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SUBCLINICAL HYPOTHYROIDISM IN TREATMENT-RESISTANT DEPRESSION

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ABSTRACT

Objective: To critically evaluate the relevance of subclinical hypothyroidism (SCH) to treatment-resistant depression (TRD), with particular attention to diagnostic distinctions and thyroid-directed therapeutic strategies.

Methodology: A narrative review of a predefined set of 13 full-text publications was undertaken. Study populations, thyroid classification, psychiatric ascertainment, interventions, numerical findings and limitations were extracted and compared. No systematic literature search or new quantitative synthesis was performed.

Results: The two included meta-analyses reached different conclusions about the SCH–depression association, including conflicting age-related findings. Neither intervention synthesis demonstrated statistically significant improvement in depressive outcomes with levothyroxine (LT4). A high SCH prevalence in selected untreated major depressive disorder populations did not establish antidepressant resistance. Other studies concerned symptom dimensions, mixed unipolar and bipolar populations, or previously treated hypothyroidism without contemporaneous biochemical assessment. Proposed mechanisms involving central hormone availability, autoimmunity, inflammatory mediators and deiodinase variation remain insufficiently validated for treatment selection. A favourable LT4/liothyronine combination-treatment case involved severe overt hypothyroidism and cannot establish efficacy in SCH.

Conclusion: SCH should not be assumed to explain antidepressant nonresponse. Thyroid replacement and liothyronine augmentation have distinct therapeutic objectives. Careful biochemical classification and independent psychiatric assessment are warranted, while direct controlled evidence in persistent SCH with rigorously characterised TRD remains insufficient within this reference set.

Keywords: Subclinical Hypothyroidism; Treatment-Resistant Depression; Major Depressive Disorder; Levothyroxine; Liothyronine; Thyroid Autoimmunity.

1 INTRODUCTION

Thyroid dysfunction and depression share clinical features that can complicate both diagnosis and treatment. Fatigue, cognitive complaints and reduced activity may accompany hypothyroidism, depressive illness or both. Nevertheless, the psychiatric consequences of overt thyroid hormone deficiency cannot be assumed to apply equally to subclinical hypothyroidism (SCH), where circulating free thyroxine remains within the reference range. Reviews describe improvement in depressive manifestations after treatment of overt hypothyroidism, while also recognising persistent symptoms despite biochemical correction. For milder biochemical abnormalities, the relationship is substantially less consistent. [1,2]

This uncertainty becomes particularly consequential when depression has not responded to treatment. A mildly elevated thyroid-stimulating hormone (TSH) concentration offers a possible explanation for nonresponse, but identifying an abnormal test does not establish that it caused the depressive disorder or prevented antidepressant benefit. The two included meta-analyses illustrate this problem: their findings differ on the association between SCH and depression, yet neither demonstrated a statistically significant improvement in depressive outcomes with levothyroxine (LT4). An epidemiological association and a clinically useful treatment effect therefore require separate evaluation. [3,4]

Thyroid hormone treatment introduces an additional distinction. Liothyronine (T3) may be added to an antidepressant as a psychiatric augmentation strategy, including in euthyroid patients, whereas LT4 replacement addresses thyroid hormone deficiency. Joffe's clinical commentary explicitly considers these competing explanations for improvement after T3 in a patient with SCH and antidepressant nonresponse. Ahmed and colleagues report improvement with LT4/LT3 combination therapy in a patient described as having TRD, but that patient initially had severe overt hypothyroidism. Neither observation resolves the efficacy of thyroid replacement in persistent SCH with confirmed TRD. [5,6]

This review examines how those distinctions affect interpretation of the evidence, the investigation of antidepressant nonresponse and the choice of thyroid-directed treatment. Its focus is the clinical relevance of SCH to TRD, with broader depression and thyroid studies considered according to their actual applicability rather than treated as direct TRD evidence.

2 MATERIALS AND METHODS

2.1 Review design and reference set

This narrative review used a predefined reference set of 13 full-text PDF publications, reproduced in the numbered bibliography. All 13 publications were retained for analysis; the set was not generated by a database search for this manuscript. It comprised two meta-analyses, one systematic review of autoimmune hypothyroidism, one narrative review, one editorial, one clinical commentary, one case report, five observational studies and one review-based letter. No external scientific sources were added. The evidence inventory is presented in Table 1. [1-13]

2.2 Data extraction and classification

The full article text, tables, figures and bibliographic information were examined. Extraction covered study design, recruitment setting, sample size, age definition, thyroid tests and reference intervals, psychiatric diagnosis or assessment instrument, treatment history, intervention exposure, outcomes and reported limitations. Thyroid findings were classified as SCH, overt hypothyroidism, euthyroid autoimmunity, variation within the reference range, TSH-only categories or historical treated thyroid disease, according to the information available. Psychiatric evidence was separated into screening symptoms, diagnosed MDD, mixed mood-disorder populations and documented antidepressant nonresponse. Treatments were classified by intent as LT4 replacement, T3 antidepressant augmentation or LT4/LT3 combination treatment.

2.3 Verification and narrative synthesis

Numerical claims were checked against the article text and relevant tables or figures. Sample sizes, percentages, effect metrics, confidence intervals and p-values were retained as reported when internally concordant. Conflicting labels or values were explicitly identified; ambiguous estimates were omitted or presented with a source qualification rather than silently corrected. Bibliographic metadata were checked against article front matter and, where needed, cross-references within the same 13-publication set. Findings available only through an included review were attributed to that review; its underlying studies were not independently reviewed or added as references.

2.4 Analytical scope

The synthesis followed predefined themes: diagnostic classification, epidemiological associations, proposed mechanisms, clinical diagnostic problems, therapeutic controversies, clinical implications and evidence limitations. Evidence was compared according to population, thyroid phenotype, psychiatric outcome and study design. No new statistical analysis, meta-analysis, formal risk-of-bias score or certainty grading was performed. Results below denote findings of this narrative synthesis, rather than results of a new patient study.

Table 1: Characteristics and applicability of the included publications

Publication	Design and population	Principal contribution	Applicability to SCH with TRD
Nuguru 2022 [1]	Narrative review of hypothyroidism and depression	Discusses HPT mechanisms, replacement and augmentation; acknowledges inconsistent evidence.	Broad thyroid and mood categories; secondary treatment summaries.
Samuels 2018 [2]	Editorial; advance article full text reviewed	Emphasises negative population and blinded intervention findings and persistent affective complaints.	Underlying cohorts/trials not independently reviewed; publication metadata cross-checked within the reference set.
Loh 2019 [3]	Meta-analysis; association analysis n=12,315; SCH n=1,700	Positive pooled categorical association; no significant pooled BDI/HDRS difference or LT4 benefit.	Mixed recruitment and outcomes; no uniform TRD population; inconsistent effect labelling.
Zhao 2018 [4]	Meta-analysis; 14 observational studies, n=5,678; SCH n=715	Overall association not significant; younger-age signal; LT4–placebo comparison not significant.	Heterogeneous definitions; single TSH assessments; not a dedicated TRD treatment study.
Joffe 2002 [5]	Clinical commentary with one treatment-refractory vignette	SCH and two unsuccessful SSRI trials; improvement after added T3.	Uncontrolled vignette; cannot separate replacement from augmentation.
Ahmed 2022 [6]	Case report; one patient with overt hypothyroidism and documented nonresponse	Improvement during LT4/LT3 combination; one Thr92Ala-DIO2 allele.	Overt disease at presentation; concurrent treatments; no control or validated genotype selection.
Kotkowska 2022 [7]	Systematic review of autoimmune hypothyroidism and depression	Discusses antibodies, cytokines, BDNF and treatment-related changes; findings are inconsistent.	Mixed thyroid states and psychiatric populations; mechanisms and response prediction unresolved.
Li 2024 [8]	Cross-sectional; 266 first-episode, drug-naïve MDD patients aged ≥50	SCH in 172/266 (64.7%); selected severe clinical population.	No healthy comparator or antidepressant failures; persistence not established.
Ma 2024 [9]	Cross-sectional NHANES; 12,502 adults	PHQ-9 associations with FT4, FT3, total T3 and TPOAb; adjusted TSH association not significant.	Screening symptoms; no causal or treatment-response inference.
Hakoshima 2026 [10]	Retrospective cross-sectional; depression n=309, mania n=91	Depression group: 9 SCH; higher FT4 associated with lower GAF.	Mixed unipolar/bipolar depression; global functioning; incomplete drug/history data.
Kumar 2026 [11]	Historical longitudinal cohort; n=6,191; euthymic/euthyroid at baseline	High and low TSH associated with small arousal/regulatory differences.	TSH categories do not establish SCH; exploratory PHQ-9 mapping; no TRD selection.
Perra 2026 [12]	Exploratory secondary cohort analysis; n=93	Lockdown PHQ-9 >4: 5/15 (33.3%) with prior	No hormonal measurements; small, imbalanced groups; screening

	aged ≥65; 15 prior hypothyroidism	hypothyroidism versus 6/78 (7.69%) without.	outcome; problematic reported OR omitted.
Trifu 2020 [13]	Review-based letter to the editor	Describes thyroid augmentation within proposed treatment schemes.	Secondary evidence; proposed sequence is not a validated guideline or comparative trial.

The inventory contains all 13 publications in the predefined reference set. HPT, hypothalamic–pituitary–thyroid; SSRI, selective serotonin reuptake inhibitor; TPOAb, thyroid peroxidase antibodies. Other abbreviations are defined after the abstract.

3 RESULTS AND DISCUSSION

3.1 Conceptual and Diagnostic Framework

3.1.1 Biochemical classification of thyroid dysfunction

SCH is defined by elevated TSH with normal free T4 (FT4). Some included publications additionally specify normal free T3 (FT3). Overt primary hypothyroidism entails thyroid hormone deficiency rather than an isolated TSH elevation; these categories must remain distinct even when their symptoms overlap. Thyroid autoimmunity is a further dimension: antibody positivity can accompany SCH, overt hypothyroidism or euthyroid autoimmune thyroiditis. An autoimmune diagnosis and a biochemical diagnosis consequently answer different questions. [2-4,7,8,10]

The TSH threshold used to identify an abnormal result varies across the evidence. Zhao and colleagues report cut-offs of 4.0–5.6 mIU/L in the included observational studies. Li and colleagues defined SCH as TSH >4.2 mIU/L with normal FT4, while Hakoshima and colleagues used a laboratory TSH reference interval of 0.5–5.0 µIU/mL. Such differences affect which participants enter the SCH category. Age also matters: Zhao's analysis identifies the absence of age-adjusted limits and reliance on single measurements as potential sources of misclassification, particularly in older populations. [4,8,10]

An elevated TSH concentration alone is insufficient to distinguish SCH from overt hypothyroidism when FT4 is unavailable. Kumar and colleagues classified thyroid status by low, normal or high TSH; the resulting groups should therefore be described as TSH categories rather than uniformly as confirmed subclinical disease. Similarly, Perra and colleagues identified previous hypothyroidism through diagnosis and replacement treatment without collecting contemporaneous thyroid hormone measurements. Their cohort cannot establish the psychiatric effects of biochemically verified SCH. [11,12]

3.1.2 Depression and treatment resistance

The psychiatric outcome also requires precise classification. A depressive symptom score, a screening threshold and a clinical diagnosis of major depressive disorder (MDD) are related but not interchangeable. Ma and colleagues studied PHQ-9 symptoms, Li and colleagues recruited patients with diagnostically confirmed MDD, and Hakoshima and colleagues evaluated global functioning in hospitalised patients with depression or mania. None of these designs directly tested antidepressant resistance. [8-10]

The included TRD literature does not apply one uniform operational definition. Joffe describes two unsuccessful antidepressant trials, whereas Ahmed and colleagues diagnose TRD after persistent symptoms during antidepressant treatment, additional psychotropic augmentation and psychotherapy. For this review, evidence concerning documented treatment nonresponse is separated from evidence concerning symptom severity or untreated MDD; treatment resistance is not inferred from a high depression score, prolonged illness or comorbid thyroid dysfunction. This distinction is especially important for Li's first-episode, drug-naïve cohort, whose participants had not demonstrated antidepressant failure. [5,6,8]

3.2 Epidemiological Evidence

3.2.1 Association signals and their limitations

Loh and colleagues included 12,315 individuals in their analysis of depression in SCH, of whom 1,700 had SCH. They reported a significantly higher frequency of depression than in euthyroid controls, with an estimate of approximately 2.4 and a 95% confidence interval (CI) of 1.84–3.02. The abstract labels this a relative risk of 2.35, the results text gives 2.36, and the corresponding plot is labelled as an odds ratio; these source inconsistencies preclude a definitive identification of the effect metric, although its direction is unchanged. In contrast, pooled comparisons of Beck Depression Inventory (BDI) and Hamilton Depression Rating Scale (HDRS) scores did not show significant differences. The signal thus depended partly on whether depression was analysed as a categorical outcome or a continuous symptom measure. [3]

The pooled association should also be interpreted in relation to recruitment. Loh's evidence combined community samples with patients evaluated in outpatient settings for suspected SCH. The latter setting may select individuals with symptoms that prompted thyroid investigation, limiting comparison with unselected populations. Variation in depression instruments and clinical ascertainment further reduces the comparability of individual studies. The meta-analysis demonstrates an association in its assembled evidence, but it does not establish that SCH causes MDD or antidepressant resistance. [3]

Li and colleagues provide a striking clinical estimate: 172 of 266 first-episode, drug-naïve Chinese patients with MDD aged at least 50 years met their SCH definition, a prevalence of 64.7%. Recruitment required a HAMD-17 score ≥ 24 . Patients with SCH had higher depressive symptom scores and several different biochemical or clinical characteristics. However, the study lacked a healthy control group, was cross-sectional and came from one psychiatric outpatient setting. Its unusually high prevalence should therefore remain an estimate for this selected population. The authors' use of age ≥ 50 years also differs from the ≥ 60 -year definitions used in the meta-analyses. [8]

3.2.2 Evidence questioning a general association

Zhao and colleagues analysed 14 observational studies with 5,678 participants, including 715 with SCH. The overall association was not statistically significant, whether expressed as a standardised mean difference (SMD) in depressive scores of 0.23 (95% CI -0.03 to 0.48; $p=0.08$; $I^2=73.6\%$) or an odds ratio (OR) for depression of 1.75 (95% CI 0.97–3.17; $p=0.064$; $I^2=64.6\%$). These estimates remain compatible with some increase in depression, but their uncertainty and heterogeneity do not support a definitive overall association. Nor should a non-significant result be interpreted as proof that every subgroup is unaffected. [4]

Samuels similarly emphasises the negative findings of large population studies and blinded LT4 interventions. Her editorial describes a large prospective study that found no association between SCH and incident depressive symptoms, including sensitivity analyses using repeated thyroid measurements. Because its underlying cohort article was not included, those findings are considered here as the editorial's synthesis rather than independently verified primary evidence. Its relevance is chiefly methodological: population recruitment, repeated measurement and adjustment for perceived stress can alter the interpretation of a thyroid–depression association. [2]

3.2.3 Age, sex and symptom phenotype

Age-related findings are directly conflicting. Loh's geriatric synthesis found an OR of 1.72 (95% CI 1.10–2.70; $p=0.020$). Zhao found an association in participants younger than 60 years, with an OR of 3.8 (95% CI 1.02–14.18; $p=0.047$), but not in older participants, whose OR was 1.53 (95% CI 0.81–2.90; $p=0.193$). The wide interval in the younger subgroup and heterogeneous older-group findings argue against using age alone to predict a clinically relevant thyroid contribution or treatment response. [3,4]

Ma's cross-sectional NHANES analysis of 12,502 adults found negative associations of depressive symptoms with FT4, FT3 and total T3, but no significant association with TSH after full adjustment. Associations with thyroid peroxidase antibodies were apparent in some age and sex strata. Statistical significance within one stratum, however, does not by itself establish a difference between strata: the reported sex interaction for the TPO-antibody association was not significant. The analysis concerns symptom burden across thyroid measurements, not a trial of treatment or a cohort of confirmed TRD. [9]

Other included studies reinforce the importance of outcome selection. In Hakoshima's depression group, higher FT4 correlated weakly with lower Global Assessment of Functioning scores ($r=-0.212$; $p<0.001$), whereas TSH did not correlate with functioning. The group included 75 patients with bipolar depression and only nine participants classified as having SCH. Kumar's longitudinal cohort linked both high and low TSH to modestly higher arousal/regulatory symptom scores, rather than to all depressive domains. Perra's small cohort found greater lockdown-period depressive symptom screening positivity among participants with previous treated hypothyroidism, without measuring thyroid biochemistry. These observations suggest heterogeneity, but none demonstrates that SCH produces treatment resistance. [10–12]

Table 2: Association and LT4 treatment findings in the two included meta-analyses

Question	Reported findings	Comparison or interpretation	Relevance to SCH with TRD
Overall categorical association	Loh [3]: reported estimate 2.35 in abstract / 2.36 in results; 95% CI 1.84–3.02; $p < 0.001^*$	Zhao [4]: OR 1.75; 95% CI 0.97–3.17; $p = 0.064$; $I^2 = 64.6\%$	Different selections and outcomes; no inference of causality or TRD risk.
Continuous depressive scores	Loh [3]: pooled BDI and HDRS group differences not significant	Zhao [4]: SMD 0.23; 95% CI –0.03 to 0.48; $p = 0.08$; $I^2 = 73.6\%$	Categorical and continuous findings need separate interpretation.
Age-related association	Loh [3], ≥ 60 : OR 1.72; 95% CI 1.10–2.70; $p = 0.020$	Zhao [4], < 60 : OR 3.8; 95% CI 1.02–14.18; $p = 0.047$; ≥ 60 : OR 1.53; 95% CI 0.81–2.90; $p = 0.193$	Age does not consistently identify an affected or treatment-responsive group.
LT4 and BDI	Loh [3]: reported $d + -1.05$; 95% CI –2.72 to 0.61; $p = 0.215$	Pooled change not statistically significant	Individual before-and-after improvement does not establish comparative efficacy.
LT4 and HDRS	Loh [3]: reported $d + -2.38$; 95% CI –4.86 to 0.10; $p = 0.060$	Pooled change not statistically significant	A near-threshold p-value is not a positive treatment finding.
LT4 versus placebo	Zhao [4]: SMD 0.26; 95% CI –0.09 to 0.62; $p = 0.143$; $I^2 = 52.9\%$	No statistically significant treatment difference	Not a direct controlled evaluation of persistent SCH with confirmed TRD.

*Loh [3] labels the overall estimate as a relative risk in the abstract and results text, but Figure 2 labels it as an odds ratio. The abstract/plot gives 2.35 and the results text gives 2.36. Values and labels are disclosed without recalculation. The reviews include overlapping primary studies; estimates from different scales or methods should not be compared directly.

3.3 Potential Pathophysiological Mechanisms

3.3.1 Thyroid regulation and central hormone availability

The included reviews describe interactions between the hypothalamic–pituitary–thyroid axis, thyroid hormone signalling and neurotransmitter systems involved in mood. They discuss altered TRH–TSH responses, circadian regulation and serotonergic or noradrenergic pathways as possible explanations for thyroid–depression relationships. These mechanisms provide biological context, but the underlying evidence covers different thyroid states, psychiatric diagnoses and experimental models. It does not identify a single mechanism demonstrated in patients with persistent SCH and confirmed TRD. [1,3,7,13]

Local hormone availability offers one explanation for discordance between circulating thyroid measurements and symptoms. The reviews discuss transport into the central nervous system and conversion of T4 to T3 by deiodinases. Reduced intracellular hormone availability despite apparently adequate circulating concentrations is sometimes termed “brain” or “tissue” hypothyroidism. This remains a proposed mechanism rather than a diagnosis that can be established by depressive symptoms or a routine peripheral thyroid profile. Samuels notes that biochemical reasoning has not consistently translated into mood benefit in controlled combination-treatment studies. [1-3]

The hypothesis must also accommodate findings that do not follow a simple deficiency model. Ma reported negative associations between several circulating hormones and depressive symptoms, whereas Hakoshima found higher FT4 associated with poorer global functioning in hospitalised patients. Kumar observed modest arousal/regulatory associations at both ends of the TSH distribution. Different populations and outcomes can explain part of this variation, but it cautions against assuming that more thyroid hormone necessarily produces better psychiatric functioning. [9-11]

3.3.2 Autoimmunity, inflammation and neurotrophic factors

Kotkowska and Strzelecki review thyroid autoimmunity alongside inflammatory mediators and brain-derived neurotrophic factor (BDNF). Their synthesis discusses overlapping cytokine profiles, changes during antidepressant or LT4 treatment and possible links with neuroplasticity. It also documents discordant antibody–depression findings and acknowledges the absence of adequate longitudinal evidence establishing relationships among depressive illness, autoantibodies and cytokine changes. These observations support investigation of shared pathways, rather than an established inflammatory explanation for SCH-associated TRD. [7]

A central unresolved issue is whether antibodies are pathogenic, markers of autoimmune susceptibility, or correlates of another relevant process. Antibody-associated mood symptoms can occur in euthyroid autoimmune thyroiditis, which separates autoimmunity from hormone deficiency. Conversely, several studies summarised in the autoimmune review did not find increased depression associated with antibodies. BDNF and inflammatory measurements are therefore insufficiently validated in this literature for assigning causation, predicting antidepressant failure or selecting thyroid hormone treatment. Changes in a biological marker during treatment cannot, by themselves, demonstrate that the marker mediated clinical improvement. [7]

3.3.3 Deiodinase variation and individual response

Ahmed's patient carried one Thr92Ala-DIO2 allele and improved after a divided-dose LT3 regimen was added to LT4. The report offers a possible connection between hormone conversion and individual response. However, a single carrier with an uncontrolled treatment history cannot establish a genotype-response relationship. Samuels describes inconsistent genetic findings and distinguishes improvements in psychological well-being from improvements in depression. Neither publication supplies a validated genetic rule for selecting patients with SCH for combination therapy. [2,6]

These mechanisms are best regarded as hypotheses that may explain variability and guide research. Their clinical value will depend on demonstrating that a proposed pathway predicts a reproducible, meaningful treatment effect in an appropriately defined population. Figure 1 separates these hypotheses from observed associations and therapeutic objectives.

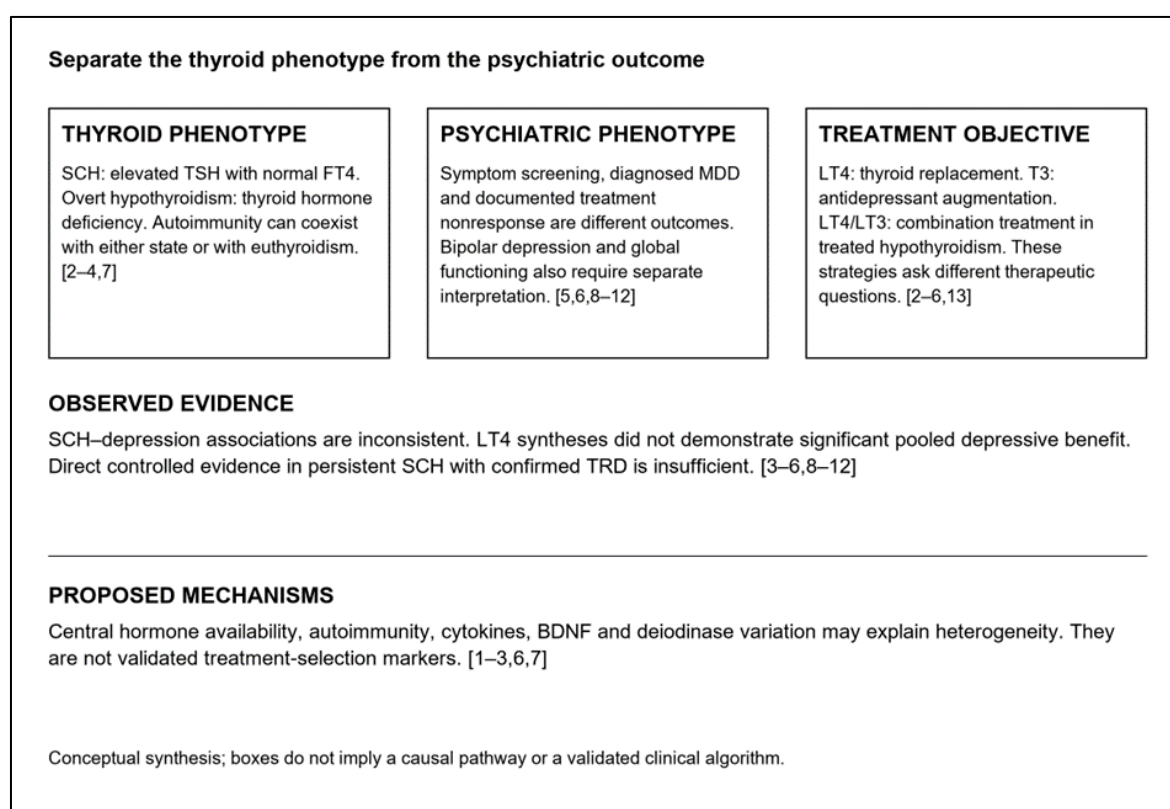


Figure 1: Conceptual framework for interpreting thyroid findings in antidepressant nonresponse.

Biochemical classification, psychiatric ascertainment and therapeutic intent are distinct. Observed associations and LT4 intervention findings are separated from proposed hormone, immune and genetic mechanisms. This original synthesis is not a validated clinical algorithm. SCH, subclinical hypothyroidism; TRD, treatment-resistant depression; MDD, major depressive disorder; TSH, thyroid-stimulating hormone; FT4, free thyroxine; BDNF, brain-derived neurotrophic factor; LT4, levothyroxine; LT3/T3, liothyronine/triiodothyronine. [1–13]

3.4 Diagnostic Challenges in Clinical Practice

3.4.1 Overlapping manifestations and outcome interpretation

Fatigue, cognitive complaints, sleep disturbance and reduced activity may complicate attribution of symptoms when thyroid disease and depression coexist. The included reviews describe these overlapping manifestations, while Kumar's

analysis specifically grouped sleep, fatigue and appetite items into an arousal/regulatory domain. A total depression score may therefore combine symptoms with different relationships to thyroid status. A change in fatigue does not necessarily indicate remission of core depressive illness, just as an unchanged total score does not exclude improvement in an individual symptom. [1,2,11]

The assessment instrument should remain visible when interpreting a result. Ma's PHQ-9 analysis included mild screening-level symptoms; Perra defined screening positivity using PHQ-9 >4; Li used a structured diagnostic interview and selected clinically severe MDD; and Hakoshima used a global functioning measure. These outcomes cannot all be labelled confirmed depressive episodes or TRD. In particular, findings from a screening threshold should not be presented as equivalent to a diagnostic interview or a documented history of unsuccessful antidepressant treatment. [8-10,12]

3.4.2 Mild TSH elevation and persistence

A mildly elevated TSH result warrants interpretation with FT4, the assay reference range and the clinical setting. Zhao identifies single-measurement classification as a limitation because transient TSH elevations may be included as SCH. Samuels describes spontaneous normalisation on repeated testing, and Li recommends repeated thyroid assessment at least three months apart to clarify diagnosis in the context of its study limitations. Together, these sources support confirming persistence rather than attributing treatment resistance to one biochemical result. They do not establish a universal repeat-testing schedule for every patient with depression. [2,4,8]

The same caution applies to isolated hormone concentrations within the reference range. Associations across FT3 or FT4 distributions may be relevant to research, but the included observational studies do not validate a psychiatric target concentration or show that adjusting treatment toward one end of the range improves TRD. Without this distinction, a statistical relationship may be converted prematurely into a therapeutic goal. [9-11]

3.4.3 Autoimmunity and comorbidity

Antibody testing can inform the autoimmune context of thyroid disease, but its psychiatric meaning remains uncertain. Kotkowska and Strzelecki advocate investigation of autoimmune hypothyroidism in patients with mood symptoms, while acknowledging fragmented and inconsistent evidence. Ma found antibody associations with symptoms in selected strata, and Li found an independent association between thyroglobulin antibodies and SCH within its MDD sample. These findings do not validate antibody titres as predictors of TRD or as indications for thyroid hormone treatment in biochemically euthyroid individuals. [7-9]

Establishing coexisting SCH and depression leaves the question of causality unresolved. Cross-sectional studies cannot determine whether thyroid changes preceded symptoms, followed them or arose through shared factors. Even a longitudinal association may remain affected by treatment changes, contemporaneous measurements and residual confounding, as Kumar explicitly recognises. Diagnostic reasoning should preserve the possibility of an independent depressive disorder rather than assuming that a thyroid abnormality explains all psychiatric symptoms. [2,8,9,11]

3.4.4 Verifying the treatment history

Before labelling the coexistence as SCH with TRD, the psychiatric record should distinguish untreated illness, incomplete response and documented unsuccessful treatment. Joffe and Ahmed provide treatment histories; the epidemiological studies generally do not. The relevant questions are what treatment was given, for how long, whether it was considered adequate and how response was assessed. Where this information is absent, the evidence should be described as depression associated with thyroid findings. This approach prevents severe drug-naïve MDD or persistent symptoms during thyroid replacement from being relabelled automatically as antidepressant resistance. [5,6,8-12]

3.5 Therapeutic Controversies

3.5.1 LT4 replacement and depressive outcomes in SCH

The decision to treat a thyroid disorder and the expectation of an antidepressant effect are separate. The reviews describe LT4 as the usual replacement treatment for hypothyroidism and summarise thyroid-related considerations for treating SCH. Those discussions do not establish that a depressive complaint alone identifies a treatment-responsive thyroid deficiency. In particular, improvement after correction of overt hypothyroidism should not be extrapolated uncritically to patients whose FT4 was normal before treatment. [1-4]

Loh's intervention synthesis comprised six studies involving 266 individuals with SCH. Treatment durations ranged from two to 12 months. Although thyroid biochemistry improved, pooled depressive outcomes did not reach statistical significance: the reported effect estimate was -1.05 for BDI (95% CI -2.72 to 0.61 ; $p=0.215$) and -2.38 for HDRS (95% CI -4.86 to 0.10 ; $p=0.060$). Some individual studies reported improvement, but the pooled results did not demonstrate

a reliable benefit. The HDRS result remains uncertain and should not be redescribed as a positive finding because its p-value approached a conventional threshold. [3]

Zhao's placebo-controlled treatment synthesis likewise found no significant difference, reporting an SMD of 0.26 (95% CI -0.09 to 0.62; $p=0.143$; $I^2=52.9\%$). This evidence is important because uncontrolled before-and-after improvement may reflect nonspecific treatment effects or changes in symptoms over time. Nevertheless, the available interventions are not a definitive trial of LT4 in a uniformly defined population with both persistent SCH and established TRD. They limit claims of routine antidepressant benefit while leaving a more narrowly specified clinical question unresolved. [4]

3.5.2 T3 augmentation as a psychiatric intervention

T3 augmentation asks whether adding liothyronine improves antidepressant response, rather than whether replacing deficient thyroid hormone reverses a depressive illness. Joffe notes that much of the older augmentation literature involved euthyroid patients, tricyclic antidepressants and open, uncontrolled designs. His clinical vignette describes a woman with TSH 8.3 mU/L and normal T4 and T3 who improved after T3 was added following two unsuccessful SSRI trials. The report cannot distinguish pharmacological augmentation from correction of thyroid dysfunction, because the same intervention could serve both proposed explanations. [5]

Trifu and colleagues place thyroid hormones within a proposed sequence of augmentation options and summarise earlier treatment literature. Their article is a review-based letter, not a comparative trial validating that treatment sequence. Its title and proposed "third line" position should therefore not be treated as a journal-independent guideline recommendation. Kotkowska and Strzelecki also distinguish evidence concerning acceleration of antidepressant response from other treatment outcomes and report different findings across antidepressant classes. The included literature supports considering augmentation as a separate topic, but does not provide a verified effect estimate for T3 specifically in SCH-associated TRD. [7,13]

3.5.3 Combination treatment and the overt hypothyroidism case

Ahmed's case is informative precisely because its phenotype is clear. At initial presentation, the patient had TSH 560 μ U/mL and FT4 0.20 ng/dL, against a reported FT4 reference interval of 0.90–2.18 ng/dL. This was severe overt hypothyroidism. Depressive symptoms persisted after LT4 restored TSH to the reference range and during antidepressant treatment, additional psychotropic augmentation and psychotherapy. Later, divided-dose LT3 with reduced LT4 was associated with marked improvement, and prescribed antidepressant drugs were gradually discontinued. [6]

The report also documents continued psychotherapy and subsequent use of S-adenosylmethionine and *Rhodiola rosea* supplements. The treatment periods were sequential, uncontrolled and of different duration; LT3 exposure, LT4 dosing and TSH differed between periods. The observation cannot isolate the contribution of LT3, its dosing schedule, the DIO2 variant or other concurrent interventions. Repeated measurements in one patient remain observations from one individual, rather than independent participants establishing comparative efficacy. The case can generate hypotheses about persistent symptoms after treatment of overt disease, but it cannot establish benefit for SCH or justify a routine divided-dose regimen. [6]

Samuels provides a counterweight to this positive observation: her editorial summarises blinded combination-treatment studies that did not consistently improve mood. It also notes that genetic or transporter-related hypotheses remain preliminary. These apparently different findings can coexist if an individual response is possible but not reliably predictable. The appropriate conclusion is uncertainty about selection and average benefit, rather than either universal effectiveness or dismissal of every individual experience. [2,6]

3.5.4 Biochemical and psychiatric treatment endpoints

A normal TSH result confirms a biochemical endpoint within the relevant treatment context; it does not demonstrate psychiatric remission. Conversely, persistence of depression after biochemical correction does not prove continuing thyroid hormone deficiency. Loh's synthesis showed improved TSH without significant pooled depressive benefit, and Samuels describes persistent affective complaints during apparently adequate replacement. The distinction requires monitoring of psychiatric outcomes independently of thyroid tests, with attention to whether the desired outcome is symptom improvement, remission or functioning. [2,3]

Perra's cohort reinforces the need to consider symptoms during ongoing replacement, but its absence of biochemical measurements means that treatment adequacy and dynamic hormone responses cannot be verified. Its proposed explanation of reduced thyroid adaptability to stress remains speculative. The observed vulnerability therefore does not justify increasing thyroid hormone doses in response to psychosocial stress. [12]

3.5.5 Risks and the boundaries of treatment inference

The included reviews warn about overtreatment and describe cardiovascular and skeletal adverse effects with high thyroid hormone exposure, especially in older patients. Trifu additionally discusses myocardial distress and occasional manic or psychotic manifestations during treatment initiation. Ahmed reports no hyperthyroid symptoms and a normal cardiac evaluation in the individual case, but this cannot establish long-term population safety. The safety discussion should therefore remain proportionate to the evidence, without implying that low-dose augmentation or a favourable single-patient assessment removes risk. [1,2,6,13]

The overall controversy reflects a mismatch between mechanistic plausibility, selected observational associations, uncontrolled improvement and inconsistent controlled treatment findings. LT4 replacement, T3 antidepressant augmentation and LT4/LT3 combination treatment require separate assessments of indication, expected benefit and safety. Table 3 contrasts these strategies without presenting an unvalidated prescribing algorithm.

Table 3: Distinct objectives of thyroid-directed therapeutic strategies

Strategy	Therapeutic objective	Evidence in the included publications	Limits and interpretation
LT4 replacement	Correct a thyroid disorder; endocrine indication assessed separately from mood complaints.	SCH treatment syntheses [3,4] did not show significant pooled depressive benefit.	Biochemical improvement does not ensure remission; no verified efficacy estimate for SCH-associated TRD.
T3 antidepressant augmentation	Improve antidepressant response; does not require that thyroid failure be the cause of depression.	Clinical commentary and secondary summaries [5,7,13]; older evidence often involved euthyroid patients and uncontrolled designs.	No directly included controlled trial specific to SCH with TRD; proposed line of treatment is not a validated ranking.
LT4/LT3 combination	Alter replacement in treated hypothyroidism; may also be described as psychiatric augmentation.	Ahmed [6]: favourable uncontrolled overt-hypothyroidism case; Samuels [2]: inconsistent controlled mood benefit.	Cannot infer SCH efficacy or genotype-based selection. Concurrent treatment, dosing changes and safety require separate evaluation.

This comparison is not a prescribing protocol. The reviews describe cardiovascular and skeletal concerns with excess thyroid hormone exposure and overtreatment. A favourable single-patient cardiac assessment does not establish long-term safety. [1,2,6,13]

3.6 Clinical Implications and Interdisciplinary Management

The evidence supports a structured distinction between the endocrine finding and the psychiatric treatment problem. In a patient with antidepressant nonresponse, thyroid assessment can identify overt disease or a persistent subclinical abnormality that deserves its own evaluation. Interpretation should retain the FT4 result, laboratory range, prior thyroid history, treatment exposure and evidence of persistence. Samuels describes thyroid screening as routine practice in depression, while the broader reviews support attention to potentially overlooked thyroid dysfunction. The rationale is diagnostic clarification; testing does not itself prove an endocrine cause of resistance. [1,2,4,8]

Psychiatric reassessment should occur alongside endocrine evaluation. The included studies show why this is necessary: severe first-episode MDD, screening-level symptoms, bipolar depression and documented nonresponse are represented in different proportions and should not be managed as one phenotype. A clear description of the depressive diagnosis, previous antidepressant trials and current symptom pattern makes the treatment question more precise. Kumar's dimensional findings suggest that sleep, fatigue and appetite may merit separate attention, but the small associations do not yet support a validated biomarker-based management strategy. [5,6,8-12]

For patients with overt hypothyroidism, correction of thyroid hormone deficiency and assessment of persistent psychiatric illness are complementary objectives. For SCH, the available intervention syntheses do not establish LT4 as a reliable treatment for depressive symptoms. If thyroid replacement is undertaken for an endocrine indication, expectations about depression should be discussed separately. If T3 is considered as psychiatric augmentation, its purpose should be explicit rather than represented as proof that SCH caused antidepressant failure. [2-5]

Joint endocrinology and psychiatry review offers a clinically reasoned way to reconcile these objectives. It can clarify thyroid classification, distinguish replacement from augmentation, interpret persistent symptoms and review treatment safety. This is an inference from the diagnostic and therapeutic uncertainties in the included evidence, not a protocol validated by the included studies. A coordinated assessment is particularly relevant when combination treatment is contemplated, biochemical values and symptoms diverge, or treatment history is complex. [2,5,6,13]

Follow-up should use both biochemical and clinically meaningful psychiatric outcomes. Symptom scales can assist assessment, but their interpretation should reflect the domain measured and the original clinical diagnosis. A favourable biochemical response with persistent depression calls for reassessment of the psychiatric disorder; an apparent psychiatric response without controlled evidence warrants caution in attributing its mechanism. The available literature does not identify an age group, antibody threshold or deiodinase genotype that can reliably select patients with SCH-associated TRD for a particular thyroid regimen. [2-4,6,7,11]

3.7 Limitations of the Evidence and Future Research Priorities

The principal evidence gap is the lack, within this reference set, of a controlled study specifically testing thyroid-directed treatment in patients with persistent biochemical SCH and rigorously characterised TRD. Most epidemiological findings concern depressive symptoms or MDD, while the clearest detailed combination-treatment case concerns overt hypothyroidism. The evidence consequently informs clinical uncertainty more strongly than it establishes a treatment recommendation for the population named in the title. [3-6,8-12]

Heterogeneity extends across TSH cut-offs, confirmation of persistence, age definitions, recruitment settings and psychiatric outcomes. Cross-sectional associations cannot establish directionality; longitudinal electronic-record studies remain vulnerable to time-varying treatment and measurement limitations. A screening threshold is not equivalent to MDD, and a functioning score is not a specific measure of antidepressant resistance. The two meta-analyses also draw partly on overlapping earlier studies and should not be interpreted as wholly independent replications. [3,4,8-12]

Source-level inconsistencies further constrain numerical interpretation. Loh reports slightly different overall relative risks in its abstract and results text. Li's description of sex susceptibility is not supported by the non-significant sex comparison in its table, and its prose and table differ on the direction of HDL-C differences. Perra reports a confidence interval for one OR that does not contain the stated estimate. These inconsistencies were not silently corrected: the review uses concordant data, identifies the Loh discrepancy in Table 2 and excludes the problematic Perra OR from its synthesis. [3,8,12]

The present review is deliberately restricted to 13 included publications and does not claim comprehensive coverage of the literature. No systematic search, independent reassessment of every study cited within the reviews or formal risk-of-bias scoring was performed. Several treatment findings are available only through secondary summaries, and one editorial was included in an advance-article version. These constraints limit conclusions about comparative efficacy and the completeness of the evidence base.

Future studies should define the thyroid phenotype with TSH and FT4, document persistence, distinguish autoimmune status and describe antidepressant adequacy and nonresponse. Controlled investigations should separate LT4 replacement from T3 augmentation and combination treatment, use psychiatric remission and functioning alongside symptom scores, and record safety and concurrent treatments. Mechanistic or genetic subgroup analyses should demonstrate reproducible treatment prediction rather than association alone. These priorities follow from the observed limitations and would make the evidence more directly applicable to patients with both SCH and TRD.

Abbreviations:

- SCH, subclinical hypothyroidism;
- TRD, treatment-resistant depression;
- MDD, major depressive disorder; TSH, thyroid-stimulating hormone;
- FT4, free thyroxine;
- FT3, free triiodothyronine;
- LT4, levothyroxine;
- LT3/T3, liothyronine/triiodothyronine;
- BDI, Beck Depression Inventory;
- HDRS, Hamilton Depression Rating Scale;
- PHQ-9, Patient Health Questionnaire-9;
- GAF, Global Assessment of Functioning;
- BDNF, brain-derived neurotrophic factor;

- CI, confidence interval;
- OR, odds ratio;
- SMD, standardised mean difference.

4 CONCLUSION

The included evidence does not establish SCH as a general cause of treatment-resistant depression. Associations with depressive outcomes vary by study design, population and outcome measure, and age-related findings conflict. Selected untreated MDD populations may show frequent SCH, but these observations cannot demonstrate antidepressant resistance. The available LT4 intervention syntheses did not demonstrate statistically significant improvement in depressive outcomes, while directly applicable controlled evidence for persistent SCH with confirmed TRD remains insufficient.

Thyroid replacement, T3 antidepressant augmentation and LT4/LT3 combination treatment should be evaluated as distinct therapeutic strategies. Improvement reported in a patient with severe overt hypothyroidism generates hypotheses but does not establish efficacy in SCH. Careful biochemical classification, confirmation of persistent abnormalities and independent psychiatric assessment can reduce inappropriate causal attribution. Interdisciplinary decision-making should preserve separate endocrine and psychiatric objectives, realistic expectations and attention to treatment safety. Further research requires clearly defined thyroid and depressive phenotypes before biological plausibility can be translated into reliable treatment selection.

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Disclosure of conflict of interest

The authors declare no conflicts of interest regarding this manuscript.

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