



24th Annual  
Pain Medicine Meeting  
November 13-15, 2025 | Austin, TX



# Inflammatory Biomarkers in Chronic Pain Predict Psychiatric Morbidity: A Multi-Network EHR Cohort



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Background

There is an increased recognition of the role of systemic inflammation, mediated through inflammatory markers like IL-6, CRP, in pathophysiology of psychiatric disorders like depression, schizophrenia and substance abuse. While bidirectional influence of chronic pain and psychiatric morbidity is also understood, large-scale, real-world estimates on this topic remain limited. We aim to bridge this gap through a cohort study using TriNetX.

Materials and Methods

We used the TriNetX US Collaborative Network (71 health systems). Adults (≥18y) with chronic pain (ICD-10: G89.21, G89.28, G89.29, G89.4, M79.7) were stratified by inflammatory status using most-recent lab thresholds, each with ≥2 instances: high inflammation (ESR ≥20 mm/h [LOINC 4537-7], CRP ≥3 mg/L [1988-5], hs-CRP ≥3 mg/L [30522-7], or haptoglobin ≥200 mg/dL [4542-7]) vs. low (≤ these thresholds). Index was first date meeting pain + lab criteria; outcomes were assessed from day 1 to 5 years. Propensity-score matching (1:1) balanced demographics (642,785 per group post-match). We ran risk analyses excluding prior outcomes and Kaplan–Meier with log-rank tests and hazard ratios (Table 1)

Table 2. Five-year psychiatric outcomes by inflammatory status (Propensity matched)

| Outcome                                | Patients at risk (High / Low) | Risk High | Risk Low | Absolute Δ (pp) | RR (95% CI)         | HR (95% CI)         | Log-rank p |
|----------------------------------------|-------------------------------|-----------|----------|-----------------|---------------------|---------------------|------------|
| Major depressive disorder (F32/F33)    | 403,812 / 426,562             | 0.192     | 0.179    | +1.3            | 1.074 (1.064–1.083) | 1.162 (1.151–1.174) | <0.001     |
| Suicidality (R45.851, T14.91, X71–X83) | 621,052 / 626,689             | 0.021     | 0.018    | +0.3            | 1.170 (1.141–1.199) | 1.247 (1.216–1.279) | <0.001     |
| Substance use disorders (F10–F19)      | 442,281 / 485,626             | 0.115     | 0.103    | +1.2            | 1.112 (1.100–1.125) | 1.188 (1.174–1.203) | <0.001     |

Discussion:

Among adults with chronic pain, elevated inflammatory biomarkers are associated with higher 5-year incidence of MDD, suicidality, and SUD. Findings support routine mental-health screening when inflammatory markers are elevated and motivate trials testing anti-inflammatory or immunomodulatory strategies alongside standard psychiatric care. Observational design and EHR limitations (measurement variability, residual confounding) apply.

Table 1. Cohort definitions and core design choices

| Design element                                            | Specification                                                                                                                                           |
|-----------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
| Data source & setting                                     | TriNetX US Collaborative Network (71 HCOs)                                                                                                              |
| Population                                                | Adults (≥18y) with chronic pain dx: G89.21, G89.28, G89.29, G89.4, M79.7                                                                                |
| Inflammatory status (≥2 lab instances; most recent value) | High if any: ESR ≥20 mm/h (LOINC 4537-7) or CRP ≥3 mg/L (1988-5) or hsCRP ≥3 mg/L (30522-7) or haptoglobin ≥200 mg/dL (4542-7); Low if all ≤ thresholds |
| Index & window                                            | First date meeting pain + lab criteria; outcomes from day 1 to 5 years                                                                                  |
| Outcomes                                                  | MDD (F32, F33); suicidality (R45.851, T14.91, X71–X83); SUD (F10–F19)                                                                                   |
| Analysis                                                  | 1:1 propensity-score matching; risk ratios; Kaplan–Meier with HRs; exclude prior outcomes                                                               |
| Other notes                                               | All definitions and estimates from the platform-generated report.                                                                                       |

Results

After matching, MDD risk over 5 years was 19.2% in the high-inflammation cohort vs. 17.9% in low-inflammation (risk ratio [RR] = 1.074, 95% CI 1.064–1.083; HR = 1.162, 95% CI 1.151–1.174; log-rank p< 0.001). Suicidality risk was 2.1% vs. 1.8% (RR = 1.170, 95% CI 1.141–1.199; HR = 1.247, 95% CI 1.216–1.279; p< 0.001). SUD risk was 11.5% vs. 10.3% (RR = 1.112, 95% CI 1.100–1.125; HR = 1.188, 95% CI 1.174–1.203; p< 0.001) (Table 2). Absolute risk differences were +1.3% (MDD), +0.3% (suicidality), and +1.2% (SUD).

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