

# Depression Research — Strengthening the Study

Self-critique & competing paradigms · quantifying causes (PAFs) · under-covered causes · the numbers · what actually prevents and heals

Objektiv AI · Claude (Anthropic) — machine-generated from open, peer-reviewed sources.  
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## Table of Contents

### 1. Why this exists

Two critical-thinking passes and three research passes were run specifically to make the project harder to fool and more useful. This report banks what they found: how to make the framing honest (red-team + competing paradigms), how to make the causal claims quantitative (population attributable fractions, E-values, avoiding double-counting), what important causes we had not yet covered, the hard population/economic numbers, and an evidence-ranked view of what actually prevents and heals depression.

### 2. Self-critique — where our framing could mislead

A skeptical reviewer would push back on five things, and they are right to:

- **The convergence funnel fits a subtype, not “depression.”** Elevated inflammation (CRP/IL-6/kynurenine) is present in roughly 25–40% of patients. Presenting a single neuroinflammation + HPA + oxidative funnel as the meeting point of all causes implies a universal biology that does not exist. Fix: label the funnel as a *subtype* model and avoid implying universality.
- **The MDD construct itself is contested.** DSM criteria generate 227+ symptom combinations; “major depression” likely is not one illness with one mechanism. Our single causal map inherits that validity problem. Fix: say so explicitly.
- **Biological framing can launder politics.** Poverty and adversity get routed into cortisol and inflammation, quietly relocating a structural problem into the individual’s brain. Fix: add a *structural/political-economy* layer — name poverty, inequality, precarity, and discrimination as “causes of the causes.”
- **WEIRD bias and modelled prevalence.** Prevalence estimates rest on instruments validated mainly in Western populations and are modelled, not measured. Fix: flag uncertainty and cross-cultural limits on the map and methodology.

- **The clinical-translation gap.** Decades of biomarker psychiatry have barely changed outcomes (STAR\*D: ~30% remit at step 1; ~67% cumulative after four steps). No biomarker yet guides routine treatment selection. Fix: state this plainly so the map doesn't imply actionable certainty.

### 3. Competing paradigms worth holding alongside ours

A serious scientist would defend several alternatives; the strongest study incorporates them rather than ignoring them:

- **Social / political-economy view** — depression as a reasonable response to bad material conditions; prevalence tracks inequality. Concede: many “causes” are downstream of political choices.
- **Network/symptom view (Borsboom)** — no latent “depression”; symptoms (sleep, rumination, anhedonia) cause each other. Implication: target high-centrality symptoms, not a presumed substrate.
- **“Stop averaging” (RDoC/biotypes)** — averaging across patients hides real subtypes; study dimensions, not the DSM category.
- **Predictive-processing / computational psychiatry** — depression as pathological precision-weighting of negative priors; a distinct, testable mechanism.
- **Evolutionary view (Nesse, Andrews)** — low mood as a partly adaptive response to unsolvable problems; cautions against treating all depressive affect as pathology.

### 4. Quantifying the causes — from a map to numbers

The biggest upgrade is to attach **population attributable fractions (PAFs)** — the share of depression that would not occur if a cause were removed — and to display *population impact* separately from *individual risk*.

Selected PAF estimates (modelled; from the 2022 meta-umbrella in *Molecular Psychiatry* and GBD 2021 risk attribution):

- Childhood maltreatment (any): PAF ~20–54% (prospective-only estimates ~20–30%); childhood sexual abuse specifically ~13.4%.
- Job strain: PAF ~17.9% (Class I evidence).
- Bullying victimisation: ~13% of DALYs in ages 15–39; intimate-partner violence ~5.7%.
- Combined metabolic cluster (obesity + inactivity + poor diet): ~10%.
- Smoking ~5–10% (partly confounded); air pollution ~2–5%; insomnia ~5–15%.

Three rules make this honest: **(1) PAFs do not sum** (overlapping causes; total preventable fraction is plausibly ~40–60%, not 100%); **(2) population impact ≠ individual risk** — a rare high-risk exposure (e.g., childhood sexual abuse, OR≈2.7) can have a smaller population share than a common low-risk one (poor sleep, air pollution); **(3) avoid double-counting mediators** — smoking→inflammation and ultra-processed-

food→obesity→inflammation share the inflammatory route, so estimate *joint* or *pathway-specific* PAFs, not a sum.

**Robustness:** report an **E-value** per association (the confounding strength needed to explain it away). For RR≈2.0 (childhood maltreatment) E≈3.4 (hard to explain away); for RR≈1.3 (air pollution) E≈1.8 (plausibly confounded). And tag each factor by **causal tier**: MR+RCT convergent / MR or natural experiment / observational with high E-value / observational low E-value.

**Recommended new visuals for the site:** a PAF bar chart with confidence intervals; a 2-D quadrant of “population impact (PAF) × individual effect (RR)” with dot colour = causal tier; an explicit *association vs causation* badge per factor; and an inflammatory-subtype toggle.

## 5. Causes we had not yet covered (high-value additions)

The map gained these factors (now on the site), each graded:

- **Medical & hormonal:** hypothyroidism (Robust), perimenopause/menopause (Moderate), PMDD / hormonal-cycle sensitivity (Robust), PCOS (Moderate), hormonal contraceptives (Moderate/contested).
- **Infection & immune:** long COVID / SARS-CoV-2 (Robust — the largest new immune-triggered cause since 2020), autoimmune encephalitis / autoimmune-depression incl. anti-NMDA-receptor (Causal for the disease; Moderate for the broader hypothesis — important because it is treatable and misdiagnosed).
- **Medical & iatrogenic:** post-stroke / vascular depression (Causal-strong), traumatic brain injury (Causal-strong), chronic pain (Robust), medication-induced depression — corticosteroids, isotretinoin, beta-blockers, interferon, some hormonal agents (Moderate).
- **Protective (under-covered):** whole-body hyperthermia / sauna (Emerging — an RCT links the IL-6 response to symptom relief), bright-light therapy (Robust seasonal / Moderate non-seasonal), purpose & meaning in life (Robust protective, large-cohort), breathwork / HRV biofeedback (Moderate).

## 6. The numbers (a quantitative impact layer)

- **Burden:** ~332 million prevalent cases; ~56 million DALYs (GBD 2021); among the top causes of years lived with disability.
- **Onset & sex:** >50% of cases begin by age ~25 (peak conditional onset ~age 15); female:male ≈ 2:1, widest in reproductive years.
- **Trend (the honest read):** absolute cases up ~59% (1990–2019) driven mainly by population growth/ageing, while **age-standardised rates are roughly flat** — except youth, where rates are genuinely rising (US adolescents reporting persistent sadness 28%–42%, 2011–2021). COVID-19 added ~53 million cases in 2020.

- **Economics:** depression + anxiety cost the global economy ~US\$1 trillion/year in lost productivity; US burden of MDD ~US\$333.7 billion (2019), of which only ~11% is direct treatment. WHO: every US\$1 invested in scaling treatment returns ~US\$4.
- **Treatment cascade:** ~33% in high-income vs ~8% in low-income countries get any care; *minimally adequate* treatment ~27% (high-income) down to ~2% (sub-Saharan Africa); first-line remission ~30%, ~67% cumulative after four steps (STAR\*D). The treatment gap exceeds 75% in low- and middle-income countries.

## 7. What actually prevents and heals — evidence-ranked

**Prevention — best-evidenced:** indicated psychological prevention (CBT/IPT for sub-threshold depression, NNT ~6–8); exercise promotion (~25% lower incident depression at ~150 min/week); multilevel anti-bullying programs (at-risk youth); poverty reduction / cash transfers (reduce distress). Promising-but-unproven at scale: perinatal CBT/IPT, nature/social prescribing, omega-3 (only in deficient subgroups), workplace organisational change.

**Treatment — best-evidenced:** antidepressants + psychotherapy (the workhorse; NNT ~7 for response); **exercise** (effect comparable to medication in mild–moderate); **task-shifted lay-counsellor therapy** (Zimbabwe’s Friendship Bench; India’s Healthy Activity Program — RCT-proven, ~US\$100/DALY); **CBT-I** for comorbid insomnia (under-used); Mediterranean-diet improvement (SMILES); internet CBT *with* human support. Promising-but-oversold: biomarker/neuroimaging/pharmacogenomic “precision” matching (CRP-stratification is closest to ready; nothing is validated for routine use), standalone mental-health apps, nature prescriptions as standalone treatment.

**The honest headline:** the highest-leverage, best-proven levers remain unglamorous — treat trauma and adversity early, keep people moving and sleeping, protect social connection, reduce poverty, and deliver good therapy at scale — with targeted toxicant/biological precision as a real but secondary layer.

## 8. Concrete upgrades applied / recommended

Applied to the site: ~15 new causes added to the interactive map; a Limitations & competing-views page; a “by the numbers” data layer; an expanded source register. Recommended next: a PAF bar chart + population-impact × individual-risk quadrant; per-factor association-vs-causation and E-value tags; an inflammatory-subtype toggle; and a structural/political-economy tier.

## 9. Sources (selected)

Meta-umbrella PAFs for mental disorders (Mol Psychiatry 2022) — <https://www.nature.com/articles/s41380-022-01586-8> · GBD 2021 risk attribution (childhood abuse, IPV, bullying) — <https://link.springer.com/article/10.1186/s12991->

025-00586-6 · Maltreatment & depression — proportional attributable fractions (Psychol Med) — <https://pubmed.ncbi.nlm.nih.gov/38717764/> · E-value sensitivity analysis (VanderWeele & Ding 2017) — <https://www.acpjournals.org/doi/abs/10.7326/M16-2607> · Pathway-specific PAFs — <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9749703/> · Biologically annotated heterogeneity / biotypes (Biol Psychiatry 2025) — <https://pubmed.ncbi.nlm.nih.gov/40633885/> · Network theory of mental disorders — <https://pmc.ncbi.nlm.nih.gov/articles/PMC5539126/> · RDoC × predictive processing (Computational Psychiatry 2024) — <https://cpsyjournal.org/articles/10.5334/cpsy.119> · Social determinants of mental health (2024) — <https://pmc.ncbi.nlm.nih.gov/articles/PMC10786006/> · Psychiatrization of poverty — <https://compass.onlinelibrary.wiley.com/doi/10.1111/spc3.12168> · GBD 2021 depression burden/trends — <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC12045679/> · COVID-19 +53M cases (Lancet 2021) — [https://www.thelancet.com/article/S0140-6736\(21\)02143-7/fulltext](https://www.thelancet.com/article/S0140-6736(21)02143-7/fulltext) · US economic burden of MDD (2019) — <https://pmc.ncbi.nlm.nih.gov/articles/PMC10499687/> · WHO return-on-investment (Lancet Psychiatry 2016) — [https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366\(16\)30024-4/fulltext](https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(16)30024-4/fulltext) · Minimally adequate treatment, 204 countries (Lancet Psychiatry 2024) — <https://pmc.ncbi.nlm.nih.gov/articles/PMC11579305/> · Age-of-onset, 29 countries (Lancet Psychiatry 2023) — [https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366\(23\)00193-1/abstract](https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(23)00193-1/abstract) · Friendship Bench RCT (JAMA 2016) — <https://www.sciencedaily.com/releases/2016/12/161229141904.htm> · Healthy Activity Program (Lancet 2017) — [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(16\)31589-6/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)31589-6/fulltext) · Exercise for depression network meta-analysis (BMJ 2024) — <https://pmc.ncbi.nlm.nih.gov/articles/PMC11131084/> · Whole-body hyperthermia RCT / IL-6 (Brain Behav Immun 2024) — <https://doi.org/10.1016/j.bbi.2024.04.040> · PMDD DASH-MC framework (Mol Psychiatry 2024) — <https://doi.org/10.1038/s41380-024-02693-4> · Post-stroke depression mechanisms — <https://doi.org/10.1016/j.pharmthera.2017.11.005> · Long COVID neuropsychiatric burden (2024) — <https://doi.org/10.3390/v16121811> · Meaning in life & mortality, UK Biobank (2024) — <https://doi.org/10.1016/j.jpsychores.2024.111971> · Bright light for non-seasonal depression — <https://pmc.ncbi.nlm.nih.gov/articles/PMC11447633/> · Depression phenotyping challenges (Nature Mental Health 2026) — <https://www.nature.com/articles/s44220-026-00629-1>

*Compiled with AI assistance — Objektiv AI · Claude (Anthropic), 2026-06-13. Estimates (PAFs, costs, prevalence) are modelled and uncertain; most exposure findings are observational. A fuller register is in data/master\_sources.csv and the project's 21\_source/files.*