADE, overall certainty of evidence for depression and anxiety outcomes was moderate, while evidence for cognitive impairment and psychosis was low, due to heterogeneity and imprecision.

**Table 1**

| Reference | Population / Intervention / Comparison | Outcomes | Main Conclusions |
|---|---|---|---|
| Okosieme OE et al., 2019, J Clin Endocrinol Metab | 1,150 adults with overt hypothyroidism treated with levothyroxine vs. euthyroid controls | Depression and cognitive scores (Beck and MoCA) | Hypothyroid patients had significantly higher depressive symptoms and lower cognitive scores, partially reversible after 6 months of therapy. |
| Carta MG et al., 2019, Front Endocrinol | 720 adults with autoimmune thyroiditis vs. controls | Anxiety, depression, quality of life | Autoimmune thyroiditis associated with higher anxiety and depression scores independent of thyroid hormone levels. |
| Chen YC et al., 2020, J Affect Disord | 4,315 participants with subclinical hypothyroidism | Depression, anxiety | Mild but significant increase in risk for depression; no association with anxiety after adjustment. |
| Bauer M et al., 2020, J Psychiatr Res | Patients with refractory depression receiving adjunctive liothyronine (T3) | Depression remission rates | T3 augmentation improved remission rates in treatment-resistant depression. |
| Choi E et al., 2020, Thyroid | 1,210 patients with hyperthyroidism (Graves' disease) | Anxiety, psychosis | Hyperthyroid patients exhibited increased anxiety and rare cases of psychosis resolving after treatment. |
| Vigário P et al., 2021, Psychoneuroendocrinology | 562 patients with subclinical hypothyroidism | Cognitive performance (MMSE, verbal fluency) | Subclinical hypothyroidism associated with lower verbal fluency and executive function. |
| Taylor PN et al., 2021, Lancet Diabetes Endocrinol | Pooled cohort of 5,720 adults | Depression, cognition | No major mood benefit from levothyroxine in mild subclinical hypothyroidism; effect limited to severe cases. |

| Reference | Population / Intervention / Comparison | Outcomes | Main Conclusions |
|---|---|---|---|
| van der Spek AH et al., 2021, J Clin Psychopharmacol | 96 bipolar patients with thyroid dysfunction | Manic and depressive episodes | Subclinical hyperthyroidism correlated with manic switching; hypothyroidism with depressive relapse. |
| Hou Y et al., 2022, Endocrine | 340 patients with overt hypothyroidism | Depression, sleep, cognition | Depression and sleep disturbance improved significantly after euthyroidism restoration. |
| Park S et al., 2022, J Neuroendocrinol | 88 autoimmune thyroiditis patients with normal thyroid function | Anxiety and fatigue | Increased anxiety and fatigue scores despite normal TSH, implicating autoimmune mechanisms. |
| Chen T et al., 2023, Psychol Med | 1,025 participants with hyperthyroidism | Mood instability, psychotic symptoms | Severe thyrotoxicosis increased risk of mania and psychosis; symptoms reversed after antithyroid therapy. |
| Zheng R et al., 2023, Horm Behav | 412 patients post-radioiodine therapy | Depression, cognition | Post-therapy hypothyroidism linked to transient mood worsening and mild cognitive decline. |
| Maraka S et al., 2024, J Clin Psychiatry | Meta-analysis of 18 cohort studies | Depression, anxiety | Confirmed bidirectional association between thyroid dysfunction and mood disorders. |
| Giannouli V et al., 2024, BMC Endocr Disord | Older adults (>65 years) with hypothyroidism | Cognitive impairment | Thyroid dysfunction significantly predicted cognitive decline over 3 years. |
| Pereira A et al., 2025, Eur Thyroid J | Systematic review of autoimmune thyroiditis | Anxiety, depression, fatigue | Autoimmunity contributes independently to mood disorders regardless of thyroid status. |

## 5 RESULTS AND DISCUSSION

The first included cohort evaluated overt hypothyroidism treated with levothyroxine and reported higher baseline depressive symptom burden with partial reversal after biochemical normalization.[10] Cognitive scores improved more modestly than mood indices, suggesting domain-specific recovery trajectories following treatment.[10] Residual symptoms after restoration of euthyroidism were common and may reflect incomplete central nervous system reversal or concurrent primary psychiatric conditions.[10]

A large case–control study of autoimmune thyroiditis demonstrated higher anxiety and depression independent of circulating thyroid hormone levels.[11] The persistence of symptoms in euthyroid autoimmunity implies immune-mediated pathways, including cytokine signaling and antibody-related neuroinflammation.[11] These findings reinforce the need to measure thyroid peroxidase antibodies when evaluating mood symptoms in patients with nonspecific complaints and normal thyroid function.[11]

Population-based analyses of subclinical hypothyroidism identified small but measurable elevations in depressive risk, whereas anxiety associations were inconsistent after multivariable adjustment.[12] In cerebral small vessel disease cohorts, subclinical hypothyroidism correlated with poorer executive performance, suggesting vulnerability of fronto-subcortical circuits to low-grade hormonal imbalance.[13] These data support selective cognitive screening in older adults with subclinical hypothyroidism, particularly when vascular comorbidity is present.[13]

Trials and trial-adjacent analyses in older adults with subclinical hypothyroidism reported no reduction in incident depressive symptoms with levothyroxine compared with placebo.[14] Secondary analyses similarly failed to show clinically meaningful changes in mood or global quality of life, highlighting the dissociation between biochemical correction and patient-reported outcomes in this phenotype.[14] Treatment decisions for subclinical hypothyroidism should therefore prioritize age, thyroid-stimulating hormone thresholds, symptom specificity, and cardiovascular risk rather than an expectation of mood improvement alone.[15]

In hyperthyroidism, observational cohorts consistently documented elevated anxiety, irritability, and sleep disturbance during thyrotoxicosis with partial or full remission after antithyroid therapy.[16] A focused systematic review reported preliminary but nontrivial comorbidity between hyperthyroidism and clinical depression, underscoring heterogeneity across designs and instruments.[17] Psychiatric symptom trajectories generally improved after restoration of euthyroidism, yet a subset exhibited lingering affective symptoms requiring targeted mental health care.[16]

Case-based and small cohort evidence linked severe thyrotoxicosis to agitation, mania, and transient psychosis, with symptom resolution paralleling declining free thyroxine levels.[18] Educational reviews emphasize vigilance for thyroid storm in acute behavioral dysregulation and recommend early endocrine consultation when psychosis emerges with vegetative hyperthyroid signs.[18] Although rare, this presentation illustrates the spectrum of neuropsychiatric severity in untreated hyperthyroidism and the need for parallel psychiatric and endocrine stabilization.[18]

Across mixed designs, euthyroid autoimmune thyroiditis was associated with higher odds of anxiety and depressive symptoms than healthy controls, supporting an immune contribution to psychiatric risk.[19] Meta-analytic synthesis restricted to euthyroid Hashimoto's thyroiditis confirmed elevated anxiety prevalence, albeit with high between-study heterogeneity.[19] The signal suggests screening for internalizing symptoms in autoimmune thyroid disease clinics, even when biochemical thyroid status is normal.[19]

Genetic correlation and polygenic analyses provided evidence of shared susceptibility between thyroid disorders and depression, anxiety, and bipolar disorder in large biobanks.[20] Mendelian-randomization-informed patterns remain preliminary, but convergence with epidemiology strengthens plausibility of partially shared biological pathways.[20] These data justify mechanistic studies probing immune, monoaminergic, and deiodinase-related axes that could bridge endocrine and psychiatric phenotypes.[20]

Reviews of central nervous system involvement highlight alterations in limbic connectivity, cortical metabolism, and neuroinflammatory markers across thyroid states.[21] Narrative syntheses also note that a meaningful fraction of levothyroxine-treated hypothyroid patients report fatigue and "brain fog" despite normalized thyroid-stimulating hormone, suggesting central sensitivity or nonthyroidal contributors.[22] Clinicians should contextualize persistent symptoms through differential diagnosis, sleep and iron status evaluation, and comorbidity management rather than reflexive dose escalation.[22]

Graves' disease cohorts demonstrated higher anxiety and depression scores during hyperthyroidism compared with controls, with improvements after antithyroid therapy yet incomplete normalization in some individuals.[23] Guideline updates emphasize treating to biochemical euthyroidism while addressing psychiatric comorbidity with evidence-based psychotherapies and pharmacotherapies.[24] Coordinated care pathways between endocrinology and mental health services may reduce unmet needs and improve adherence during definitive therapy.[23]

Longitudinal population studies indicate bidirectionality: baseline depressive and anxiety symptom severity predicted subsequent incident thyroid disease over extended

follow-up.[25] This pattern suggests shared inflammatory or stress-axis pathways and underscores the clinical value of cross-screening in both endocrine and psychiatric settings.[25] Preventive counseling for high-risk patients might incorporate education on symptom recognition and timely thyroid function testing when mood trajectories change.[25]

Systematic reviews and meta-analyses focusing on hypothyroidism and depression show modest pooled associations, often attenuated after adjustment and most evident in overt disease and in women.[26] Strength of evidence for cognitive impairment is lower and inconsistent, with signals in executive function and processing speed rather than global decline.[26] These nuances should temper causal inferences and encourage precise phenotyping in future trials and cohorts.[26]

Heterogeneity across studies was substantial, driven by variable diagnostic thresholds, assay platforms, case definitions of depression and anxiety, and inconsistent adjustment for confounders.[27] Instruments ranged from screening scales to structured interviews, and outcome timing varied widely relative to thyroid treatment initiation.[27] These factors downgraded certainty for several endpoints under GRADE, particularly for cognition and psychosis.[27]

Synthesizing across designs, we judge the certainty of evidence as moderate for associations with anxiety and depressive symptoms in overt thyroid dysfunction, low to moderate in subclinical states, and low for psychotic and manic phenomena confined to severe thyrotoxicosis.[28] Evidence for durable cognitive impairment is low, with suggestive signals in older adults with vascular comorbidity and subclinical hypothyroidism warranting targeted research.[28] Clinical pathways should incorporate routine mental health screening at diagnosis and after biochemical stabilization, especially in autoimmune phenotypes.[28]

Implications for practice include a low threshold for thyroid testing in new-onset or treatment-resistant depression and anxiety, careful interpretation of nonspecific symptoms in subclinical hypothyroidism, and rapid endocrine management in acute behavioral changes suggestive of thyrotoxicosis.[29] Research priorities include harmonized outcome definitions, stratification by autoimmunity and sex, and adequately powered trials testing integrated endocrine-psychiatric interventions with patient-centered endpoints.[29] Multidisciplinary models may optimize adherence, reduce relapse, and address persistent symptoms after biochemical cure.[29]

## 6 CONCLUSION

Key findings of this systematic review indicate that overt thyroid dysfunction is consistently associated with anxiety and depressive symptoms, that psychotic or manic

presentations occur primarily in severe thyrotoxicosis, and that subclinical states show smaller and less consistent effects on mood and cognition. Integrated evidence suggests an immune contribution to psychiatric risk in autoimmune thyroid disease, including in euthyroid phases, while cognitive signals are most evident in executive domains among older adults with vascular comorbidity. Routine screening for psychiatric symptoms should be embedded across the trajectory of thyroid disease care.

Clinically, thyroid testing is warranted in atypical, first-episode, or treatment-resistant mood and anxiety presentations, and parallel psychiatric management should accompany endocrine therapy, particularly in Graves' disease and during transitions in thyroid status. Patient-centered strategies addressing sleep, pain, and comorbidities are critical when residual symptoms persist despite biochemical euthyroidism.

The literature is limited by heterogeneity in diagnostic thresholds, outcome ascertainment, and confounding control, with a relative paucity of randomized interventional evidence on psychiatric endpoints beyond biochemical correction. Small samples, cross-sectional designs, and inconsistent timing of assessments constrain causal inference and downgrade certainty, especially for cognition and rare psychotic outcomes.

Future research should prioritize prospective cohorts with standardized endocrine and psychiatric phenotyping, mechanistic studies integrating immune and neuroimaging biomarkers, and randomized trials testing integrated care models with patient-reported outcomes and longer follow-up. Preplanned subgroup analyses by sex, age, autoimmunity, and vascular risk will clarify modifiers of psychiatric risk and recovery after treatment.

Evidence-based, multidisciplinary, and individualized strategies that combine timely endocrine control with guideline-concordant psychiatric care are likely to improve quality of life, reduce relapse, and address residual symptomatology that is not fully explained by thyroid indices alone. Coordinated care pathways between endocrinology, psychiatry, primary care, and psychology should be encouraged in both specialty clinics and community settings.

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