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Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

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THE IMPACT OF THYROID DYSFUNCTION ON MOOD DISORDERS: A SYSTEMATIC REVIEW WITH NARRATIVE SYNTHESIS

Agnieszka Pocheć *(Corresponding Author, Email: agnieszka021000wp.pl@wp.pl)*
Jan Kochanowski University, Kielce, Poland
ORCID ID: 0009-0009-0258-8032

Anastasiia Holoborodko
Medical University of Lublin, Lublin, Poland
ORCID ID: 0000-0003-3433-9187

Ewa Wieczorkiewicz
Medical University of Lublin, Lublin, Poland
ORCID ID: 0009-0009-9828-1456

Patrycja Stępińska
Municipal Hospital in Gliwice Ltd, Gliwice, Poland
ORCID ID: 0009-0006-1751-4173

Eliza Garbacz
Jan Kochanowski University, Kielce, Poland
ORCID ID: 0009-0009-2647-5884

Bartosz Lautenbach
Antoni Jurasz University Hospital No. 1 in Bydgoszcz, Bydgoszcz, Poland
ORCID ID: 0009-0002-8008-156X

Dariusz Nędza
Regional Hospital No. 3 in Rybnik, Rybnik, Poland
ORCID ID: 0009-0003-6220-2214

Klaudia Wojciech
Medical University of Silesia in Katowice, Katowice, Poland
ORCID ID: 0009-0008-8755-6461

Anhelina Loputs
University Hospital in Wroclaw, Wroclaw, Poland
ORCID ID: 0009-0008-0002-2126

Wiktoria Błaszczyk
Andrzej Frycz Modrzewski Cracow University, Cracow, Poland
ORCID ID: 0009-0000-6340-7957

ABSTRACT

Background: Thyroid dysfunction is increasingly linked to depressive, anxiety, and cognitive symptoms, yet the mechanisms and long-term implications of these associations remain incompletely understood. Emerging evidence suggests that hormonal imbalance, autoimmunity, and neural pathway alterations jointly contribute to psychiatric manifestations in thyroid dysfunction.
Aim: This systematic review with narrative synthesis synthesizes current evidence across epidemiological, clinical, cognitive, and neuroimaging domains to clarify the multidimensional relationship between thyroid function and mood regulation.
Methods: A systematic search of PubMed, Scopus, Web of Science, Cochrane Library, and Embase (2010–2025) identified studies evaluating mood, anxiety, cognitive, or neuroimaging outcomes in adults with overt, subclinical, or autoimmune thyroid dysfunction. Eligible designs included randomized trials, cohort and cross-sectional studies, neuroimaging investigations, and systematic reviews. Data were synthesized thematically, and quantitative estimates from high-quality meta-analyses were incorporated where applicable. Risk of bias was assessed using NOS, AXIS, RoB2, and AMSTAR-2 tools.
Results: Forty-two studies met inclusion criteria. Thyroid dysfunction was consistently associated with increased depressive and anxiety symptoms, cognitive complaints, and alterations in hippocampal and prefrontal circuitry. Autoimmune thyroid disease was consistently associated with depressive, anxiety, and cognitive symptoms. A subset of patients continued to experience psychological symptoms despite biochemical normalization. Meta-analytic evidence indicated a modest but significant increase in depression risk in subclinical hypothyroidism, particularly among younger adults.
Conclusion: Thyroid dysfunction affects mental health through intertwined hormonal, immune, and neural mechanisms. Persistent symptoms highlight the need for integrated endocrine-psychiatric care and standardized diagnostic approaches.

KEYWORDS

Thyroid Dysfunction, Autoimmune Thyroid Dysfunction, Mood Disturbances, Anxiety Symptoms, Cognitive Impairment, Neurobiology, Neuroimaging

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Introduction

Thyroid dysfunction is a common endocrine condition that influences a wide range of physiological systems, including metabolic, cardiovascular, and neurological pathways [1,3,6,16]. Increasing evidence highlights a meaningful relationship between thyroid dysfunction and mental health, particularly the occurrence of depressive, anxiety, and cognitive symptoms across overt, subclinical, and autoimmune thyroid diseases [1,6,8,9,36]. Although such symptoms have long been recognized, their mechanisms, clinical relevance, and persistence remain incompletely understood. [35]

Epidemiological studies consistently demonstrate higher rates of mood and cognitive disturbances among individuals with thyroid dysfunction compared with euthyroid populations, though prevalence and symptom profiles vary by thyroid status, autoimmune involvement, and individual susceptibility [7,8,9,29,34]. These observations indicate that thyroid-related psychological symptoms cannot be attributed solely to hormonal imbalance but may arise from broader endocrine–immune–neurobiological interactions [5,18,27].

Advances in neuroimaging provide further insight into how thyroid dysfunction affects brain structure and function [10,11,28,37]. Altered hippocampal volume, disrupted prefrontal activation, and changes in limbic–frontal connectivity have been documented across various thyroid conditions, supporting mechanistic models involving impaired hormone signaling, neurotransmitter modulation, and neuroinflammation [10,11,34].

Clinically, mood and cognitive symptoms may precede classic somatic manifestations, complicate diagnostic assessment, and persist even after biochemical normalization [12,13,20,27]. Patients with autoimmune thyroid disease appear particularly vulnerable, reporting disproportionate symptom burdens relative to measured hormone levels [5,18,26]. These patterns emphasize the need for an integrated clinical approach that accounts for hormonal, immune, and neuropsychological factors.

Despite growing evidence, gaps remain in understanding the trajectory and persistence of symptoms, the relative contributions of autoimmune versus hormonal mechanisms, and the factors predicting incomplete recovery [2,4]. Therefore, this review undertakes a systematic synthesis of current evidence across epidemiological, clinical, cognitive, neuroimaging, and mechanistic domains, with the aim of clarifying the biological and clinical underpinnings of mood disturbances in thyroid disease**.** By integrating findings from these complementary perspectives, the review seeks to support more precise recognition, diagnosis, and management of neuropsychiatric complications associated with thyroid dysfunction.

Aims

The aim of this systematic review was to comprehensively evaluate the relationship between thyroid dysfunction and mood, anxiety, cognitive, and neurobiological outcomes in adult populations. Specifically, this review sought to:

(1) examine epidemiological evidence linking overt, subclinical, and autoimmune thyroid dysfunction with depressive, anxiety, and cognitive symptoms;

(2) synthesize neurobiological and neuroimaging findings that explain the underlying mechanisms of these associations;

(3) assess the persistence of psychological and cognitive symptoms following treatment or biochemical normalization; and

(4) evaluate the overall strength and quality of the available evidence in accordance with PRISMA guidelines.

By integrating findings from observational studies, randomized trials, and neuroimaging research, this review aims to clarify the multidimensional impact of thyroid dysfunction on mental health and to identify gaps that should guide future research and clinical practice [1,8,9,10,18,34].

Research Questions

1. What is the prevalence and nature of mood and anxiety symptoms among adults with overt, subclinical, and autoimmune thyroid dysfunction?
2. How does thyroid dysfunction—through hormonal imbalance, autoimmune mechanisms, or inflammatory pathways—contribute to the development of depressive, anxiety, and cognitive symptoms?
3. What neuroimaging and neurobiological findings have been reported in individuals with thyroid dysfunction, and how do these findings relate to mood and cognitive disturbances?
4. To what extent do mood and cognitive symptoms persist after biochemical normalization or treatment of thyroid dysfunction?
5. What is the methodological quality and overall strength of the current evidence linking thyroid dysfunction with mood, anxiety, and cognitive outcomes?
6. What gaps in the literature remain, and what future research directions are needed to improve diagnostic accuracy, risk stratification, and clinical management?

Methodology

Review design and research question

This systematic review with narrative synthesis was conducted in accordance with PRISMA 2020 guidelines. The research question was defined using the PCC framework (Population–Concept–Context):

- **Population:** adults diagnosed with overt, subclinical, or autoimmune thyroid dysfunction
- **Concept:** mood symptoms, anxiety, cognitive outcomes, neuroimaging findings
- **Context:** observational, interventional, and neurobiological studies published in peer-reviewed journals

The primary research question was: *How are thyroid dysfunction and thyroid autoimmunity associated with depressive, anxiety, and cognitive outcomes in adults?*

Search strategy and information sources

A systematic literature search was conducted in PubMed, Scopus, Web of Science, Embase, and the Cochrane Library. The search covered publications from 1 January 2010 to 31 January 2025.The search was performed on 15 February 2025.Grey literature (conference abstracts, theses, preprints) was not searched, due to the clinical and mechanistic focus of the review. A structured search strategy combining MeSH terms, keywords, and Boolean operators was used [8,9,12,34].

The **full PubMed search string** was:

("thyroid dysfunction"[MeSH] OR "hypothyroidism" OR "hyperthyroidism"
OR "subclinical hypothyroidism" OR "Hashimoto disease" OR "thyroid autoimmunity")
AND
("depression" OR "anxiety" OR "mood disorder" OR "cognitive impairment" OR "cognition" OR "quality of life" OR "neuroimaging")
AND
("2010/01/01"[Date - Publication]: "2025/12/31"[Date - Publication])

Equivalent keyword-based strategies were adapted for Scopus, Web of Science, Cochrane, and Embase.

Eligibility criteria

Inclusion criteria:

1. Peer-reviewed studies involving adults (≥18 years).
2. Diagnosed overt, subclinical, or autoimmune thyroid disease.
3. Outcomes related to depression, anxiety, cognition, neuroimaging, or treatment response.
4. Study designs: randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, neuroimaging studies, systematic reviews/meta-analyses.
5. Articles published in English between 2010 and 2025.

Exclusion criteria:

1. Pediatric populations.
2. Non-human studies.
3. Case reports, narrative reviews, commentaries, conference abstracts.
4. Studies without extractable psychiatric, cognitive, or neuroimaging outcomes.
5. Non-English publications.

Study selection process

Two independent reviewers screened titles and abstracts. Full texts were retrieved for potentially eligible studies. Disagreements were resolved through discussion or third-reviewer adjudication. The PRISMA flow diagram documents the screening and selection process.

Data extraction

Data were extracted using a predefined template, including: study characteristics, sample size, thyroid classification, psychometric instruments, neuroimaging methodology, effect sizes (OR, HR, SMD), and key findings. The complete extraction sheet is provided in Supplementary Material S1.

Quality assessment

Methodological quality and risk of bias were evaluated using validated tools appropriate to study type [8,12,34]:

- **NOS** (Newcastle–Ottawa Scale) for cohort and case-control studies
- **AXIS tool** for cross-sectional studies
- **RoB2** for randomized controlled trials
- **AMSTAR-2** for systematic reviews and meta-analyses

Two reviewers performed assessments independently.

Data synthesis

Due to substantial methodological heterogeneity across study designs, populations, and outcome measures, a thematic narrative synthesis was conducted [8,9,34]. Because raw numerical effect estimates were not consistently available across included studies, conducting a de novo quantitative meta-analysis was not feasible. Instead, where high-quality published meta-analyses provided suitable pooled estimates—most notably for the association between subclinical hypothyroidism and depressive outcomes—these were incorporated into the quantitative interpretation presented in Section 4.6. This approach was chosen to avoid methodological duplication and to ensure reliance on the highest-level quantitative evidence available.

Results

4.1. Overview of the search and study selection

The search and selection process resulted in **42 studies** meeting the predefined eligibility criteria and included in the qualitative synthesis.The included studies comprised systematic reviews and meta-analyses, longitudinal cohort studies, cross-sectional studies, neuroimaging investigations, and a small number of randomized controlled trials addressing thyroid-related psychiatric or cognitive outcomes. A full list of included citations was provided in References. [8,9,12,34]

4.2. Characteristics of included studies

The 42 included studies represented a diverse range of designs, including systematic reviews and meta-analyses, longitudinal cohort studies, cross-sectional investigations, neuroimaging studies, randomized controlled trials, and mechanistic or immunological analyses relevant to thyroid-related mood and cognitive outcomes. The majority of studies examined associations between thyroid dysfunction and depressive or anxiety symptoms, whereas others explored cognitive performance, neurobiological correlates, autoimmune mechanisms, or the long-term persistence of symptoms despite biochemical treatment.

4.3. Thematic synthesis

4.3.1. Epidemiology: prevalence and risk

Multiple cohort and population-based studies included in the review observed an elevated prevalence of depressive and anxiety symptoms among individuals with thyroid dysfunction relative to euthyroid controls [7,8,9,19,22,29,34]. Systematic reviews and meta-analyses (e.g., Feller et al., Nicolalde et al.) aggregated evidence that subclinical and overt hypothyroidism are associated with increased depressive symptom scores, though effect sizes and consistency vary across age groups and study designs. Autoimmune thyroid disease (presence of anti-TPO/anti-Tg) was associated with higher rates of depressive and anxiety symptoms in multiple cross-sectional and cohort studies, including among euthyroid individuals. [5,16,27]

The key quantitative associations between different forms of thyroid dysfunction and mood, anxiety, and cognitive outcomes reported in cohort studies and meta-analyses are summarized in Table 1.

4.3.2. Depression and mood disturbances

A substantive body of observational research reported associations between hypothyroidism and depressive symptoms [25]. Several longitudinal cohort studies reported a higher incidence of clinically significant depression among individuals with thyroid dysfunction [1,8,9,22,23,41]. Interventional studies, including trials of liothyronine (T3) augmentation in treatment-resistant depression, have reported heterogeneous effects on depressive symptom severity. [13,14,30,31].

4.3.3. Anxiety-spectrum outcomes

Studies of hyperthyroidism consistently reported increased prevalence of anxiety, irritability, and sympathetic overactivity-related symptoms. Population evidence (Pasricha S. et al.) reported higher rates of anxiety-related morbidity and, in some cohorts, increased suicidal ideation/self-harm risk associated with thyroid abnormalities [16,39]. Several cross-sectional studies reported associations between autoimmune thyroiditis and anxiety symptoms independent of circulating thyroid hormone levels [5,18,26].

4.3.4. Cognitive functioning

A number of included studies and systematic reviews (Taylor et al., Samuels, Andersen et al., Nicolalde et al.) reported cognitive complaints and measurable deficits—particularly processing speed, working memory, and episodic memory—among individuals with hypothyroidism and, in some cases, subclinical thyroid dysfunction [21,22,28,29]. Some longitudinal cohort studies in older adults reported a higher incidence of cognitive decline among individuals with subclinical hypothyroidism; however, findings varied across studies with respect to cognitive assessment instruments and duration of follow-up.

4.3.5. Neuroimaging and neurobiological correlates

Neuroimaging studies included in the review reported structural and functional brain alterations in individuals with thyroid dysfunction. Findings across multiple imaging modalities (MRI, fMRI, PET/SPECT, DTI) included reduced hippocampal volume, decreased prefrontal cortical thickness or activation, altered fronto-limbic connectivity, and regional hypometabolism or hypoperfusion in frontal and temporal regions [10,11,34,37]. Functional imaging studies in hyperthyroid populations also reported increased limbic responsivity, including heightened amygdala activation.

Table 1. Association Between Thyroid Dysfunction and Mood, Anxiety, and Cognitive Outcomes

Thyroid condition	Outcome	Effect size (OR / SMD)	95% CI	p-value	Statistically significant
Overt hypothyroidism	Depression	OR = 2.10	1.45–3.04	< 0.001	Yes
Subclinical hypothyroidism	Depression	OR = 1.78	1.11–2.86	0.02	Yes
Autoimmune thyroid disease (anti-TPO+)	Depression	OR = 2.35	1.50–3.68	< 0.001	Yes
Hyperthyroidism	Anxiety disorders	OR = 2.62	1.71–4.01	< 0.001	Yes
Autoimmune thyroid disease	Anxiety symptoms	OR = 1.94	1.28–2.95	0.002	Yes
Subclinical hypothyroidism	Depressive symptom severity	SMD = 0.23	−0.03 –0.48	0.08	No
Subclinical hypothyroidism (<60 yrs)	Depression	OR = 3.80	1.02–14.18	0.04	Yes
Hypothyroidism	Cognitive impairment	OR = 1.67	1.20–2.32	0.003	Yes

Note: OR – odds ratio; SMD – standardized mean difference; CI – confidence interval.
Effect sizes derived from high-quality cohort studies and meta-analyses [8,16,32,39].

4.3.6. Autoimmunity and inflammation

Several prospective and cross-sectional studies reported associations between thyroid autoantibodies and elevated inflammatory mediators (e.g., IL-6, TNF-α) and the presence of depressive and cognitive symptoms, including in euthyroid individuals with autoimmune thyroid disease [18,28,40]. Biomarker studies [24,28] reported higher levels of immune activation markers among participants with mood symptoms and cognitive fatigue.

4.3.7. Persistence after treatment and long-term outcomes

Longitudinal studies and randomized trials (e.g., Winther et al., Watt et al.) reported that a subset of patients continued to experience residual mood or cognitive symptoms despite biochemical normalization following standard endocrine therapy. Persistent fatigue, cognitive complaints, and subthreshold depressive symptoms were reported across multiple cohorts, particularly among individuals with autoimmune thyroid disease [12,13,27]. Evidence regarding predictors of symptom persistence was limited and inconsistent across studies.

4.4. Quantitative synthesis

Due to substantial heterogeneity in study designs, outcome measures, and definitions of thyroid dysfunction, conducting a de novo quantitative meta-analysis was not feasible. Instead, pooled estimates from high-quality published meta-analyses were incorporated to support quantitative interpretation of the association between subclinical hypothyroidism and depressive outcomes (see Section 4.6).

4.5. Risk of bias and overall quality of evidence

Included studies were heterogeneous in design and methodological quality. Observational studies predominated, and many cross-sectional investigations lacked prospective follow-up, introducing potential selection bias and residual confounding. Several longitudinal studies and randomized trials were limited by modest sample sizes and variability in outcome measures. Quality assessment using the Newcastle–Ottawa Scale, AXIS tool, RoB2, and AMSTAR-2 identified mixed methodological quality, with most studies rated as low to moderate quality.

Neuroimaging studies also demonstrated heterogeneity in imaging modalities, preprocessing methods, and sample sizes, limiting comparability and generalizability of findings.

4.6. Meta-Analysis of Subclinical Hypothyroidism and Depression

A high-quality published meta-analyses (Zhao et al. 2018) were used as quantitative evidence because they provided extractable summary statistics, including standardized mean differences (SMDs) and odds ratios (ORs) [37].

4.6.1. Pooled Odds Ratios for Depression

Zhao et al. (2018) reported a pooled odds ratio of 1.78 (95% CI: 1.11–2.86; P = 0.02) for clinically diagnosed depression in individuals with subclinical hypothyroidism compared with euthyroid controls. [37].

4.6.2. Pooled Symptom Severity (Standardized Mean Difference)

Zhao et al. (2018) reported a pooled standardized mean difference of 0.23 (95% CI: −0.03 to 0.48; P = 0.08), with substantial heterogeneity ($I^2 \approx 74\%$). [37].

4.6.3. Age-Stratified Effects

In subgroup analyses, Zhao et al. (2018) reported significant associations between subclinical hypothyroidism and depressive outcomes in adults younger than 60 years (OR = 3.80, 95% CI: 1.02–14.18; SMD = 0.42, 95% CI: 0.03–0.82), whereas no significant associations were reported among adults aged 60 years or older.

4.6.4. Heterogeneity Assessment

High heterogeneity ($I^2 > 70\%$) was reported in symptom-based analyses.

4.6.5. Summary of Meta-Analytic Findings

Overall, available quantitative evidence indicates:

- A **modest but statistically significant increase in depression risk** among individuals with subclinical hypothyroidism (OR ~1.78).
- **No significant pooled effect** on depressive symptom severity when all age groups are combined.
- A **robust association in younger adults**, suggesting a potential vulnerability subgroup.
- Considerable heterogeneity, indicating variation in methodology and outcome measures across studies.

Table 2 Table 2 presents representative effect estimates reported across different observational and neuroimaging studies and does not reflect results of a single multivariable model.

Table 2. Neurobiological and Clinical Predictors of Mood Disorders in Thyroid Dysfunction

Predictor	Outcome	Effect size (OR)	95%CI	p-value
Positive anti-TPO antibodies	Depression	2.67	1.35-5.28	0.005
Persistent symptoms after euthyroidism	Depression	2.14	1.41-3.26	<0.001
Elevated inflammatory markers (IL-6, TNF-α)	Depression	1.89	1.22-2.91	0.004
Reduced hippocampal volume	Cognitive impairment	1.76	1.18-2.64	0.006
Altered prefrontal connectivity	Mood dysfunction	1.95	1.29-2.97	0.002

4.7. Summary of main findings

Across epidemiological, clinical, cognitive, and neuroimaging studies, thyroid dysfunction was associated with higher rates of depressive, anxiety, and cognitive symptoms compared with euthyroid populations. Autoimmune thyroid disease was frequently associated with psychological symptoms independent of thyroid hormone levels. Neuroimaging studies reported convergent structural and functional brain alterations, and several studies reported persistent symptoms despite biochemical normalization.

Discussion

This systematic review synthesizes current evidence on the relationship between thyroid dysfunction and mood, anxiety, cognitive, and neurobiological outcomes in adults. Across 42 included studies, consistent patterns emerged linking both overt and subclinical thyroid abnormalities—particularly autoimmune thyroid disease—to disturbances in emotional regulation, cognitive performance, and neural circuit integrity. Taken together, these results reinforce the concept that thyroid dysfunction has clinically relevant neuropsychiatric correlates and highlight the importance of considering endocrine, immune, and neural factors jointly when interpreting mental health outcomes in affected individuals.

Mood and Anxiety Outcomes in Thyroid Dysfunction

A large proportion of included observational and population-based studies demonstrated elevated rates of depressive and anxiety symptoms in individuals with hypothyroidism, hyperthyroidism, or autoimmune thyroiditis. The magnitude of these associations varied across study designs and populations, but the directionality was consistent, with thyroid dysfunction conferring increased vulnerability to mood disturbances [38].

Hyperthyroidism was frequently associated with heightened anxiety, irritability, and sympathetic hyperarousal, while hypothyroidism was more strongly related to depressive symptoms, anhedonia, and psychomotor slowing. Importantly, several studies suggested that autoimmune processes—rather than hormone levels alone—may contribute to the development of mood symptoms. Elevated thyroid antibodies were associated with depressive and anxiety symptoms even in euthyroid individuals, supporting an immunological mechanism of affective dysregulation. Reviews and clinical overviews (Hage & Azar; Biondi; Pearce et al.) emphasize plausible biological mechanisms (thyroid hormone effects on serotonergic and noradrenergic systems, neuroinflammation) that support observed epidemiologic links [1,5,6,15,17].

Cognitive Impairment and Neuropsychological Functioning

Evidence from longitudinal, cross-sectional, and neuropsychological studies indicates that cognitive functioning—particularly domains such as processing speed, attention, working memory, and episodic memory—may be negatively affected in both overt and subclinical hypothyroidism. The magnitude of impairment, however, is heterogeneous [21,29,41]. Some large population-based studies observed only mild subjective cognitive complaints, whereas others reported measurable declines using standardized cognitive instruments.

Older adults with subclinical hypothyroidism appeared susceptible to cognitive decline in certain cohorts, although findings were not entirely consistent across studies. This suggests the possibility of age-dependent vulnerability but also underscores methodological variability in cognitive assessment tools and definitions of thyroid dysfunction [21,24,34,35,43].

Neurobiology

Neuroimaging studies included in this review consistently reported structural and functional brain alterations associated with thyroid dysfunction. Findings across MRI, fMRI, PET, SPECT, and DTI modalities included reduced hippocampal volume, decreased prefrontal cortical thickness or activation, altered fronto-limbic connectivity, and regional hypometabolism in frontal and temporal regions. These imaging data provided biological plausibility for the mood and cognitive symptoms described in clinical and epidemiological studies.

These findings align with mechanistic hypotheses suggesting that thyroid hormones influence serotonergic signaling, cerebral perfusion, synaptic plasticity, and mitochondrial function [42]. In parallel, autoimmune and inflammatory processes—including elevated cytokines such as IL-6 and TNF-α—may exacerbate neuroinflammation and contribute to neural network dysregulation. Together, these mechanisms offer a biologically plausible pathway linking thyroid dysfunction to mood and cognitive disturbances [10,11,37,32].

Interpretation of Meta-Analytic Findings

The meta-analytic component of this review provides additional quantitative support. The pooled odds ratio indicated a statistically significant increase in the likelihood of depression among individuals with subclinical hypothyroidism. In contrast, pooled symptom severity (SMD) did not reach statistical significance when all age groups were combined, likely due to substantial heterogeneity in psychometric instruments, sample characteristics, and diagnostic criteria across studies.

Importantly, age-stratified analysis revealed that younger adults (<60 years) exhibited a markedly stronger association between subclinical hypothyroidism and depressive symptoms. This finding highlights a potential vulnerability subgroup and suggests that age may be an important moderator of thyroid-related mood disturbances. The inconsistency between diagnostic outcomes (ORs) and symptom-based scales (SMDs) further underscores the need for standardized assessment methods in future research.

Persistence of Symptoms After Treatment

Several included studies demonstrated that a notable subset of individuals continues to experience residual fatigue, low mood, and cognitive symptoms even after biochemical euthyroidism is restored through levothyroxine therapy. This phenomenon was particularly prominent in those with autoimmune thyroid disease, suggesting that symptoms may be driven partly by immune-mediated mechanisms rather than thyroid hormone deficiency alone. Persistent symptoms after treatment may therefore require a multidimensional management approach incorporating psychological, neurocognitive, and immunological perspectives [12,13,27,40].

Clinical Implications

The findings of this review have several clinical implications:

- Routine evaluation of mood and cognitive symptoms should be incorporated into assessments of patients with thyroid dysfunction.
- Clinicians should consider not only biochemical values but also patient-reported symptoms, as autoimmunity and inflammation may contribute independently to psychological outcomes.
- For patients with persistent symptoms despite biochemical normalization, additional diagnostic frameworks—including neuropsychological testing or evaluation for autoimmune or inflammatory markers—may be warranted.
- Younger adults with subclinical hypothyroidism may represent a group at higher risk for depressive symptoms and may benefit from closer clinical monitoring.

Research Implications

This review highlights several important gaps in the literature:

1. **Lack of standardized outcome measures:** Future studies should adopt unified diagnostic criteria and psychometric tools to ensure comparability.
2. **Need for prospective, controlled designs:** Many available studies are cross-sectional, limiting causal inference.
3. **Role of autoimmunity and inflammation:** Mechanistic research is needed to clarify how immune processes influence neuropsychiatric outcomes independently of thyroid hormone levels.
4. **Neuroimaging biomarkers:** Larger, multi-center imaging studies could further elucidate structural and functional brain changes.
5. **Tailored treatment strategies:** Research should explore whether addressing autoimmune/inflammatory processes improves psychological outcomes beyond hormone replacement alone.

These findings complement the broader qualitative synthesis and underscore the need for more uniform diagnostic and psychometric criteria in future prospective studies.

Strengths of this review

This review has several methodological strengths, including the use of a comprehensive multi-database search strategy and systematic screening procedures. The quality of the included studies was rigorously evaluated using validated tools (NOS, AXIS, RoB2, and AMSTAR-2), ensuring a transparent appraisal of methodological robustness. A further strength is the integration of clinical, epidemiological, neuroimaging, and immunological evidence into a unified framework, which allows for a more multidimensional understanding of thyroid-related mood and cognitive disturbances. The review also highlights age-specific effects and autoimmune mechanisms that are rarely synthesized across domains, enhancing the clinical relevance and interpretability of the findings.

Limitations

This systematic review has several limitations that should be considered when interpreting the findings. First, substantial heterogeneity across the included studies—encompassing differences in design, population characteristics, diagnostic thresholds for thyroid dysfunction, and psychometric instruments—limited direct comparability and restricted the feasibility of conducting a de novo meta-analysis. Such variability likely contributed to inconsistent effect sizes, particularly for symptom-based outcomes.

Second, most studies were observational and cross-sectional, which limits causal inference. Only a small number of longitudinal and randomized controlled studies were available, many with modest sample sizes, making it difficult to determine the directionality and temporality of associations between thyroid dysfunction and psychological outcomes.

Third, assessment of thyroid status was not standardized. Variations in TSH and free hormone cutoffs, inconsistent measurement of thyroid antibodies, and differing laboratory reference ranges may have introduced classification bias, particularly in studies of subclinical hypothyroidism.

Fourth, outcome measures for depression, anxiety, and cognition varied widely across studies. The use of heterogeneous self-report scales, clinician-administered tools, and diagnostic interviews introduces measurement bias and may partially explain the mixed cognitive findings.

Fifth, many studies insufficiently controlled for relevant confounders such as comorbid autoimmune conditions, chronic illness, medication use, or socioeconomic factors. Inadequate adjustment may inflate or obscure true associations.

Sixth, although neuroimaging findings provide valuable insights, most imaging studies used small samples and heterogeneous methodologies, limiting generalizability.

Finally, publication bias cannot be excluded, and in a few cases, full-text availability was limited. Studies reporting significant associations may be more likely to be published, potentially overestimating observed effects.

Despite these limitations, the review synthesizes evidence across epidemiological, clinical, cognitive, and neuroimaging domains and identifies consistent patterns relevant to both research and clinical practice [8,9,13,34].

Conclusions

This systematic review demonstrates that thyroid dysfunction—both overt and subclinical, particularly when driven by autoimmune mechanisms—is consistently associated with an increased burden of depressive and anxiety symptoms, cognitive difficulties, and alterations in neural structure and function. While the strength of these associations varies across study designs and populations, the convergence of evidence across epidemiological, clinical, neuropsychological, and neuroimaging domains underscores the multidimensional impact of thyroid dysregulation on mental health.

The meta-analytic findings further indicate that individuals with subclinical hypothyroidism have a modest but significantly increased risk of depression, with younger adults showing the strongest associations. However, variability in diagnostic thresholds, psychometric measures, and methodological approaches limits the ability to draw definitive causal conclusions. Persistent symptoms reported by some patients despite biochemical normalization suggested that mood and cognitive impairments may arise from pathways beyond thyroid hormone levels alone, including autoimmunity and inflammation.

Clinically, these results highlight the importance of incorporating mental health assessment into routine thyroid care, paying particular attention to patients with autoimmune thyroid disease and those who continue to experience psychological symptoms despite standard treatment. From a research perspective, future studies should prioritize standardized definitions of thyroid dysfunction, consistent outcome measures, prospective longitudinal designs, and adequately powered neuroimaging and biomarker investigations.

Overall, this review emphasizes the need for a holistic understanding of thyroid-related mental health symptoms and calls for integrated clinical strategies that address endocrine, immunological, and neuropsychological domains. Such an approach may ultimately improve diagnostic precision, guide personalized treatment, and enhance the quality of life for individuals living with thyroid dysfunction [1,5,8,9,18,26,32,33,34].

Disclosure

Author Contributions

Conceptualization: Agnieszka Pocheć

Methodology: Agnieszka, Pocheć, Ewa Wieczorkiewicz,Eliza Garbacz

Software: Dariusz Nędza, Bartosz Lautenbach

Formal analysis: Anhelina Loputs, Klaudia Wojciech

Investigation: Eliza Garbacz, Agnieszka Pocheć

Resources: Wiktoria Błaszczyk, Dariusz Nędza, Eliza Garbacz,

Data curation / Check: Agnieszka Pocheć, Klaudia Wojciech

Writing – original draft preparation: Anastasiia Holoborodko,Ewa Wieczorkiewicz, Patrycja Stępińska

Writing – review and editing: Eliza Garbacz, Bartosz Lautenbach, Dariusz Nędza, Klaudia Wojciech, Wiktoria Błaszczyk, Anhelina Loputs

Supervision: Agnieszka Pocheć

Visualization: Klaudia Wojciech, Anhelina Loputs

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