Depression Research — Gaps, Cross-References & Frontiers

A critical map of what we don't know, the connections no one has made, the live pipeline, and the datasets to mine

Objektiv AI · Claude (Anthropic) — machine-generated from open, peer-reviewed sources. Not medical advice.

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1. Why this document

The companion *Comprehensive Evidence Synthesis* maps what is reasonably established about the causes of depression. This document does the opposite and arguably more useful job: it maps the **edges** — where the evidence is thin, contradictory, or missing; the **cross-references** that fall between disciplines and have never been tested together; the **research that is live right now**; and the **datasets** large enough to actually settle some of these questions. It is deliberately skeptical. The goal is to point a real research program (and a public project) at the highest-value unknowns rather than re-litigating the settled.

A single theme runs through all of it: depression research is rich in **single-exposure associations** and poor in **causal, cross-domain, interaction-aware** evidence. The opportunity is to mine the interaction space — combinations of exposures acting through shared biology — using the large datasets now available, with the discipline (pre-registration, replication, causal triangulation) that the field has often lacked.

2. The biggest gaps and contradictions

1. The serotonin theory was dismantled but never replaced. The 2022 umbrella review found no consistent serotonin–depression link; the 36-author rebuttal defended nuance but produced no replicated alternative. The field lacks a falsifiable, mechanism-level successor. *Resolve by:* pre-registered metabolomic + SERT-PET studies in never-medicated, deeply phenotyped cohorts with genetic controls.

2. Neuroinflammation: causal direction is genuinely contested. IL-6 and CRP are elevated in depression, and some Mendelian-randomization (MR) studies support a causal role for IL-6 — but others find weak or null effects for CRP, and results shift with the choice of genetic instrument, raising instrument-validity concerns. *Resolve by:* well-powered, multi-instrument, subtype-stratified MR (inflammatory vs non-inflammatory depression).

3. BDNF/neuroplasticity contradicts itself by brain region. BDNF is down in hippocampus/PFC but *up* in amygdala/nucleus accumbens in depression — opposite predictions from one model. Peripheral BDNF is a weak biomarker, and no human evidence shows plasticity change is *necessary* (vs merely correlated) for recovery.

4. Antidepressants: the same effect size, opposite conclusions. All major analyses agree the drug–placebo gap is small-to-moderate (SMD ≈ 0.30); FDA-file analyses show published trials overstate effects by ~50%. Whether this is "clinically meaningful" remains unresolved because the field has no agreed threshold.

5. Gut microbiome: animal causation, human ambiguity. Rodent FMT transfers depression-like behaviour, but human taxa-level MR is inconsistent and FMT RCTs are small, mostly secondary-outcome, and heterogeneous in delivery and donor. The 2025 meta-analysis (12 RCTs, n≈681) shows a large effect but "substantial heterogeneity."

6. Exercise: large claimed effects, fragile designs. The 2024 BMJ network meta-analysis suggests exercise rivals antidepressants, but exercise trials are essentially unblindable, effects shrink when high-bias studies are removed, and control conditions are rarely expectation-matched.

7. Social media and youth depression: direction unresolved. A 2025 within-person cohort suggests use precedes symptoms; other work emphasises reverse causation; effect sizes are small (r ≈ 0.05–0.21). Objective device logging and randomized restriction trials are needed.

8. Childhood adversity is the strongest risk factor — and the hardest to make causal. ACEs cannot be cleanly genetically instrumented (parental behaviour, exposure and child genetics are correlated), so the causal pathway (epigenetic HPA/immune programming) remains plausible but unconfirmed at the human level. Gene × early-environment studies are underpowered.

9. Vitamin D and omega-3: associations shrink in mega-trials. Observational links are strong; VITAL and MooDFOOD found no prevention benefit in healthy/replete populations; omega-3 helps existing (inflamed) depression but not prevention. Much of the observational signal is reverse causation and lifestyle confounding.

10. Psychedelics: functional unblinding threatens every estimate. Participants guess allocation with near-perfect accuracy; under matched-expectancy conditions, psilocybin's advantage over active comparators narrows sharply. Expectancy may explain much of the effect. Active-placebo designs are essential.

11. The missing-heritability gap. Twin heritability ≈ 37%; GWAS SNP-heritability ≈ 8–10%; polygenic scores predict only ~2–3% of clinical variance. No coherent model integrates rare variants, GxE and assortative mating.

12. One label, hundreds of disorders. DSM-5 major depression admits 227 symptom combinations; neuroimaging/biomarker work finds 2–6 biotypes that don't map onto DSM specifiers. Treating depression as unitary in causal research dilutes real, subtype-specific effects.

3. Field-wide methodological problems

Cross-sectional dominance (temporal order unknown); pervasive reverse causation (depression itself changes diet, sleep, smoking, biology, even blood–brain-barrier permeability); publication bias (~50% inflation in antidepressant trials); self-report measurement error (PHQ-9 agreement with clinical diagnosis is poor); functional unblinding in behavioural/psychedelic trials; small N and the winner's curse; weak animal-to-human translation; diagnostic lumping; and **WEIRD-sample bias** — the causal evidence base is overwhelmingly Western, while the highest burdens sit in under-studied low- and middle-income populations.

4. Unexplored cross-references and interaction hypotheses

These are specific, testable bridges between literatures that rarely meet. Each is flagged with how it could be tested.

1. **Microplastics → gut dysbiosis → kynurenine shift → depression.** Dietary microplastics may shift the microbiome to upregulate IDO1, diverting tryptophan to neurotoxic kynurenine. *Test:* fecal microplastic quantification + 16S + plasma kynurenine/tryptophan + PHQ-9 in an existing cohort.
2. **PM2.5 × polygenic risk → IDO1-mediated neuroinflammatory depression.** A confirmed gene×pollution interaction (OR ~3.2 at high PRS + high PM2.5) may be mediated by kynurenine metabolism. *Test:* UK Biobank — residential PM2.5 × depression PRS × quinolinic/kynurenic ratio, causal mediation.
3. **Ultra-processed food as a bundled vector.** Emulsifiers + microplastics + low fibre + glycaemic load + aluminium may jointly collapse the gut barrier and raise IL-6, rather than any single ingredient. *Test:* composite "UPF toxicity index" + IL-6 trajectory + PHQ-9 in a dietary cohort/RCT.
4. **IL-6 as the shared mediator across smoking, UPF, pollution, loneliness, poor sleep.** A combined "inflammation load" score may predict depression better than any single exposure, with diminishing returns after IL-6 saturation. *Test:* SEM with repeated IL-6 in a longitudinal survey.
5. **Cadmium as the hidden mediator of the smoking–depression link.** Much of smoking's effect may run through cadmium (oxidative stress, zinc competition), not nicotine. *Test:* NHANES — urinary cadmium + selenium + PHQ-9 + smoking, mediation.
6. **PFAS × thyroid × circadian rhythm.** PFAS suppress thyroid hormones that entrain clock genes; chronic low-grade hypothyroxinaemia may desynchronise circadian/serotonin rhythms. *Test:* NHANES PFAS subsample + free T4 + actigraphy + PHQ-9.
7. **Non-additive PFAS + heavy-metal mixtures.** A 2025 finding that PFOS *antagonises* metal effects on depression suggests additive models are wrong. *Test:* in-vitro dose-grid (cadmium + PFOS) then BKMR in NHANES.

8. **Early adversity × prenatal pollutant window → epigenetic inflammatory phenotype.** Concurrent psychosocial and chemical "hits" may potentiate HPA/immune methylation beyond additivity. *Test:* ABCD/AURORA — ACE scores + prenatal exposure proxies + NR3C1/FKBP5 methylation.
9. **Gut–liver–brain axis: subclinical fatty liver (MASLD) as a hidden driver.** UPF-driven liver inflammation may produce a distinct anhedonic "metabolic depression." *Test:* UK Biobank MRI liver-fat + IL-6 + PNPLA3 MR.
10. **Vagal tone (HRV) as a moderator of inflammatory vulnerability.** Low HRV may mark a deficient anti-inflammatory reflex, so any pro-inflammatory exposure hits harder. *Test:* wearable HRV × pollution/diet load × later PHQ-9, moderated mediation.
11. **Light-at-night × metabolic dysfunction.** Chronic LAN may suppress BMAL1, impair insulin sensitivity and raise inflammation. *Test:* UK Biobank accelerometry + satellite night-lights + metabolomics → depression.

Top priorities (feasible with existing data, high novelty): #6 (PFAS×thyroid×circadian — NHANES already holds every variable), #2 (PM2.5×PRS×kynurenine — UK Biobank), #9 (MASLD via PNPLA3 MR — strong instrument), and #1 (microplastics×gut×kynurenine — near-zero prior literature).

5. Ongoing research and the near-term pipeline

Psychedelics. Compass Pathways' COMP360 psilocybin met its primary endpoint in *both* Phase 3 trials (COMP005, COMP006) for treatment-resistant depression; long-term data and a full FDA submission are expected through 2026 — potentially the first psychedelic medicine approval. Cybin's CYB003 (deuterated psilocybin) is in Phase 3 (APPROACH/EMBRACE/EXTEND) as an adjunct for major depression. MDMA-assisted therapy for PTSD was **rejected** by the FDA (2024) over blinding and data-integrity concerns — a cautionary precedent.

Inflammation-stratified treatment. A tocilizumab (IL-6 blocker) RCT in inflamed treatment-resistant depression is underway; meta-analyses now show anti-inflammatory agents work *specifically* in elevated-CRP patients, pushing the field toward mandatory biomarker stratification.

Genetics. The PGC's 2024–25 depression GWAS (688,808 cases) found 697 loci and, for the first time, implicated specific neuronal cell types — opening a GWAS-to-drug-target pipeline and far stronger MR instruments.

Exposome. EU's EXPANSE integrates exposome + health data on tens of millions of Europeans (with a dedicated social-exposome/mental-health arm); NIEHS's HHEAR lets any US cohort add untargeted chemical profiling — the infrastructure for ExWAS at scale now exists.

Metabolic psychiatry. Oxford's DIME ketogenic-diet RCT for treatment-resistant depression reported (2026) a 25% vs 9% remission signal; Basel's KETO-MOOD tests whether microbiome change mediates the effect.

Microbiome & microplastics. FMT/psychobiotic trials continue; microplastics-and-brain work is moving from hazard identification (bioaccumulation confirmed) toward exposure–outcome studies.

Inflection points (1–3 years): a possible psilocybin approval; the first CRP-stratified anti-inflammatory results; the first GWAS-derived drug target entering trials; and confirmation (or not) of metabolic/ketogenic and microbiome causal effects.

6. The datasets to mine

Mega-cohorts/biobanks. UK Biobank (~500k; genetics, 1,500-field exposome, imaging, accelerometry, metabolomics/proteomics, NHS linkage) — the workhorse for MR and ExWAS. All of Us (~800k, diverse, EHR + WGS + wearables) — replication and equity. MoBa, ALSPAC, Generation Scotland — developmental and family-based designs. NESDA — deep biological subtyping.

Epidemiology/surveillance. NHANES (open; ~250 chemical analytes + PHQ-9) — the chemical-exposome discovery engine. IHME GBD / GHDx and WHO GHO — country-level burden for ecological and mapping work.

Genetics. PGC MDD summary statistics (open) — MR instruments; FinnGen (register-linked GWAS, open sumstats); Million Veteran Program (diverse, EHR-linked).

Microbiome. American Gut/Microsetta and the Dutch Microbiome Project/LifeLines — MbWAS and microbiome–metabolome–depression triangulation.

Environmental layers. US EPA air quality, ACAG global satellite PM2.5, and VIIRS night-lights — link to any geocoded cohort for pollution and light-at-night hypotheses.

Exposome initiatives. EXPANSE (EU) and HHEAR (NIEHS) — continental-scale exposure characterisation.

Best triangulation combinations. ExWAS discovery in NHANES → replication in UK Biobank → diverse replication in All of Us. MR for PM2.5/IL-6/smoking using PGC + FinnGen + MVP instruments (check cross-ancestry concordance). Microbiome MR (Dutch Microbiome/Microsetta sumstats) → PGC outcome, with NESDA for mechanism. Developmental chain MoBa → ALSPAC → ABCD. Global ecological panel: GBD burden + satellite PM2.5 + night-lights + WHO treatment-gap.

7. What to do first

1. **Run the four "desk-ready" interaction analyses** (PFAS×thyroid×circadian in NHANES; PM2.5×PRS×kynurenine and MASLD-PNPLA3-MR in UK Biobank; microplastics×gut×kynurenine where samples exist) — all feasible with existing data and high novelty.
2. **Adopt subtype stratification** (at minimum CRP-high vs CRP-low) in every analysis to stop diluting real effects.

3. **Pre-register and hold out replication cohorts** before any AI/ML interaction-mining; report nulls.
4. **Build the global ecological panel** to contextualise the map and test whether rising urbanisation/pollution precedes rising burden.

8. Sources (selected)

Serotonin umbrella review (Mol Psychiatry 2022) — https://pubmed.ncbi.nlm.nih.gov/35854107/ · 36-expert reply — https://pubmed.ncbi.nlm.nih.gov/37322062/ · MR of depression — review (PMC10666459) — https://pmc.ncbi.nlm.nih.gov/articles/PMC10666459/ · Encompassing MR of MDD (Nature Mental Health 2025) — https://www.nature.com/articles/s44220-025-00471-x · IL-6 MR — https://www.sciencedirect.com/science/article/pii/S0889159121000842 · Exercise network meta-analysis (BMJ 2024) — https://pubmed.ncbi.nlm.nih.gov/38806193/ · Vitamin D dose-response meta-analysis — https://www.cambridge.org/core/journals/psychological-medicine/article/effect-of-vitamin-d-supplementation-on-depression/8F18452740B621CC04F441F037A2513B · Expectancy in psychedelic trials — https://www.sciencedirect.com/science/article/abs/pii/S2451902224000557 · PRS×environment systematic review — https://www.nature.com/articles/s41398-025-03793-7 · FMT meta-analysis — https://pmc.ncbi.nlm.nih.gov/articles/PMC12536323/ · Air pollution × gene interaction (GWEIS) — https://www.sciencedirect.com/science/article/pii/S0147651324011977 · UPF & gut barrier (Nat Rev Gastro Hepatol 2024) — https://www.nature.com/articles/s41575-024-00893-5 · PFAS×metals mixture & depression (PMC12194989) — https://pmc.ncbi.nlm.nih.gov/articles/PMC12194989/ · Gut–liver–brain axis (2025) — https://onlinelibrary.wiley.com/doi/10.1155/mi/6733477 · Microplastics in human brain (Nature Medicine 2024) — https://www.nature.com/articles/s41591-024-03453-1 · PGC depression GWAS (Cell 2024) — https://www.cell.com/cell/fulltext/S0092-8674(24)01415-6 · Compass COMP006 — https://ir.compasspathways.com/ · DIME ketogenic RCT — https://pubmed.ncbi.nlm.nih.gov/41637092/ · EXPANSE — https://expanseproject.eu/ · HHEAR — https://hhearprogram.org/ · UK Biobank — https://www.ukbiobank.ac.uk · All of Us — https://www.researchallofus.org · NHANES — https://wwwn.cdc.gov/nchs/nhanes/ · IHME GHDx — https://ghdx.healthdata.org/ · PGC downloads — https://pgc.unc.edu/for-researchers/download-results/ · FinnGen — https://www.finngen.fi/en/public-data-releases · Million Veteran Program — https://www.research.va.gov/MVP/

Compiled with AI assistance — Objektiv AI · Claude (Anthropic), 2026-06-13. A fuller source register is in data/master_sources.csv and the project's 21_source/ files. Most exposure findings cited are observational; causal claims rest on Mendelian-randomization and trials and are labelled as such.