Depression — What Actually Causes It?

A Comprehensive Evidence Synthesis (Foundation v2.0)

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Not medical advice.

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1. Executive summary

Depression is the leading cause of disability worldwide — roughly **332 million people** as of the Global Burden of Disease 2021 estimates — and its burden is still rising. Yet the explanation most people carry, that depression is simply a **serotonin "chemical imbalance,"** has collapsed under the weight of its own evidence. After six parallel deep-research reviews of the current literature (biological, environmental, dietary/gut, lifestyle, psychosocial, and treatment), one conclusion is unavoidable: **depression has no single cause.** It is the common end-point of many interacting pathways.

What we *can* piece together is more useful than a single villain. The strongest causes cluster into a small number of categories, and — crucially — many of them appear to **converge on the same downstream biology**: chronic, low-grade **neuroinflammation**, a dysregulated **stress-hormone (HPA) axis**, and **oxidative stress**, which together degrade neuroplasticity and mood regulation. This "convergence funnel" is the organising hypothesis of this document. It is testable, it explains why so many different exposures each show a small effect, and it tells us both what to **measure** (inflammatory and stress biomarkers) and what to **target** (the funnel, not just each input).

Three headline takeaways:

- **The heavyweight causes are developmental and social.** Childhood adversity/trauma and loneliness are among the most strongly evidenced — and most modifiable — population-level drivers. They should not be eclipsed by the (real but generally smaller) chemical exposures.
- **A short list of factors has genuine *causal* support** (from genetics and trials), not just correlation: childhood adversity, loneliness, smoking, physical inactivity, insomnia, inflammation (IL-6), and metabolic dysfunction. These are where prevention and treatment have the most leverage.
- **Many popular beliefs are wrong or overstated** — including the "pristine community has no depression" myth, the idea that psilocybin "detoxes" the brain, that

taurine is harmful, and that "detox" cleanses cure anything. Correcting these sharpens the project rather than weakening it.

2. How to read this synthesis

This report keeps every theory open but follows the evidence, and it deliberately separates **association** (a statistical link, easily confounded) from **causation** (supported by genetics or trials). Throughout, each factor carries an explicit **evidence grade**:

Grade	Meaning
Causal (strong)	Supported by Mendelian randomization (genetic natural experiments) and/or randomized trials.
Robust	Consistent large prospective cohorts/meta-analyses; causation likely but not nailed.
Moderate	Real association across studies; substantial confounding remains.
Emerging	New or mechanistic signal; human causal evidence immature.
Contested	Evidence mixed, weak, or actively disputed.

A companion machine-readable file (data/exposure_evidence_matrix.csv, 40 factors) and a master source register (data/master_sources.csv, 52 sources) accompany this report and power the public website's interactive table.

3. The reframe: from "chemical imbalance" to a system

In 2022 a widely-read umbrella review (Moncrieff et al., *Molecular Psychiatry*) found **no consistent evidence** that depression is caused by low serotonin. A 36-author rebuttal countered that serious researchers never held the simplistic version, and that serotonin still matters to how some drugs act — but both sides agree the "low serotonin = depression" story is not supported. Antidepressants (SSRIs) do help many people with moderate-to-severe depression (network meta-analysis of 522 trials, Cipriani 2018), but they likely work through **neuroplasticity and anti-inflammatory** effects, not by correcting a deficiency.

What replaced the imbalance model is the **biopsychosocial** consensus: biological, psychological and social factors continuously interact, and **no single factor explains a large share of risk.** The productive question is therefore not "what is *the* cause?" but **"how do the causes interact, and where do they converge?"**

4. The convergence model — the pattern

If there is a unifying pattern, the strongest candidate is the body's **inflammation–stress–oxidation axis**:

- **Neuroinflammation.** Meta-analyses repeatedly find elevated **IL-6, CRP and TNF-α** in depression, and Mendelian randomization supports a **causal** role for IL-6. An estimated 30–50% of patients have an "inflammatory subtype."
- **HPA-axis dysregulation.** Chronic stress keeps cortisol/CRH elevated, damaging the hippocampus and feeding back into inflammation.
- **Oxidative stress and mitochondrial dysfunction.** Several toxicants act here, releasing inflammatory signals that close the loop.

These three loops are **mutually reinforcing**, and they meet at shared nodes — the **kynurenine pathway** (inflammation diverts tryptophan from serotonin toward neurotoxic metabolites), **reduced BDNF/neuroplasticity**, and a more permeable **blood–brain barrier** that lets peripheral inflammation reach the brain.

The explanatory power is that **most of the exposures below plausibly feed the same funnel**: smoking raises IL-6 and delivers cadmium; ultra-processed food is pro-inflammatory and fibre-poor; air pollution, metals, mould and microplastics provoke oxidative/inflammatory responses; chronic stress, adversity and loneliness set the immune and stress thermostats high; poor sleep amplifies all of it. If correct, this is why dozens of unrelated-seeming factors each show a small association with depression — and it points to **reducing exposure *and* damping the funnel** (anti-inflammatory diet, sleep, exercise, stress/trauma treatment, and — in inflamed patients — targeted anti-inflammatories) as the route to prevention and healing.

5. The evidence, domain by domain

5.1 Biological core

Neuroinflammation (Causal — strong). The most reproducible biological signal; IL-6 has MR causal support, making it the leading hub candidate. **HPA-axis/chronic stress (Robust).** Elevated morning cortisol prospectively predicts depression. **Oxidative stress & mitochondrial dysfunction (Moderate).** Plausible shared mechanism for chemical exposures. **Low BDNF/neuroplasticity (Robust, mediator).** Suppressed by stress and inflammation; restored by ketamine, psilocybin, exercise. **Kynurenine pathway (Robust).** Explains how inflammation lowers serotonin *without* a primary deficiency. **Glutamatergic dysfunction (Robust).** Target of ketamine's rapid effect. **Polygenic genetic risk (Robust).** ~37% twin heritability; a 2024 GWAS (n=688,808) found 697 associations — risk is highly polygenic and gene×environment dependent. **Serotonin deficiency (Contested).** Not supported as a primary cause. **Blood–brain-barrier permeability (Emerging).** A gate converting peripheral exposures into brain inflammation.

5.2 Environmental & chemical exposome

Air pollution — PM2.5/NO2 (Robust). UK Biobank (n≈389,000, ~11 years): higher exposure → incident depression with no apparent safe threshold — among the strongest environmental signals, and one not on the project's original list. **Cadmium (Moderate)** — leading metal contributor in NHANES mixtures, but heavily confounded by smoking (its main source). **Lead (Moderate)**, strongest as a developmental risk. **Mercury (Contested)** — null/inverse in NHANES, a healthy-fish-eater confounder. **PFAS (Contested)** — inconsistent, sometimes antagonistic in mixtures; weaker than the popular narrative. **Microplastics/nanoplastics (Emerging).** A 2024 *Nature Medicine* study found microplastics bioaccumulating in human brain tissue, rising over time and higher in dementia brains; animal models show depressive-like behaviour. Human causation is unresolved (a leaky barrier in illness could let more in). This is the project's most promising **novel frontier**, best paired with ultra-processed food as the delivery vector. **Aluminium (Emerging)** — a real neurotoxin, but dietary sources are processed/baked goods, tea, cocoa, additives and antacids — *not* primarily energy drinks or cans. **Pesticides/organophosphates (Moderate)** — poisoning shows a strong link; chronic low-level exposure weaker. **Endocrine disruptors (Moderate)** and **mould/damp housing (Moderate)** — the latter partly psychosocial, mediated by *perceived control* over one's home.

5.3 Diet, gut & metabolic

Gut microbiome dysbiosis (Moderate, emerging causal). A meta-analysis of 12 randomized fecal-transplant trials (n≈681) found a large reduction in depressive symptoms, and microbiota transfer reproduces depression-like behaviour in animals — though trials are small and hard to blind. **Ultra-processed food (Robust).** A 2024 *BMJ* umbrella review (~9.9 million people) and pooled cohorts link higher UPF intake to depression (HR ≈ 1.22–1.32). UPF is the best candidate for a single **"vector"** bundling additives, microplastics, aluminium, low fibre, high glycaemic load and displaced omega-3. **Mediterranean/whole-food diet (Moderate, protective).** The SMILES RCT showed markedly higher remission; meta-analyses confirm benefit. **Omega-3/EPA (Robust)** treats existing (especially inflamed) depression but does **not** prevent it in healthy people. **Vitamin D (Moderate)** helps mainly when deficient. **Metabolic syndrome/insulin resistance/obesity (Robust)** — bidirectional MR shows depression causally raises metabolic syndrome; shared inflammatory biology runs both ways.

5.4 Lifestyle, substances & sleep

Smoking (Causal — strong). Bidirectional Mendelian randomization; the smoking→depression effect is **partly mediated by IL-6** — a clean example of the inflammation funnel. (Cigarette smoke carries ≈7,000 chemicals, ~70 carcinogens.) **Physical inactivity / exercise (Causal — strong, protective).** MR shows objectively-measured activity protects; a 218-trial network meta-analysis found exercise's effect **comparable to antidepressants. Insomnia / circadian disruption (Causal — strong).** Insomnia↔depression is the best-established single sleep finding; sleep also **mediates** the effects of smoking, alcohol, energy drinks and screens. **Alcohol (Robust)** — bidirectional;

the “moderate drinking protects” claim is sick-quitter bias. **Cannabis (Moderate)** — adolescent use shows a dose-dependent link to adult depression. **Energy drinks (Moderate)** — associated with anxiety/depression/suicidality in youth, most likely via caffeine + sugar + sleep disruption (not taurine). **Sedentary/TV (Moderate)** — MR implicates passive TV-watching specifically.

5.5 Psychosocial, developmental & societal

Childhood adversity/trauma (Causal — strong). Across exposome-wide analyses, ACEs are the **top-ranked** exposure for mental-health outcomes (umbrella review, n≈14.7 million; clear dose-response), biologically embedded via HPA and immune programming. **Loneliness/social isolation (Causal — strong).** Bidirectional MR confirms loneliness and depression each cause the other. **Low SES/poverty/food insecurity (Robust).** Cash-transfer natural experiments show a causal poverty→depression pathway; food-insecurity effects reverse quickly on restoration. **Discrimination/minority stress (Robust).** The ~2× higher rate in women largely reflects exposure (violence, caregiving, inequality) and measurement, not primarily biology. **Work stress/job strain (Robust). Urbanicity/low greenspace/poor housing (Moderate). Social media in adolescents (Contested).** The science is genuinely unsettled: large meta-analyses find a small-to-moderate association ($r \approx 0.09–0.21$), larger for girls and younger teens, and bidirectional — real enough to warrant attention to algorithmic/age design, but not the settled cause it is often portrayed as.

5.6 Global epidemiology

Depression burden is rising fastest in high-income regions (partly better detection, partly COVID-19, which added ~53 million cases in 2020 alone), while the largest absolute burdens sit in populous lower- and middle-income countries with the widest treatment gaps. Cross-country differences reflect measurement tools, stigma, and social conditions as much as “true” prevalence — a caution against naive between-country comparisons.

6. What we can piece together — the integrated picture

Sorting every factor by causal certainty yields a clear, defensible structure:

Tier	Factors (direction)
Causal core (act here first)	Childhood adversity ▲, loneliness ▲, smoking ▲, physical inactivity ▲ (exercise protects ▼), insomnia/circadian disruption ▲, neuroinflammation/IL-6 ▲, metabolic dysfunction ▲
Robust contributors	Air pollution ▲, ultra-processed food ▲, alcohol ▲, low SES/food insecurity ▲, discrimination ▲, job strain ▲, HPA/chronic stress ▲, omega-3

	insufficiency ▲, Mediterranean diet ▼
Moderate / context-dependent	Cadmium, lead, pesticides, endocrine disruptors, mould (partly psychosocial), gut dysbiosis, vitamin D deficiency, sugar load, cannabis, sedentary/TV, urbanicity/greenspace
Emerging frontier	Microplastics/nanoplastics, aluminium, blood–brain-barrier permeability, "metabolic psychiatry"
Contested / overstated	Serotonin deficiency, PFAS, mercury-from-fish, social-media-as-primary-cause

The **pattern** is twofold. First, the causal core is dominated by **social/developmental** factors (adversity, loneliness, SES) and **modifiable lifestyle** factors (smoking, exercise, sleep) — *not* by chemical exposures. Second, almost everything routes through the **inflammation–stress–oxidation funnel**, which is why combinations matter: the realistic future of discovery is **interaction-mining** (e.g., low-fibre diet × high cadmium × poor sleep × high genetic risk) across pooled datasets, not one-exposure-at-a-time studies.

7. Premise corrections (consolidated)

- **"Remote/pristine communities have no suicide or depression" — false.** Indigenous populations (e.g., Aguaruna/Awajún in Peru; First Nations in Canada; Indigenous Brazilians) often have **elevated** suicide tied to colonisation, cultural disruption and loss of autonomy. The protective factor is **cultural continuity and self-determination** — connection and agency, not the absence of chemicals.
- **Psilocybin does not "detox" the brain.** It is a 5-HT2A agonist that drives **neuroplasticity** and psychological flexibility within therapy.
- **Taurine is not harmful.** It is an abundant brain amino acid with antidepressant signals in animal models; in energy drinks the concerns are caffeine, sugar and sleep loss.
- **Aluminium's main source is food, not energy drinks/cans.**
- **"Detox" cleanses don't remove industrial chemicals** — though specific body-burden reduction is real (see §9).
- **Cigarettes contain ~7,000 chemicals (≈70 carcinogens)** — and smoking is one of the few *causal* exposures here.
- **Moderate alcohol is not protective.**
- **Mercury-from-fish is not an established population driver.**

8. From causes to cures — prevention & treatment

Evidence-based now: SSRIs/SNRIs (moderate–severe), CBT/behavioural activation, **exercise** (effect comparable to antidepressants), **CBT-I** for insomnia (also lowers incident

depression), ECT (severe/refractory), esketamine and rTMS (treatment-resistant). **Research-stage / promising:** psilocybin-assisted therapy (two Phase-3 trials met endpoints by 2026; not yet FDA-approved), anti-inflammatory agents **stratified by CRP/IL-6** (the inflammatory subtype), Mediterranean-diet adjunct, probiotics (third-line adjunct). **Hype / unsupported:** generic "detox" for depression, chelation in non-poisoned people, MDMA-for-depression (MDMA-for-PTSD was FDA-rejected in 2024), supplement megadosing.

The most original contribution of this project is the **synthesis itself**: showing which interventions touch the most pathways at once. For most people the **highest-leverage bundle** is: don't smoke; move daily; protect sleep; eat a whole-food, fibre-rich diet; build and defend social connection; treat trauma and chronic stress — with targeted toxicant reduction and inflammation-guided treatment as secondary, precision layers.

9. "Cleansing the body" — answered honestly

Reframe "detox" into three things that are actually supported. **(1) Cut exposure at the source** — quitting smoking (cadmium + thousands of toxicants), reducing ultra-processed food (plastics, additives, aluminium), filtering water/air, fixing damp. **(2) Evidence-based body-burden reduction for *specific* toxicants** — PFAS via fibre, blood/plasma donation, or clinical anion-exchange resin (a controlled crossover trial cut serum PFOS ~38%); supervised chelation **only** for genuine heavy-metal poisoning. **(3) Damp the downstream funnel** — sleep, fibre/plant diversity, exercise, and an anti-inflammatory diet target the inflammation/oxidation pathway where exposures actually do harm. What does **not** work: juice cleanses, charcoal, foot pads, or DIY chelation for "wellness."

10. Reproducible-research methodology & the AI discovery engine

This synthesis was produced by six parallel literature reviews and consolidated into a graded matrix. The forward research program is built to move claims **up the evidence ladder**: cross-sectional screen → prospective cohort → causal triangulation (Mendelian randomization, natural experiments) → randomized trials.

The "connections no one has made" goal is realised through **exposome-wide association studies (ExWAS)** scaled with machine learning across pooled global cohorts (NHANES, UK Biobank, All of Us, ABCD, FinnTwin and others). The method screens thousands of exposures with correction for multiple testing, mines **interactions and non-linearities** (gradient boosting, causal forests, with SHAP interpretation), layers in **multi-omics** (inflammation, microbiome, metabolomics) to test the convergence funnel, and — critically — treats every AI-surfaced pattern as a **hypothesis** that must **replicate** in an independent cohort and survive a causal test. Pre-registration, held-out replication, and publication of null results are non-negotiable guardrails; without them, broad data-mining manufactures false positives.

All data, source lists, and the scripts that build them are published for reproduction (see the project's data/ and 21_source/ folders, and the website's Methodology and Data pages).

11. Limitations

Confounding is severe (poverty, stress, sleep, smoking and diet cluster together); causation is genuinely hard to establish; reverse causation is everywhere (depression changes diet, sleep, smoking, even blood–brain-barrier permeability); measurement for the newest angles (microplastics especially) is immature; and many promising associations will not survive causal testing. This document is a **map and a research plan**, not medical advice.

12. Sources

A curated, grouped source register (52 references) is published as data/master_sources.csv and on the website's Sources page; a fuller tagged list is in 21_source/KALLFORTECKNING.md. The strongest causal evidence cited here comes from Mendelian-randomization studies (smoking, IL-6, loneliness, insomnia, physical activity, metabolic syndrome) and randomized trials/meta-analyses (antidepressants, exercise, FMT, omega-3, diet, PFAS reduction); the large majority of *exposure* findings are observational and are labelled accordingly.

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