



THE INFLUENCE OF DEPRESSIVE SYNDROME ON THE OCCURRENCE OF GALLSTONE DISEASE IN REPRODUCTIVE-AGE WOMEN WITH SUBCLINICAL HYPOTHYROIDISM

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Abstract

Background: Subclinical hypothyroidism (SCH), depressive symptoms and gallstone disease may coexist in reproductive-age women, yet the nature and direction of their relationships remain uncertain. **Objective:** To critically examine evidence linking thyroid dysfunction, depressive syndrome and cholelithiasis, and to propose a clinically feasible strategy for testing whether depression is associated with gallstones among women with SCH. **Methods:** A focused narrative synthesis of clinical guidelines, observational studies, Mendelian-randomization analyses and mechanistic literature was undertaken. **Results:** Thyroid dysfunction may alter cholesterol handling, bile secretion and biliary motility. Studies in broader populations report associations between depressive symptoms and gallstones; a 2024 analysis of 7,707 participants found progressively higher odds across depression-severity categories. However, these estimates cannot be directly generalized to reproductive-age women with SCH, and causal inference remains limited. **Conclusion:** A combined endocrine, psychiatric and hepatobiliary assessment is biologically plausible and research-worthy, but a direct causal influence of depressive syndrome on gallstone occurrence in this specific population has not been established. Prospective studies with rigorous confounder control are needed.

Keywords: Subclinical hypothyroidism; reproductive-age women; depressive syndrome; cholelithiasis; gallstones; thyroid-stimulating hormone; metabolic risk; PHQ-9.

Introduction and relevance of the topic

Gallstone disease is a common hepatobiliary condition influenced by sex, age, obesity, insulin resistance, reproductive factors and lipid metabolism. Reproductive-age women represent a clinically important population because pregnancy history, estrogen exposure, contraceptive use and metabolic health can influence biliary risk. At the same time, depressive symptoms can affect physical activity, eating patterns,





sleep and adherence to treatment. These overlapping pathways make an endocrine–psychiatric perspective scientifically relevant, while also creating substantial potential for confounding.

SCH is defined by an elevated thyroid-stimulating hormone (TSH) concentration with free thyroxine (FT4) within the reference interval. Interpretation should use assay- and population-appropriate thresholds and confirm persistent abnormalities rather than relying on one isolated test [1,2]. The present article addresses a specific question: among women of reproductive age with SCH, is depressive syndrome associated with a higher prevalence or subsequent incidence of gallstones, independently of established metabolic and reproductive risk factors?

Thyroid status and hepatobiliary physiology. Thyroid hormones participate in systemic energy expenditure, hepatic lipid turnover and gastrointestinal function. A plausible relationship between hypothyroidism and biliary stones involves reduced cholesterol metabolism, altered bile secretion and impaired relaxation of the sphincter of Oddi. Laukkarinen and colleagues reviewed these mechanisms, particularly in relation to common bile duct stones [3]. Mechanistic plausibility does not demonstrate that every case of mild SCH causes gallstone formation, and gallbladder stones must be distinguished from common bile duct stones. In a 2024 cross-sectional study of 180 patients with gallstone disease, 35 (19.44%) had SCH and 20 (11.11%) had overt hypothyroidism [4]. These are proportions within a selected gallstone sample—not the incidence of gallstones among all patients with SCH, and not a valid estimate of excess risk without a comparable control group. The study therefore supports further investigation rather than definitive causality.

TSH elevation can coexist with dyslipidemia, adiposity and insulin resistance, all of which may influence biliary cholesterol saturation. These factors could mediate part of a thyroid–gallstone association or confound an observational comparison. Thyroid autoimmunity, medication exposure and variation in iodine intake may introduce further heterogeneity. Repeating TSH and FT4 testing, documenting thyroid-peroxidase antibodies where appropriate and measuring a fasting lipid profile would improve the validity of a dedicated study.

1. Depression and gallstone disease: current evidence. Depressive syndrome is not synonymous with a high screening score. Validated questionnaires quantify symptom burden, whereas a clinical diagnosis requires assessment of duration, functional impairment, differential diagnoses and safety. In SCH, fatigue,



sleep disturbance and cognitive complaints may overlap with depression and lead to symptom misclassification. This overlap makes structured assessment essential.

Li and colleagues studied 18,141 older Chinese adults and reported an adjusted relative risk of 1.33 (95% confidence interval [CI] 1.12–1.58) for gallstone disease over five years among participants with probable depression [5]. Their Mendelian-randomization analysis suggested an association in European-ancestry data (odds ratio [OR] 1.21, 95% CI 1.07–1.37), but did not provide comparable evidence in East-Asian data; the authors characterized the causal evidence as weak. The cohort's older age distribution limits applicability to fertile-age women.

Evidence from population-based analyses. Wang and colleagues analyzed 7,707 participants using US National Health and Nutrition Examination Survey data and evaluated depression severity with the Patient Health Questionnaire-9 (PHQ-9) [6]. Relative to the reference category, reported adjusted odds of gallstones were higher for mild depression (OR 1.58, 95% CI 1.31–1.90), moderate depression (OR 2.07, 95% CI 1.59–2.67) and severe depression (OR 2.41, 95% CI 1.70–3.34). A Mendelian-randomization component also supported a possible association. Nevertheless, cross-sectional analyses cannot determine whether depression preceded gallstone formation, and genetic instrumental-variable assumptions require scrutiny.

Neither the Li nor Wang study was designed specifically for reproductive-age women with biochemically confirmed SCH. Accordingly, applying their effect sizes directly to this target group would be inappropriate. A stronger design should determine whether depression adds predictive information after controlling for body mass index (BMI), waist circumference, parity, pregnancy history, diabetes, diet, physical activity, medications and thyroid function.

2. Potential biological and behavioral pathways. Three broad classes of pathways warrant testing. First, metabolic mechanisms may connect depressive symptoms with central adiposity, altered HDL cholesterol and insulin resistance. In the Li study, waist circumference was estimated to mediate part of the depression–gallstone relationship [5]; this result is hypothesis-generating rather than proof of a universal mechanism. Second, behavioral factors—sleep disruption, reduced activity and dietary changes—could influence metabolic status. Third, neuroendocrine stress pathways may affect autonomic regulation and gastrointestinal motility, although direct evidence for a depression-driven biliary mechanism in SCH remains insufficient.



These pathways are not mutually exclusive. For example, SCH and depressive symptoms may each correlate with higher BMI, while BMI independently increases gallstone risk. Without a prespecified causal diagram, investigators may overadjust for mediators or fail to adjust for confounders. Separating total associations from direct associations is therefore important. Prospective temporal ordering, repeated measures and mediation analyses with defensible assumptions would strengthen interpretation.

3. Specific scientific hypothesis. Primary hypothesis: among reproductive-age women with persistent SCH, clinically significant depressive symptoms are associated with a higher frequency of ultrasonographically confirmed gallstones than in women with SCH without significant depressive symptoms, after adjustment for major metabolic and reproductive confounders. Secondary hypothesis: central adiposity and lipid abnormalities partially account for any observed association. These hypotheses remain untested in the proposed study population and should not be presented as established results.

Proposed methodology for a dedicated clinical study. Design: A prospective observational cohort would best assess incident gallstone formation; a cross-sectional baseline analysis could address prevalent gallstones but not causation. Eligibility could include nonpregnant women aged 18–49 years with elevated TSH and normal FT4 on repeat testing using laboratory-specific ranges. The protocol should prespecify how treated thyroid disease, recent pregnancy, prior cholecystectomy, acute illness, severe hepatic disease and medications affecting thyroid measurements or gallstone risk are handled. Local ethics approval and written informed consent are essential.

Exposure assessment: Use the PHQ-9 as a standardized symptom screening instrument and, where feasible, a structured clinical interview to identify depressive disorders. Record prior depressive episodes, antidepressant exposure and symptom duration. Outcome assessment: Perform fasting abdominal ultrasonography using a consistent protocol; distinguish gallbladder stones, sludge and common bile duct stones. Sonographers ideally should be unaware of depression status. For a longitudinal cohort, repeat ultrasound at prespecified intervals and record cholecystectomy or new biliary symptoms.

Covariates: age, BMI, waist circumference, parity, pregnancy history, hormonal contraception, smoking, physical activity, dietary patterns, fasting lipids, glycemic status, TSH, FT4, thyroid autoantibodies and relevant drugs. A directed acyclic graph



should identify a minimal sufficient adjustment set. Selection bias may arise if participants are recruited only from specialist clinics, while reverse causation may occur if painful biliary disease worsens mood. Both should be explicitly considered.

4. Statistical analysis plan. Describe continuous variables using means with standard deviations or medians with interquartile ranges, as appropriate, and categorical variables as counts and percentages. Estimate prevalence ratios or adjusted odds ratios for cross-sectional outcomes and hazard ratios for incident gallstones in prospective follow-up. Prespecify depressive-symptom categories and also analyze PHQ-9 continuously to avoid unnecessary loss of information. Report effect sizes with 95% CIs rather than relying only on p values.

Assess collinearity, missing-data patterns and model fit. Multiple imputation may be appropriate when assumptions are defensible. Sensitivity analyses should consider alternative TSH thresholds, excluding antidepressant users, adjustment for reproductive factors and separation of gallbladder from ductal stones. Sample size must be calculated from an expected outcome frequency and target precision or power; it cannot be justified merely by an arbitrary target number of participants.

Clinical implications. The literature supports a multidisciplinary approach when thyroid abnormalities, depressive symptoms and hepatobiliary complaints coexist. For patients with SCH, clinical assessment should establish whether TSH elevation persists, whether symptoms have alternative explanations and whether thyroid treatment is indicated according to current guidance. NICE recommends considering levothyroxine in adults with TSH ≥ 10 mIU/L on two occasions three months apart, while selected symptomatic adults under 65 with lower persistent elevations may be offered a time-limited trial [2]. Such recommendations do not establish that levothyroxine prevents gallstones or treats depressive disorders.

A positive depression screen should prompt appropriate clinical evaluation, not automatic assignment of a psychiatric diagnosis. Ultrasound should be driven by biliary symptoms and clinical indications; the reviewed evidence does not justify routine ultrasound screening solely because a woman has SCH or depression. Similarly, gallstone treatment should follow accepted hepatobiliary practice rather than assumptions about thyroid causation.

5. Limitations of the available evidence. The strongest limitation is indirectness: existing studies examine thyroid dysfunction and gallstones or depression and gallstones largely in separate populations. No result summarized



here establishes the joint interaction of SCH and depressive syndrome specifically in fertile-age women. Many estimates derive from observational designs with residual confounding, uncertain temporality, selection effects and potential measurement error. Mendelian randomization offers complementary evidence but is sensitive to instrument validity, pleiotropy and ancestry differences.

Further limitations include variation in the definition of SCH, inconsistent differentiation between gallbladder and ductal stones, and the distinction between depressive symptoms and major depressive disorder. Hormonal exposure, pregnancy history and age may modify associations. Therefore, an observed correlation in a broad adult sample should not be interpreted as a causal effect in reproductive-age women.

6. Conclusion. Available clinical and mechanistic literature provides a coherent rationale for investigating the intersection of SCH, depression and gallstone disease. Thyroid dysfunction may influence biliary cholesterol metabolism and motility, while depressive symptoms show epidemiological associations with gallstones in several broader populations. However, the claim that depressive syndrome independently increases gallstone occurrence among reproductive-age women with SCH is not yet proven. A carefully designed, adequately powered prospective study with confirmed thyroid status, standardized depression assessment, ultrasound-defined outcomes and robust confounder control is required before causal or preventive recommendations can be made.

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