

The Bile-Brain Hypothesis

A Falsifiable Translational Research Agenda for Bile-Acid Signaling and Neuropsychiatric Disease

CRITICAL EVIDENCE APPRAISAL · CAUSAL MODELS · TEN PROPOSED EXPERIMENTS

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This paper is a hypothesis and research-protocol proposal, not a systematic review, a report of completed experiments, or a clinical treatment guideline. Proposed sample sizes are illustrative and require formal power calculations.

Abstract

Background. Bile acids are cholesterol-derived molecules that mediate intestinal lipid absorption and regulate metabolic and immune signaling. Experimental studies implicate selected bile acids in neurovascular permeability and neuronal function, while rare disorders of sterol metabolism provide clear examples of neurological and psychiatric manifestations. A targeted serum metabolomics study has also identified altered bile-acid profiles in schizophrenia. Whether these circulating differences are causal, compensatory, or secondary remains unresolved [1,7-13].

Objective. To critically integrate the existing evidence, distinguish competing causal explanations, and define a staged experimental program capable of establishing or refuting a clinically meaningful bile-acid-related neuropsychiatric subtype.

Approach. This hypothesis paper is a selective critical synthesis of verified primary studies, clinical trials, regulatory evidence, and methodological guidance through October 2026. It proposes ten experiments spanning independent biomarker replication, disease specificity, longitudinal temporality, bile-acid kinetics, microbial transformations, blood-brain barrier exposure, human neural target engagement, genetic triangulation, controlled feeding, and biomarker-stratified randomized intervention. No new patient data are reported.

Interpretation. The evidence supports neurological consequences of defined sterol disorders and experimental neuroactive effects of bile acids, but does not establish bile-acid deficiency as a general cause of primary psychosis. The highest-value near-term study is a carefully controlled, multicenter replication of individual bile-acid signatures with psychiatric and metabolic disease controls. Intervention trials require prior evidence of reproducibility, physiologically credible target engagement, and safety.

Conclusion. Bile-acid dysregulation is a plausible candidate mechanism or modifier in a biological subset of neuropsychiatric disease, not an established unifying explanation. A prospectively defined, falsification-oriented research program is essential before biomarker-driven treatment claims can be justified.

Keywords: bile acids; schizophrenia; psychosis; metabolic psychiatry; FXR; TGR5; neurovascular biology; metabolomics; causal inference; precision medicine.

Principal inference: A biological association between serum bile acids and psychosis is not equivalent to deficient intestinal bile, deficient cerebral exposure, or a correctable cause of schizophrenia. These are separate hypotheses requiring separate tests.

1. Introduction and scope

The relationship between metabolism and psychiatric illness can be approached from two directions. One begins with established metabolic diseases, such as cerebrotendinous xanthomatosis (CTX) and Niemann-Pick disease type C, and asks how their molecular defects affect the nervous system. The other begins with a common psychiatric syndrome and searches for metabolic differences associated with it. The former can provide compelling disease-specific causal evidence; the latter often yields associations whose direction and significance are uncertain [1,11-13].

Bile acids are an attractive focus because they occupy several physiological compartments. Hepatic synthesis converts cholesterol into primary bile acids; conjugation, intestinal transport, microbial transformation, ileal reabsorption, and hepatic feedback determine their circulating composition. Through FXR and TGR5, bile acids also act as signaling ligands affecting metabolic and inflammatory pathways. This multifunctionality supplies plausible links to

brain physiology but simultaneously creates abundant opportunities for confounding [19].

We use *neuropsychiatric manifestations* to include symptoms occurring in known neurological or metabolic disease, and *primary psychotic disorders* to refer to syndromes in which no specific underlying disease has yet been established. The terms must not be conflated. A rare sterol disorder causing psychosis does not imply that ordinary schizophrenia is caused by the same mechanism.

The purpose of this manuscript is therefore not to assert causation or propose an empirically unvalidated treatment protocol. Its purpose is to articulate a falsifiable, mechanism-specific agenda while preserving established psychiatric care and distinguishing biomarker association from causal mediation and therapeutic action.

2. A compartment-resolved biological hypothesis

2.1. Digestion, synthesis and endocrine signaling are distinct

Bile acids facilitate intestinal micelle formation and absorption of dietary lipids and fat-soluble vitamins. They are synthesized from cholesterol and recycled through the enterohepatic circulation. Steroid hormones also derive from cholesterol, but their production does not require dietary animal fat because human tissues synthesize cholesterol endogenously. An animal-free diet can be nutritionally adequate when essential nutrients, especially vitamin B₁₂, are reliably supplied. Thus, inadequate animal-fat consumption should not be equated with defective steroidogenesis or psychosis.

Insufficient bile delivery to the intestinal lumen, increased circulating bile acids in cholestasis, and altered ratios of individual bile acids are physiologically different states. They may coexist or have different effects. Low serum CDCA, for example, does not prove inadequate intestinal delivery; a high serum total-bile-acid concentration in cholestasis does not prove adequate intestinal fat absorption.

2.2. A proposed pathway must identify its molecular species and target

For each candidate mechanism, four quantities are needed: the identity of the bile-acid species, its concentration in the relevant compartment, the receptor or physicochemical target it engages, and the direction of the resulting functional effect. The phrase "bile imbalance" is insufficiently precise. Hydrophobic and hydrophilic species may have distinct or opposing actions. A serum-derived index of receptor affinity cannot substitute for measured receptor activity in cerebral tissue.

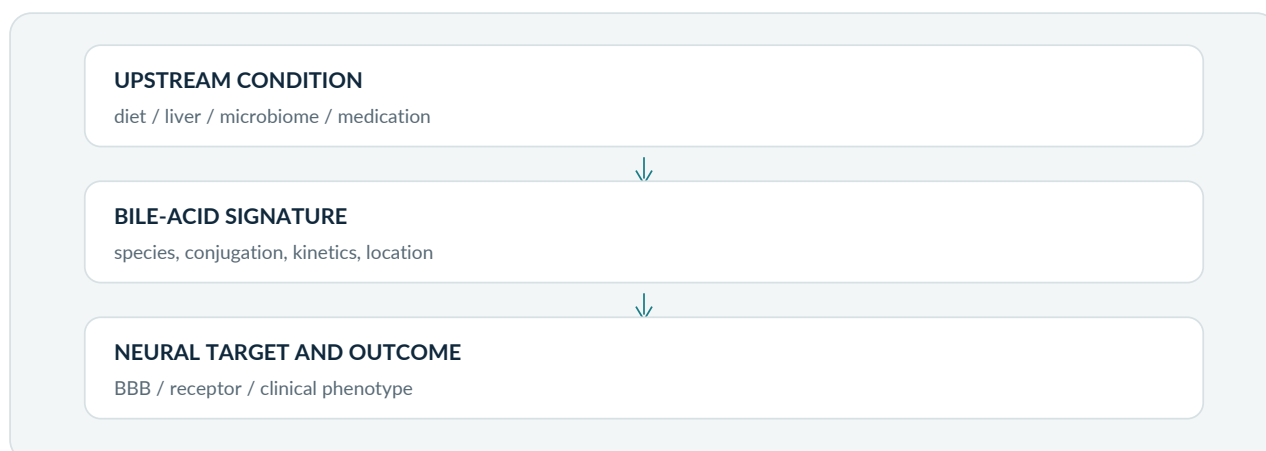


Figure 1. The proposed causal chain contains distinct measurement domains. Altering one link does not establish the downstream links.

2.3. Direct neural exposure is not assured

Healthy brain tissue is protected by highly selective endothelial transport. In humans with severe acute neurological conditions, bile acids were detected in ventricular CSF only at very low concentrations; concurrent serum concentrations were not reliably correlated with CSF levels [9]. This study does not define normal brain exposure, but it does warn against treating serum metabolomics as a direct neural exposure assay. MFSD2A-mediated lipid transport also demonstrates that endothelial membrane composition is itself part of barrier physiology [7].

3. What the evidence currently establishes

3.1. Rare sterol disease supplies disease-specific causation

CTX is caused by pathogenic variants affecting CYP27A1, with impaired bile-acid synthesis and abnormal sterol metabolism. Neurological and psychiatric complications are recognized features. In 2025, the US FDA approved chenodiol for adults with CTX on the basis of a trial demonstrating important biochemical effects; long-term observational evidence indicates that earlier treatment is associated with more favorable neurological trajectories, while established psychosis may remain comparatively refractory [11,12]. These observations support the importance of sterol metabolism but do not generalize to schizophrenia.

Niemann-Pick type C offers a different natural experiment: impaired intracellular lipid trafficking, rather than inadequate luminal bile, can produce behavioral disturbance and psychosis. A selected cohort of 19 adults included ten with prior psychotic episodes, highlighting clinical overlap between rare neurodegenerative disease and primary psychiatric syndromes [13]. Such cohorts are selected and cannot be used to estimate the prevalence of these disorders among people presenting with psychosis.

3.2. Schizophrenia serum metabolomics is intriguing but not causal

Qing and colleagues measured 40 serum bile acids in 108 drug-free patients with schizophrenia and 108 healthy controls, split into discovery and validation groups. Lower CDCA, UDCA, several other species, total bile acids, and unconjugated bile acids were reported in both sets [1]. An eight-variable classifier yielded AUCs of 0.758 and 0.732 using separately optimized thresholds; critically, the validation AUC decreased to 0.671 when the discovery threshold was applied. The validation groups also had age and sex differences, and "drug-free" did not necessarily mean lifetime antipsychotic-naïve. None of these limitations nullifies the finding, but they weaken diagnostic and causal inference.

A separate observational study in major depressive disorder connected microbial composition, selected bile-acid species, and cognitive performance. It is consistent with symptom-specific metabolic associations yet cannot establish that microbial transformation or bile acids caused impairment [14]. Establishing specificity against psychiatric and gastrointestinal disease controls is therefore essential.

3.3. Experimental neural and neurovascular biology has limited human translation

In rats with bile-duct obstruction, Quinn and colleagues showed that elevated circulating bile acids could increase blood-brain barrier permeability through a Rac1-dependent process involving occludin phosphorylation [8]. Human imaging has more recently identified greater mean BBB leakage in a small schizophrenia-spectrum sample (41 patients and 40 controls), but leakage did not correlate significantly with symptom severity or cognition [10]. These results support neurovascular inquiry, not a demonstrated bile-acid-mediated cause of psychosis.

The single published UDCA augmentation case in treatment-resistant schizophrenia reported substantial clinical improvement after UDCA introduction, but concurrent discontinuation of another medication, multiple ongoing drugs, and absence of controls preclude attribution to UDCA [2]. Its appropriate evidentiary status is hypothesis-generating.

3.4. Counterevidence must shape the hypothesis

Schizophrenia risk is polygenic and strongly implicates excitatory and inhibitory neuronal biology; a large GWAS identified associations at 287 loci [3]. Complement C4A variation supplies additional neuroimmune genetic evidence [4]. Antipsychotic maintenance treatment substantially reduces relapse risk in randomized trials [6]. A meta-analysis documented disturbed glucose regulation in first-episode, minimally treated patients [5], but the direction of causation remains unresolved.

Nutritional and metabolic interventions are not uniformly effective. NEURAPRO, a multicenter trial of 304 people at ultra-high risk of psychosis, found no preventive benefit from omega-3 supplementation under the tested conditions [15]. A 2026 ketogenic-diet study supports feasibility and metabolic change, but the most prominent four-month psychiatric improvements arose during an extension without a continuing randomized comparison [16]. Neither result establishes bile-acid mediation. Controlled trials of linoleic-acid intake have also not shown a general increase in common circulating inflammatory markers [20], contradicting a simple equation between ordinary seed-oil consumption and systemic inflammation.

4. Competing causal explanations

A rigorous research program must distinguish at least five explanations: (A) a direct pathogenic bile-acid deficiency or excess; (B) a modifier of an independent neural vulnerability; (C) a metabolic consequence of illness, treatment, diet, or sleep; (D) a shared upstream cause independently affecting brain and liver; and (E) a compensatory response. These possibilities are not distinguished by a single case-control metabolomic comparison.

Model	Distinct prediction	Observation that would weaken it
Primary causal pathway	Specific abnormality precedes illness and engages a neural target	No temporal precedence or no target engagement
Disease modifier	Biomarker predicts response or course in a prespecified subgroup	No biomarker-by-treatment interaction
Consequence	Biomarker shifts after symptoms, feeding changes, or treatment	Persistent baseline abnormality before clinical onset
Shared cause	Association attenuates after appropriate common causes are measured	Direct perturbation affects relevant neural function
Compensation	Reversing the biomarker fails to help or worsens physiology	Correction reproducibly improves mechanistic and clinical endpoints

A falsifiable study must name the relevant bile-acid molecule, sample compartment, direction of change, target, and outcome before data collection. Failure of one proposed link must not be explained away automatically by substituting a new mechanism. Any alternative mechanism requires fresh evidence and independent testing.

5. The ten-study translational program

The following designs are proposals rather than registered studies. Enrollment figures are planning scenarios, not formal statistical calculations. Each stage should be revised by clinicians, analytical chemists, biostatisticians, neurologists, and research ethics committees before implementation. Experiments may proceed in parallel where appropriate, but patient intervention requires convincing evidence from earlier mechanistic stages.

Experiment 01 | Independent biochemical replication

Question. Is a prespecified bile-acid signature reproducibly associated with antipsychotic-naïve first-episode psychosis?

Design. Prospective, multicenter, matched case-control investigation. An illustrative target is 300 first-episode antipsychotic-naïve patients, 300 matched healthy controls, and 150 psychiatric controls without psychosis. Enrollment and allocation require pilot-based power analysis. Standardize fasting duration, blood collection clock time, meal timing, specimen processing, BMI, smoking, liver status, sleep, medications and recent antibiotics. Measure individual bile acids by isotope-dilution targeted LC-MS/MS with harmonized calibrators and blinded quality-control specimens.

Prespecified support. Replicate direction and magnitude for the exact prespecified species, including CDCA and UDCA, across independent recruitment centers. Provide effect sizes, confidence intervals, multiplicity-adjusted results, and diagnostic performance without threshold re-optimization.

Falsification / narrowing rule. A difference that vanishes after standardization or does not replicate meaningfully undermines the proposed diagnostic signature. Serum differences alone do not establish deficient intestinal bile or central nervous system exposure.

Experiment 02 | Disease specificity and external validity

Question. Does the profile distinguish psychosis from other psychiatric and metabolic conditions?

Design. Use a fully independent cohort with schizophrenia-spectrum illness, bipolar I disorder, major depression, metabolic dysfunction-associated steatotic liver disease, selected ileal disease or bile-acid diarrhea, and healthy comparators. Collect matching clinical, hepatic and nutritional data. Evaluate the locked score from Experiment 01 with no re-fitting in the external sample.

Prespecified support. Measure calibration, discrimination, decision-curve usefulness, and incremental information beyond age, sex, BMI, liver markers, metabolic status, medications and established clinical predictors.

Falsification / narrowing rule. If the signal is ubiquitous across liver and metabolic diseases, reject schizophrenia-specific diagnostic claims. Retain investigation only as a broader biological marker if reproducible.

Experiment 03 | Longitudinal temporality

Question. Does the biochemical abnormality precede symptom emergence or deterioration?

Design. Follow a prospectively defined clinical-high-risk population and matched comparators for two to three years. Collect fixed-interval serum panels and event-triggered samples near symptom deterioration, without delaying standard clinical treatment. Record stress, diet, sleep, physical activity, drugs and treatment changes as time-varying exposures.

Prespecified support. Assess whether earlier bile-acid measurements improve prediction of later psychosis or worsening beyond baseline clinical risk using predeclared longitudinal models. Analyze within-person changes and sensitivity to time-dependent confounding.

Falsification / narrowing rule. A signal that reliably follows, rather than precedes, symptoms supports a downstream or compensatory explanation. Temporal association by itself never proves causality.

Experiment 04 | Physiological source and kinetic partitioning

Question. Which component of enterohepatic metabolism generates the signature?

Design. Undertake a controlled-feeding physiology study of biomarker-positive and negative participants. Measure serial fasting and postprandial individual bile acids, serum C₄, FGF19, stool bile acids, liver chemistry, intestinal transit and microbial transformation potential. A specialized sub-study may use validated stable-isotope tracer kinetics following safety and method review.

Prespecified support. Build an identifiable kinetic model separating candidate changes in synthesis, feedback, transformation, recycling and clearance. Evaluate reproducibility within participants.

Falsification / narrowing rule. If very different physiological defects generate the same serum pattern, abandon claims that a low serum level uniquely indicates insufficient production.

Experiment 05 | Defined microbial biotransformation

Question. Can a specific bacterial enzyme system cause the candidate chemical changes?

Design. Identify associations between functional microbial genes and bile-acid species, then test prespecified transformations in controlled anaerobic cultures. Where feasible use isogenic loss and restoration of candidate bile-acid-transforming genes; measure products, bacterial growth and off-target metabolites.

Prespecified support. Show that targeted manipulation changes the expected molecule with a quantitative mass balance, and that the biochemical change is necessary for a relevant downstream cellular response.

Falsification / narrowing rule. Abandon claims of microbial mediation if bacterial effects cannot be causally linked to a defined bile-acid conversion. Broad fecal transplantation effects are not proof of bile-acid mediation.

Experiment 06 | Human BBB exposure and permeability

Question. Does the serum signature predict neural exposure or neurovascular barrier changes?

Design. Combine selected human DCE-MRI phenotyping with human iPSC-derived endothelial models. Obtain paired serum/CSF only when CSF is collected for independent clinical indications and participants consent. Use free-fraction-adjusted concentration ranges, relevant species and controls for nonspecific detergent toxicity.

Prespecified support. Predeclare associations between individual bile-acid species and MRI transfer parameters, then test matching permeability, transcytosis and tight-junction responses in human cell models.

Falsification / narrowing rule. If associations do not replicate and physiological concentrations have no endothelial effect, reject the proposed direct permeability mechanism while leaving indirect peripheral signaling open.

Experiment 07 | Human neuronal target engagement

Question. Do implicated bile acids alter dopamine, NMDA or GABA signaling at credible human exposures?

Design. Use human neuronal cultures, appropriately characterized receptor-expressing cells, and neural co-cultures. Measure electrical currents, firing, dopamine release, viability, membrane integrity and mitochondrial stress. Separate effects mediated by FXR, TGR₅ and direct receptor interactions using selective genetic or pharmacological perturbations and rescue.

Prespecified support. Demonstrate a reproducible species-specific dose-response, receptor dependence and functional effect within credible free concentration ranges supported by exposure data.

Falsification / narrowing rule. Effects restricted to supraphysiologic concentrations or associated with nonspecific membrane disruption should not be extrapolated to patients.

Experiment 08 | Human genetic and rare-disease triangulation

Question. Do inherited perturbations of bile-acid pathways predict psychiatric vulnerability?

Design. Integrate available bile-acid quantitative-trait GWAS with psychiatric genetics. Evaluate instruments for strength, pleiotropy and tissue specificity before any Mendelian randomization. Separately characterize psychiatric and neurological phenotypes in confirmed CTX and other relevant rare-disease registries.

Prespecified support. Look for concordant direction among genetic perturbation, circulating species, tissue-level mechanism and psychiatric outcomes; compare alternative neural and metabolic pathways.

Falsification / narrowing rule. If appropriate instruments show no reproducible association or strong pleiotropy undermines inference, do not present genetic data as supporting a causal bile pathway.

Experiment 09 | Controlled dietary perturbation

Question. Does the source and composition of fat measurably modify the candidate pathway?

Design. Use a randomized energy-matched, nutritionally adequate crossover feeding protocol comparing prespecified saturated, monounsaturated and linoleic-rich fat compositions within established safety parameters. Hold total fat, energy, protein, fiber and meal timing as similar as feasible. Measure biochemical compliance and repeated bile-acid profiles.

Prespecified support. Quantify within-person changes in the locked bile-acid signature, C4/FGF19 physiology and validated neural proxy measures only if earlier mechanistic studies justify them.

Falsification / narrowing rule. If fatty-acid substitution fails to change the implicated target, reject the proposed dietary correction strategy. No human experiment needs deliberate exposure to severely degraded frying oils.

Experiment 10 | Biomarker-stratified randomized intervention

Question. Does correcting a validated bile-acid-related pathway improve meaningful psychiatric outcomes?

Design. Only after successful target validation, randomize within prespecified biomarker-positive and negative strata to mechanism-specific adjunctive therapy or matched control, while maintaining standard psychiatric care. UDCA is one candidate, not the default. Predefine the appropriate clinical population, PANSS or another valid primary symptom measure, functionality, adverse events, follow-up and laboratory target engagement. Power the study for the biomarker-by-treatment interaction if precision treatment is the claim.

Prespecified support. Require credible target engagement and clinically important benefit versus control. A strong precision-treatment claim additionally requires a properly tested interaction and independent replication.

Falsification / narrowing rule. If the biological abnormality is corrected but clinical differences are absent with adequately narrow confidence intervals, reject or narrow the therapeutic mechanism. A negative underpowered or non-engaging trial is inconclusive.

6. Decision gates, analytical standards and feasibility

The trial is not a substitute for mechanistic validation. A rational program should pass four explicit gates: (1) reproducible species-level abnormality; (2) specificity and temporality sufficient to support an informative phenotype; (3) credible target engagement at plausible human concentrations; and (4) a safe intervention shown to affect the intended pathway. Only then is a large efficacy trial justified. Figure 2 summarizes the sequence.

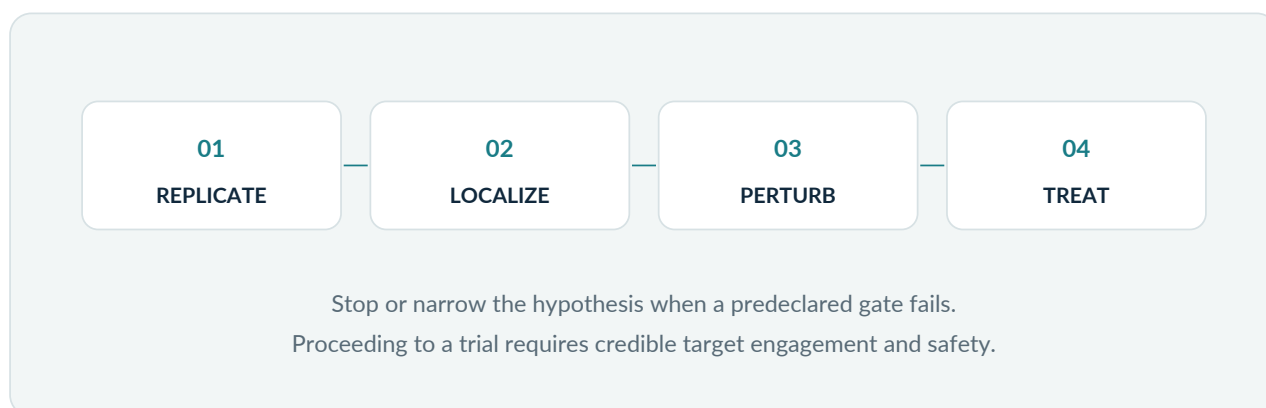


Figure 2. Proposed stop/go gates. Advancement is conditional; failure at any stage must narrow or suspend the claim rather than expand it retrospectively.

6.1. Statistical principles

The primary metabolomic analysis should be species-specific and preregistered, with explicitly declared transformations, outlier policy, missing-data handling, and multiple-comparison correction. Predictive scores must be locked before independent validation. Continuous biomarker values should not be dichotomized on an opportunistically chosen threshold. Wherever feasible, report calibration, discrimination and added value over a clinical baseline rather than AUC alone.

Longitudinal and treatment studies should state the causal estimand, specify time-varying covariates and consider intercurrent events such as antipsychotic initiation, acute hospitalization and diet change. Statistical mediation analyses do not prove pathway causation absent strong assumptions; genetic instruments must satisfy relevance and exclusion restrictions. A biomarker-specific treatment claim requires a formal interaction analysis, not merely a significant result in one subgroup and a nonsignificant result in another.

6.2. Analytical standardization and tissue compartment

Repeated specimen acquisition, standardized fasting and collection times, validated bile-acid calibrators, stable-isotope internal standards, freeze-thaw control and cross-site quality controls are indispensable. Serum, stool, lumen, CSF and interstitial brain tissue are distinct compartments. A low serum concentration cannot be assigned a meaning such as "brain bile deficiency" without independent evidence for that transfer and target relation.

6.3. Ethics, safety and clinical boundaries

No proposed study justifies withdrawal of effective psychiatric treatment, prolonged fasting in medically vulnerable people, unsupported bile-acid supplementation, unnecessary lumbar puncture, or deliberate exposure to oxidized cooking oils. Patients with suspected organic psychosis or delirium require standard diagnostic assessment and timely treatment. Any therapeutic trial must comply with research ethics approval, trial registration, safety monitoring, pharmacovigilance and prespecified stopping criteria. Trial protocols and reports should follow SPIRIT 2025 and CONSORT 2025 [17,18].

7. Evidence grading and falsification matrix

Proposition	Current status	Minimum future evidence
Rare sterol or trafficking disorders can produce neuropsychiatric manifestations	Established, disease-specific [11-13]	Better natural history and early diagnosis
Some serum bile acids differ in schizophrenia	Preliminary association [1]	Independent, well-matched replication
Relevant bile acids alter neurovascular physiology	Animal/cell evidence [8]; indirect human observations [10]	Exposure-matched human target studies
A specific bile-acid pathway initiates common primary psychosis	Not established	Temporal, genetic, mechanistic convergence
Dietary fat substitution corrects a causally relevant pathway	Not established	Controlled feeding and target engagement
Biomarker-selected bile-acid intervention improves psychosis	Not established	Adequately powered stratified randomized trial

The research goal is not to protect the hypothesis against negative data. A scientifically successful program may end by rejecting the strong bile-causation claim, validating a nonspecific metabolic biomarker, or discovering an actionable but rare physiological subtype. Each outcome would clarify the field.

8. Discussion

8.1. Mechanistic plausibility does not establish common causation

The attraction of a unifying bile-brain theory lies in the number of physiological interactions it can potentially accommodate. That same flexibility is its greatest scientific liability. Liver metabolism, intestinal microbes, immune activity, mitochondrial function and brain signaling interact through many pathways; merely drawing arrows among them cannot determine which direction is operative in humans. A parsimonious explanation should use the fewest causal steps required by the data and distinguish disease-specific mechanisms from general markers of ill health.

8.2. The strongest theory is likely to be conditional

A conditional hypothesis asks whether bile-acid dysregulation contributes to a defined phenotype in a definable set of patients. It predicts a specific molecular signature, a mechanistically credible tissue effect, and an interaction with a targeted treatment. Importantly, successful adjunctive therapy would not necessarily imply that bile-acid changes initiated the illness. A drug may modify a downstream pathway without correcting genetic or neurodevelopmental vulnerability.

8.3. Diet is a separate testable exposure

The present evidence does not warrant claims that ordinary seed oils cause psychosis, that animal fats are uniquely required for steroid hormone synthesis, or that a vegan diet intrinsically causes schizophrenia. Nutrient deficiency and actual fat malabsorption are legitimate medical problems, and repeated high-temperature fat oxidation raises independent food-chemistry questions. These concerns must be evaluated separately from the hypothesis of abnormal bile-acid receptor signaling. Experiment 09 is designed to test dietary effects without assuming the answer.

8.4. What would make the theory clinically important?

A clinically meaningful advance would emerge if a prospectively defined biochemical signature identified a subgroup whose symptoms, functioning or longitudinal prognosis improved with a well-tolerated mechanism-specific intervention. The improvement would have to exceed established care, justify any additional testing burden, and replicate across research settings. A negative result would be equally informative if the study achieved target engagement and excluded a clinically meaningful effect with adequate precision.

9. Limitations of this manuscript

This is a narrative, hypothesis-driven critical appraisal rather than a preregistered systematic review. The cited studies were selected for biological and methodological relevance, not by an exhaustive database search with formal risk-of-bias adjudication. Some mechanistic evidence comes from rodents or cultured cells and should not be treated as evidence of human clinical benefit. Rare-disease findings have limited generalizability to common psychiatric syndromes. The proposed study sizes and designs are illustrative, and no new empirical data or meta-analysis were generated for this paper.

The paper also cannot determine whether any particular circulating bile-acid abnormality is causal, compensatory or secondary in a given patient. The current evidence does not justify treating primary schizophrenia with UDCA, prolonged fasting, dietary fat manipulation or experimental microbiome interventions outside appropriate research or established indications.

10. Conclusion

Disorders of sterol synthesis, lipid trafficking and nutrient absorption establish that metabolic disturbances can cause neurological injury and psychiatric manifestations. Laboratory evidence further supports receptor- and compartment-specific actions of bile acids, while small human studies report altered serum profiles in psychosis and depression. Nevertheless, the causal bridge from circulating bile acids to clinically relevant neural exposure, psychiatric symptom generation and reproducible treatment response has not been built.

The next advance will not come from another broad assertion that metabolism matters. It will come from a sequence of disconfirmable experiments that resolves the molecular species, the affected compartment, the pathway, the temporal direction and the subgroup-specific therapeutic effect. The near-term priority is independent case-control replication under rigorous collection conditions, followed by disease-specific controls and prospective temporality. Intervention is justified only after relevant human physiology and safe target engagement have been established.

Bottom line. The bile-brain hypothesis is scientifically plausible as a conditional, mechanism-specific contributor to selected neuropsychiatric phenotypes. It is **not** established as a general cause of psychosis or as a rationale for routine bile-acid treatment. The proposed ten-study program is designed to distinguish those outcomes.

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Verified primary and methodological sources. DOI/URL links are active in the PDF. References are selectively chosen for relevance; this is not a systematic bibliography.

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Document and methodological statement

Classification: Original hypothesis and research agenda based on a critical narrative synthesis. **Research status:** No experiment proposed in this paper is represented as completed, enrolled or registered. **Authorship:** Prepared for Absurd Health Institute without attribution of patient data or external investigator authorship. **Clinical caution:** The document does not replace established diagnostic, psychiatric, neurological or hepatobiliary care. **Evidence cutoff:** 16 October 2026.