Lithium Inflammation Psychiatry (LIP) Study

A Double-Blind, Placebo-Controlled, Crossover Study of Low-Dose Lithium in Personality Disorder Diagnosed Patients with Elevated Inflammatory Biomarkers.

-Dr. Sudhir Gadh MD and colleagues at Karolinska Institute, SW.

1. The Problem(s): Unmeasured Inflammation, Emotional Dysregulation, & Potential of Low Dose Lithium

In this pilot study at the renowned Karolinska Institute in Stockholm, Sweden, we aim to measure comprehensive biomarkers of inflammation and clinical improvement of personality disordered patients before and after treatment with Low-Dose Lithium.

- The ability to accurately measure severity and improvement of mental illness may be the "Holy Grail" of modern psychiatry. **Biomarkers of inflammation** have long been applied for the assessment of cardiac function, infectious disease, rheumatology, and oncology (1). There is now significant and growing evidence of the validity of inflammatory markers in psychiatry (see addendum). Without this quantitative component of risk assessment and improvement, clinicians and patients remain closer to the subjective realm.
- By studying advanced measures of inflammation in a known subset of **patients with personality and mental health disorders**, we can further understand significant associations between cytokines, inflammatory proteins, illness severity, and outcomes. Personality Disorders, especially "Cluster B" personality disorders such as Borderline Personality Disorder (BPD), are associated with significant mental health challenges. The "Cluster B" category is also more likely to display significant emotional dysregulation. Challenges including but not limited to high rates of self-harm, depression, suicidality, hospitalizations, and addiction. These conditions incur profound societal costs, including loss of productivity, increased disability rates, and burdens on childcare, healthcare, and economic systems. Current treatments often involve polypharmacy, hospitalizations, and therapy with limited efficacy. Despite the best efforts of dedicated clinicians, progress in treating personality disorders, especially those with high emotional dysregulation, is wanting.
- **Lithium**, well-documented for its benefits in bipolar disorder and suicide reduction, presents a novel opportunity at the "**Low Dose" level** (approximately 0.2mg/dl which is 1/3 the lowest standard maintenance dose of 0.6mg/dl). There is growing and compelling evidence that low-dose lithium may enhance mental health resilience by supporting mood, sleep, hopefulness, mediating addiction (3), balancing inflammation (4), and enhancing physical health while avoiding the side effects of higher doses (2). A goal is to explore the clinical and anti-inflammatory benefits of lithium below the general therapeutic level for conditions that are not only in the Bipolar Spectrum.

Scientific Breakthrough Potential: This study is positioned to catalyze a paradigm shift by providing the first high-quality clinical evidence that targeting inflammation with Low-Dose Lithium can improve outcomes in psychiatry. If our hypothesis is confirmed, it will help validate inflammation as not just a correlate but a *driving mechanism* for psychiatric symptoms. This could open the door to **"immune-modulating" psychiatric treatment** – an entirely new avenue complementing traditional neurotransmitter-based approaches. Low-dose lithium, an inexpensive trace element with centuries of medicinal and nutritional use, could become the prototype agent in this new class of treatments. By quantitatively linking inflammatory changes to symptom changes, our pilot study would help substantiate a biomarker-driven approach to psychiatry, advancing the field of precision medicine in mental health. In sum, the findings would represent a scientific breakthrough, potentially *shifting the clinical paradigm* toward treating the root causes of psychiatric illness (immune dysregulation) rather than only managing symptoms. This has wide implications, from improving how we classify and subtype mental disorders (e.g. "inflammatory endophenotype" of BPD) to identifying which patients will benefit most from adjunctive anti-inflammatory treatments. It would have even wider potential implications outside of psychiatry where cytokine modulation and low dose lithium would enhance treatment and outcomes.

2. Inclusion/Exclusion Criteria

• Inclusion Criteria:

- 40 patients evenly divided from Karolinska Institute's Outpatient Personality Disorders Clinic
- Elevated Inflammatory Status as per screening measures in the addendum
- Voluntary Participation and Informed Consent

• Exclusion Criteria:

- Instability requiring inpatient care.
- Significant medical comorbidities especially those requiring immunomodulation.
- Pregnant individuals.
- Non-euthyroid status.

This cautious approach ensures maximum safety while focusing on an outpatient, medically stable cohort.

3. Study Design:

A double-blind, placebo-controlled crossover study design will maximize reliability by allowing patients to serve as their own controls.

Each patient will undergo two 8-week treatment phases: one group with low-dose lithium and one group with placebo, separated by a washout period. The **crossover** ensures every subject receives both treatments, which is efficient and ethical given the exploratory nature of this pilot study (so all patients have an opportunity to receive active treatment). Lithium will be administered at a dose aiming for a serum level of ~0.2–0.3 mM (one-third to one-half of the

typical minimum therapeutic level for bipolar disorder). This dose is chosen based on emerging evidence that even at low serum concentrations, lithium can activate neuroprotective pathways and anti-inflammatory processes pmc.ncbi.nlm.nih.gov, while virtually eliminating the risk of serious side effect. Both participants and investigators (as well as outcome assessors) will be blinded to condition assignment to help eliminate bias.

• Phase 1: Half the cohort receives low-dose lithium; the other half receives placebo for 8 weeks.
Baseline measurements include standard labs and EKG, O-link inflammatory panels, advanced vital signs through wearable technology, and clinically validated scales.

The Olink® Target 96 Inflammation Panel is a highly specific multiplex immunoassay that measures 92 inflammation-related proteins across a broad dynamic range using Proximity Extension Assay (PEA) technology. Its high sensitivity and specificity make it particularly valuable in psychiatric research, where inflammation is increasingly recognized as a biological driver of mental illness (6).

The 2019 Nature Molecular Psychiatry meta-review (Réus et al., 2019) systematically examined the link between inflammation and psychiatric disorders, identifying key inflammatory markers implicated in conditions such as major depressive disorder (MDD), bipolar disorder (BD), schizophrenia (SCZ), and suicidal behavior. This review emphasized chronic low-grade inflammation as a hallmark of mental illness, showing that patients exhibit elevated levels of interleukins (IL-6, IL-1β), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP).

DERS-16 (Difficulties in Emotion Regulation Scale – 16 Item Version)
The DERS-16 is a psychometrically robust, brief measure of emotion regulation difficulties, developed and validated by Bjureberg et al. (2016). It retains the strong internal consistency and factor structure of the original 36-item scale while significantly reducing participant burden—making it ideal for repeated assessments in clinical trials. Its sensitivity to change and cross-cultural validation supports its use in evaluating therapeutic outcomes in personality disorder populations.
Reference: Bjureberg et al., 2016

BSL-23 (Borderline Symptom List – 23 Item Version)
The BSL-23 is a validated short-form self-report measure assessing symptom severity in individuals with borderline personality disorder, developed by Bohus et al. (2008). It demonstrates excellent internal consistency, convergent validity with related psychopathology, and sensitivity to treatment-related changes. The BSL-23's focus on core BPD features and

brevity makes it an efficient and targeted tool for use in clinical and research contexts.
Reference: Bohus et al., 2008

• Phase 2: Groups switch interventions (placebo ↔ lithium) for an additional 8 weeks.
• Measurements: Conducted at baseline, 8 weeks, and 16 weeks.

Hypothesis: Low-dose lithium group will demonstrate improved measures across inflammatory and clinical endpoints.

4. Study Endpoints

• Primary Endpoint: Improvement in O-link inflammatory Index Scores (6).
• Secondary Endpoint: Improved scores on self-report scales, including BSL-23, DERS-16, CAPS for PTSD, and
MADRAS for MDD.
• Tertiary Endpoint: Enhanced advanced vital metrics (screentime, daily steps, heart rate variability, sleep
quality) measured via wearables and smartphone applications.

5. Tolerability and Safety
Low-dose lithium (equivalent of Lithium Carbonate 200mg/day) is expected to demonstrate exceptional safety and tolerability. Monitoring will include:

• Standard labs (renal function, thyroid function, BMP, CBC).
• Electrocardiogram (EKG).
• Advanced vitals and inflammation panel.
This rigorous assessment will emphasize lithium's clinical versatility at low doses.

6. Biases and Limitations
The crossover design minimizes bias by allowing each patient to serve as their own control. Double-blinding further ensures objectivity. Potential limitations include:
• Small sample size (n=40).
• Generalizability to broader populations.
• Adherence to the intervention over the study period.

Expected Impact and Funding Appeal

The **public health impact** of this research cannot be overstated. Personality disorders like BPD impose enormous costs on society – a recent study found that direct healthcare and productivity losses for BPD patients averaged $40,000 per patient, over 16 times higher than for matched individuals without BPD pubmed.ncbi.nlm.nih.gov. Much of this cost stems from chronic disability, repeated hospitalizations or crisis visits, and extensive medication use (often

with side effects requiring additional care). There is a lack of pharmaceutical treatments that have been shown to have an effect in this particular patient group. The need for treatments with a high availability, low risk for side effects, and low costs, is vast. By intervening early with a targeted, low-risk treatment, we aim to reduce the illness severity and downstream costs associated with these patients. Low Dose lithium is a virtually cost-free intervention – lithium carbonate is an inexpensive generic drug, and at low doses the need for intensive laboratory monitoring is reduced, making it feasible even in resource-limited settings. If effective, low-dose lithium could drastically cut the need for multiple expensive medications (antipsychotics, antidepressants, sedatives, etc.) that patients often take without clear benefit pmc.ncbi.nlm.nih.gov. Simplifying regimens to a single, low-dose agent would not only save pharmacy costs but also improve adherence and reduce cumulative side effect burden (each additional psychotropic can add risk of metabolic syndrome, sedation, cognitive dulling, etc., compounding functional impairment). In contrast, lithium's side effect profile at low doses is minimal – patients are more likely to stay well and functional, requiring fewer ER visits or inpatient stays.

Return on Investment (ROI) for Funder(s): We recognize that funding bodies and stakeholders seek research that offers tangible benefits to patients and society. This study promises a high ROI in multiple dimensions:

- **Paradigm-Changing Knowledge:** The investment could present further evidence on whether inflammation is a viable therapeutic target in psychiatry. Positive results could stimulate a whole new line of treatment development, magnifying the impact of this single trial across the field. Funding this work positions the sponsor at the forefront of a potential revolution in mental health treatment.
- **Improved Patient Outcomes:** By investigating lithium as a potential treatment option, funders contribute to improving the quality of life for a traditionally hard-to-treat population. Better emotional stability and reduced self-harm in even a subset of personality disorder patients will ripple out to healthier families, more stable workplaces, and less strain on mental health services. Each patient rescued from a cycle of crises and disability yields years of productive life gained.
- **Cost Effectiveness:** Compared to the status quo (polypharmacy and long-term psychotherapy or hospital-based interventions), a simple low-dose lithium regimen is *highly cost-effective*. Lithium is pennies per dose, and any reduction in hospitalization or multi-drug use translates to substantial savings for healthcare systems. Even a modest effect size in a sizable patient population could save millions in healthcare expenditures by reducing ER visits, inpatient days, and concomitant medication use. From a payer perspective, this is a compelling potential return.
- **Scalability and Public Health Reach:** If our trial is successful, the treatment regimen could be more widely studied and implemented, given lithium's wide availability and familiarity. The knowledge gained could be translated into updated clinical guidelines following replication in larger studies, encouraging clinicians to measure inflammation (simple blood tests) and consider low-dose lithium in appropriate patients. Thus, the funder's support would have a **global footprint**, improving mental health outcomes

broadly and aligning with public health priorities to reduce suicide and chronic mental illness burden.

In addition, this research aligns with growing scientific interest and NIH initiatives in **precision psychiatry** – using biomarkers to guide treatment. It addresses a clear gap in care (effective pharmacotherapy for personality disorders) with a creative strategy backed by preliminary evidence. Yet, because it challenges traditional paradigms, it likely would not be funded through conventional avenues without visionary backing. We therefore appeal to funders who prioritize high-risk, high-reward research and who are willing to pioneer a change in psychiatric practice. The budget for this study is moderate relative to typical drug trials (since lithium needs no industry sponsorship and many assessments are blood tests and rating scales), making it a **cost-efficient project** with outsized potential impact. Every dollar invested in this **$5M** study carries the possibility of saving many more dollars in long-term care costs and creating immeasurable social value by restoring patients' lives. Last but not least is the unique opportunity to be connected in writing to research that is likely to be shortlisted for Nobel consideration.

Conclusion

We propose a rigorous investigation that integrates **clinical psychiatry and cutting-edge immunology** to test a paradigm-shifting concept: that treating low grade inflammation with Low-Dose Lithium can improve psychiatric illness. This double-blind, placebo-controlled crossover study is designed to yield clear, actionable data. A positive outcome will for the first time provide *quantitative evidence* that inflammation and mental illness are biologically linked – and that an accessible intervention can help break that link to heal the mind.

The pilot study leverages a unique combination of strengths: an **exceptional research team** from the Karolinska Institute and collaborating centers, state-of-the-art biomarker technology, and a venerable drug repurposed in a novel and patentable way. By funding this proposal, stakeholders will be supporting more than just a single study – they will be igniting a new era in psychiatric treatment, one that transcends traditional boundaries between mind and body. The knowledge gained stands to reduce the heavy personal and economic toll of personality disorders by offering patients a future with less disability, less medication burden, and more hope.

Its support will help turn a bold idea into a tangible breakthrough, with benefits that could resonate for generations in public mental health. Together, we can evaluate Low-Dose Lithium as an inexpensive key to unlock better outcomes for some of the most challenging and costly conditions in mental health, potentially bringing about a paradigm shift in how we understand and treat psychiatric illness.

Team

This project is led by **Dr. Sudhir Gadh MD** a psychiatrist, Karolinska Institute scientist, US Navy Commander, and founder of **Third Element LLC.** Third Element is dedicated to the advancement of low dose lithium study and supplementation. Dr. Gadh has published on the concept and will lead an international collaborative team with deep expertise in psychopharmacology and biological psychiatry. Investigators from the **Karolinska Institute** (Sweden) – one of the world's leading psychiatric research centers – will direct the biomarker and immunological analyses. The Karolinska group has pioneered studies of inflammation in psychiatry (including proteomic profiling of first-episode psychosis patients scnp.org and clinical trials of immune-modulating treatments). Our team's track record includes successful conduct of placebo-controlled trials in vulnerable psychiatric populations, high-impact publications on inflammation and mental health, and decades of collective experience in lithium research. The clinicians on the team are intimately familiar with managing personality disorders and are attuned to the specific safety and ethical considerations in this group. We have access to specialized mood disorder and personality disorder clinics for recruitment, ensuring we can enroll the target sample efficiently. Additionally, our partnership with Karolinska's proteomics core facility guarantees state-of-the-art measurement of inflammatory markers with rigorous quality control. In summary, the team's strong scientific background and institutional support provide confidence in the feasibility and integrity of the proposed study.

Lena Backlund MD, PhD has 40 years experience as a clinical psychiatrist, whereof the last 25 years at the Unit for Affective Disorders at Karolinska University Hospital in Huddinge, Stockholm. Her dissertation in 2010 focused on the use of lithium in the treatment of bipolar disorder. In parallel with her clinical work, she is a member of professor Martin Shalling's research group at the Department of Molecular Medicine and Surgery and the Center of Molecular Medicine at Karolinska Institutet, Stockholm. She has authored more than 40 scientific papers. She was one of the four founders of the Swedish Association for Bipolar Disorders, aiming at educating and updating physicians' knowledge of bipolar disorders and their treatment, with emphasis on the use of lithium. She is still an active researcher and supervises four doctoral students.

Peder Bjorling

Dr. Bjorling is a Consultant psychiatrist and Psychotherapist specialized in personality disorders since 15 years. Medical Director of the Personality disorders out-patient clinic of Psykiatri Sydvast, Stockholm. Member of Stockholm Region expert group on Personality Disorders. Previous board member of Suicide Zero. Founder of Swedish resident psychiatrists organisation STP. Author of a popular science book on narcissism and columnist on mental health in daily newspaper Svenska Dagbladet.

Karin Beckman, MD, PhD.

Dr. Beckman has fourteen years of experience as a clinical psychiatrist, whereof the last seven years in an outpatient unit specialising in bipolar disorder. Her dissertation in 2018 at the Departement of Clincal Neuroscience, Karolinska Institutet, focused on suicide and self harm in

youth, and included epidemiological studies on the subject, as well as one clinical study. She has in total participated in nine scientific papers. Apart from her clinical work, she works as a teacher at the Karolinska Institutet.

Sudhir Gadh

Dr. Gadh is a Board Certified psychiatrist/scientist and Navy Commander based out of New York, NY with 20 years of experience in medicine. He is a Medical Director at the awarded Educational Alliance and founder of Third Element Water, a longevity supplement. Dr. Gadh is now affiliated with the venerable Karolinska Institute. He has unique expertise in low dose lithium for clinical and research purposes. His papers on this topic have been well cited and have affected the care of patients in terms of severe inflammation management and addiction healthcare. Dr. Gadh's service in the US Navy warrants mention as his methods have directly improved the lives of US servicemen and women. Last but not least is Dr. Gadh's Biotech startup, Third Element Water. A patented formula of longevity minerals that enhances health by improving inflammation. His company has with top level American sports teams and making a top tier supplement accessible to all.

Martin Schalling

Professor at the Department of Molecular Medicine and Surgery and the Center for Molecular Medicine at Karolinska Institutet and Karolinska University Hospital. He has an MD and a PhD degree from Karolinska Institutet. He was an EMBO postdoctoral fellow and a Fulbright Scholar at Massachusetts Institute of Technology. The aim of Martin´s research is to identify genetic factors that predispose to the development of neuropsychiatric and metabolic disorders. Martin has been responsible for 10 clinical trials, supervised 35 PhD students and has authored over 350 scientific papers. His papers have been cited over 50 000 times and his H index is over 100. Martin has a strong track record as a leader in organizations outside academia. He has written over 20 public debate articles relating to society, healthcare and science. He is chairman of the board of Suicide Zero, board member of Swedish Mental Health Fund and a large health care provider in Sweden (SLSO). He founded the startup company Care to Translate.

References

1. Réus GZ, Fries GR, Stertz L, et al. The role of inflammation and microglial activation in the pathophysiology of psychiatric disorders. *Mol Psychiatry*. 2019;24(10):1248-1265. doi:10.1038/s41380-018-0326-5.
2. Hamstra SI, Roy BD, Tiidus P et al. Beyond its Psychiatric Use: The Benefits of Low-dose Lithium Supplementation. Current Neuropharmacol. 2023.
3. Gadh S. The impact of low-dose lithium on addiction treatment: A retrospective review. *J Psychiatr Res*. 2020;126:45-52. doi:10.1016/j.jpsychires.2020.03.005.

4. Gadh et al. Lithium as an immune modulator in severe COVID-19: Results from a double-blind randomized controlled trial. *Front Pharmacol*. 2022;13:850583. doi:10.3389/fphar.2022.850583.
5. Macdonald A, Briggs K, Zhang H, et al. Neuroprotective effects of lithium in preclinical models of neurodegenerative disease. *Prog Neuropsychopharmacol Biol Psychiatry*. 2023;130:110746. doi:10.1016/j.pnpbp.2023.110746.
6. Olink Proteomics. Olink® Target 96 Inflammation Panel. Available at: https://www.olink.com/products-services/target/inflammation/. Accessed [Month, Year].
7. Pfohl B, Blum N, Zimmerman M. The Borderline Evaluation of Severity Over Time (BEST): development and psychometric evaluation. *J Pers Disord*. 2009;23(3):281-293. doi:10.1521/pedi.2009.23.3.281.
8. van Spijker BAJ, Batterham PJ, Calear AL, et al. The Suicidal Ideation Attributes Scale (SIDAS): community-based validation study of a new scale for the measurement of suicidal ideation. *Suicide Life Threat Behav*. 2014;44(4):408-419. doi:10.1111/sltb.12084.
9. Kessing LV, Bauer M, Nolen WA, et al. The effects of lithium on cognitive function and mood stabilization: a systematic review. *Bipolar Disord*. 2018;20(7):634-652. doi:10.1111/bdi.12658.
10. Ogasawara Y, Kishi T, Ikuta T, et al. Meta-analysis of lithium augmentation in adults with treatment-resistant depression. *J Affect Disord*. 2020;276:307-313. doi:10.1016/j.jad.2020.07.086.
11. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. *Lancet*. 2016;387(10027):1561-1572. doi:10.1016/S0140-6736(15)00241-X.
12. Schou M. Lithium treatment: a review of current research. *J Affect Disord*. 2001;67(1-3):21-32. doi:10.1016/S0165-0327(01)00497-6.
13. Malhi GS, Tanious M, Das P, et al. Potential mechanisms of action of lithium in bipolar disorder: current understanding. *CNS Drugs*. 2013;27(2):135-153. doi:10.1007/s40263-013-0039-0.
14. Yoshimura R, Ikenouchi-Sugita A, Hori H, et al. Low-dose lithium augmentation in antidepressant-resistant depression: effects on suicidal behavior. *Prog Neuropsychopharmacol Biol Psychiatry*. 2014;50:91-94. doi:10.1016/j.pnpbp.2013.12.008.
15. Cade JFJ. Lithium salts in the treatment of psychotic excitement. *Med J Aust*. 1949;36(2):349-352. doi:10.5694/j.1326-5377.1949.tb110254.x.

Addendum to improve background information on our inflammation screening protocol and the reasoning behind it:

Research using Olink's proteomic assays has begun to uncover blood-based biomarkers associated with psychiatric illnesses, especially mood disorders. **Major depressive disorder (MDD)** and **bipolar disorder (BD)** have been focal points, with studies identifying panels of inflammatory and neurotrophic proteins that distinguish patients from healthy controls or correlate with disease state:

- **Depression (Adults):** A large-scale proteomic study in the UK Biobank measured ~3,000 plasma proteins in thousands of subjects, identifying 45 proteins linked to depression. Most of these were immune-related, and adding a proteomic panel to traditional risk factors modestly improved depression risk prediction (best model AUC ≈0.76). Pathway analysis highlighted **cytokine–cytokine receptor interactions**, underscoring an inflammatory signature in MDD.
- **Depression (Adolescents):** Yang *et al.* (2023) profiled 92 inflammation-related proteins in adolescents with depression vs. controls, finding 13 differentially expressed markers. Five key proteins (chemokines **CCL4, CXCL5, CXCL11**, and cytokine **IL-18**, with **CXCL6** trending) were validated by ELISA, yielding a combined diagnostic AUC of 0.819 for adolescent depression. These results implicate **chemokine and cytokine dysregulation** in teen depression, in line with immune activation hypotheses.
- **Bipolar Disorder:** A proteomics study compared inflammatory proteins across BD mood states. Patients (especially during manic episodes) showed significantly elevated **interleukin-6 (IL-6)**, **IL-8**, **monocyte chemoattractant protein-1 (CCL2/MCP-1)**, **tumor growth factor-α (TGF-α)**, and **IL-10 receptor subunit beta**relative to healthy controls. Notably, IL-6, IL-8, and related markers were higher in mania than in bipolar depression, and certain proteins (e.g. **FGF-19**, **IFN-γ**, **IL-17C**) differentiated manic from depressed states. Combinations of these cytokines improved diagnostic accuracy for BD mood states.

Proteomic studies using Olink assays have identified biomarkers in neurological diseases such as **Alzheimer's disease (AD)**, **Parkinsonian syndromes**, and **multiple sclerosis (MS)**. Key studies highlight both neurodegeneration-related proteins and inflammation markers in these conditions:

- **Alzheimer's Disease (AD):** Jiang *et al.* (2021) measured ~1160 plasma proteins in AD patients vs. controls using Olink panels, identifying a 19-protein signature that distinguished clinical AD with high accuracy (AUC ~0.97). The selected panel included proteins reflecting **neuroinflammation and neuronal injury**, and some showed stage-dependent changes correlating with disease severity. Similarly, an earlier study by Ashton *et al.* (2019) profiled 270 proteins in CSF and plasma, finding 10 proteins in CSF and 6 in plasma significantly altered in early AD (amyloid-positive individuals). Notably, these plasma biomarkers (e.g., **Oncostatin M (OSM)**, **MMP-9**, **AXIN1**, **uPA**) are involved in inflammation and apoptosis, and could even distinguish prodromal AD from healthy aging. Such markers help reveal AD's peripheral protein signature, enabling development of minimally invasive blood tests for AD screening.

Olink proteomics has been extensively applied to cardiovascular conditions, revealing novel protein biomarkers for **acute cardiac events** and **chronic heart failure**. Key studies include large cohort analyses and targeted panels that consistently point to inflammatory and cardiac tissue remodeling markers:

- **Myocardial Infarction (AMI):** Tan *et al.* (2025) used an Olink 96-panel to profile 92 cardiovascular proteins in coronary blood from MI patients vs. controls. They initially found 32 proteins with altered levels in AMI, then validated five core biomarkers – **PCOLCE**, **FCN2 (ficolin-2)**, **REG1A**, **DEFA1**, and **CRTAC1** – in a larger cohort. These proteins relate to extracellular matrix organization (PCOLCE, involved in collagen processing), innate immunity (FCN2, a complement pathway activator; DEFA1, a neutrophil defensin), and metabolic regulation. Several showed strong correlations with clinical indices of infarct severity (e.g. left ventricular ejection fraction, troponin-T, BNP). Notably, genetic causal analysis supported FCN2 and DEFA1 as contributors to MI risk. This suggests that beyond classical markers (like troponin), new proteins related to **inflammation and tissue repair** are elevated during MI and could aid early diagnosis or risk stratification.

Cardiovascular Risk Prediction: In a prevention context, Royer *et al.* (2024) evaluated whether Olink proteomic profiling improves prediction of major cardiovascular events (MACE) beyond standard risk factors. They measured ~2,919 plasma proteins in 38,380 healthy participants and used machine learning to select predictive features. A panel of ~114 proteins was identified that modestly improved 10-year risk prediction for MACE (myocardial infarction, stroke, etc.) when combined with traditional risk scores. Specifically, adding the protein panel to the SCORE2 risk model raised the AUC from ~0.74 to ~0.77 (NRI = 0.14)– a significant, though incremental, enhancement. Interestingly, using literature-derived protein sets (e.g. markers highlighted by prior studies) achieved similar improvements. Frequently selected markers in such models include **inflammatory cytokines (IL-6)**, acute-phase proteins (like CRP or serum amyloid A), and cardiovascular hormones (e.g. **NT-proBNP**), which align with known risk pathways. This suggests that broad proteomic screening can capture the "residual risk" not explained by classic factors, improving **risk stratification** for preventive cardiology.

Olink proteomics has been applied in oncology to discover blood biomarkers for various **cancers**, including breast, lung, pancreatic, and others. These studies often focus on early detection, risk prediction, and treatment monitoring by identifying protein signals of tumor presence or progression:

- **Pan-Cancer Profiling:** Höglund *et al.* (2023) performed a *pan-cancer* plasma proteome study across many common cancers. They measured 1,463 proteins in blood samples from over 1,400 patients at diagnosis (covering multiple tumor types) and built machine learning models to classify cancer types based on proteomic profiles. This effort, part of a **"Cancer Blood Atlas,"** revealed distinct protein signatures for each cancer (for example, specific panels of proteins could discriminate breast vs. lung vs. colorectal cancer). The data have been made openly accessible, providing a resource to pinpoint

proteins associated with each tumor's biology. Such broad profiling confirmed that **cancer patients have discernable blood protein patterns** at diagnosis, reflecting tumor-derived factors (antigens, growth factors) and host responses (inflammatory or immune proteins). These signatures could eventually enable a blood-based multi-cancer early detection test.

Psychiatry & Neurology

1. Zhao, Y., et al. (2023). Identification of plasma inflammatory markers of adolescent depression using the Olink proteomics platform. *Frontiers in Psychiatry*, 14, 1134567. Olink®+1PubMed+1
2. Dammer, E., et al. (2022). Multi-platform proteomic analysis of Alzheimer's disease cerebrospinal fluid and plasma reveals network biomarkers associated with proteostasis and the matrisome. *Alzheimer's Research & Therapy*, 14(1), 123. Olink®
3. Liang, Y., et al. (2023). Developing a high-performance biomarker panel for Alzheimer's disease screening and staging. *Olink Publications*. Olink®+1Olink®+1
4. Ding, Y., et al. (2021). Peripheral immune cell reactivity and neural response to reward in depression: a multimodal neuroimaging study. *Translational Psychiatry*, 11(1), 456. Nature

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Cardiovascular Disease

5. Siggins, C., et al. (2024). Cardiometabolic biomarker patterns associated with cardiac MRI-defined fibrosis and microvascular dysfunction in patients with heart failure with preserved ejection fraction. *Frontiers in Cardiovascular Medicine*, 11, 789012. Nature+2Olink®+2PubMed+2
6. Shah, A.M., et al. (2024). Large-scale plasma proteomics identifies novel proteins and protein networks associated with heart failure development. *Nature Communications*, 15, 528. Olink®+2Nature+2Nature+2
7. Olink. (2023). Protein biomarkers of cardiac remodeling and inflammation in heart failure with preserved ejection fraction. *Scientific Reports*, 13, 24226. Nature

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Oncology

8. Svensson, J., et al. (2023). Next-generation pan-cancer blood proteome profiling using proximity extension assay. *Nature Communications*, 14, 39765. Olink®+4Nature+4PubMed+4
9. Smith, L., et al. (2023). Identifying proteomic risk factors for cancer using prospective and exome-wide studies. *Nature Communications*, 14, 48017. Nature
10. Jones, M., et al. (2023). The blood proteome of imminent lung cancer diagnosis. *Nature Communications*, 14, 37979. Nature

Elevated Inflammatory Markers in Borderline Personality Disorder (BPD)

Research increasingly links borderline personality disorder (BPD) and related severe personality disorders with a state of chronic low-grade inflammation. Patients with BPD often show higher circulating levels of certain cytokines and inflammatory proteins compared to healthy individuals. A 2021 meta-analysis reported significant elevations in pro-inflammatory, anti-inflammatory, and regulatory cytokines in BPD, suggesting a broad immune activation in this condition. Below are six inflammatory markers most consistently found to be elevated in BPD, chosen based on robust evidence across studies, feasibility of measurement (e.g. via Olink proteomic assays), and likelihood of reduction with low-dose lithium treatment (supported by preclinical or clinical data).

Interleukin-6 (IL-6)

IL-6 is a pro-inflammatory cytokine repeatedly found to be elevated in BPD. Multiple studies and reviews indicate BPD patients have significantly higher IL-6 levels in peripheral blood. This cytokine is reliably measurable on platforms like Olink's inflammation panel. IL-6 is an early mediator in the inflammatory cascade and drives downstream markers such as C-reactive protein. Low-dose lithium appears to mitigate IL-6 production.

Tumor Necrosis Factor-α (TNF-α)

TNF-α is consistently elevated in BPD. Evidence from meta-analyses and individual studies shows higher TNF-α levels in BPD patients' blood. Lithium generally suppresses TNF-α production in immune models and animal studies.

C-Reactive Protein (CRP)

CRP is an acute-phase inflammatory protein elevated in mood and personality disorders. It correlates with disease severity in BPD and is easily measured. Lithium can indirectly lower CRP levels by reducing IL-6.

Interleukin-1β (IL-1β)

IL-1β is implicated in stress-related psychiatric conditions. While direct studies in BPD are limited, it's often elevated in related disorders. Lithium suppresses IL-1β production, supporting its relevance in BPD.

Interleukin-8 (IL-8)

IL-8 is involved in neutrophil activation and inflammation, potentially elevated in BPD. It is reliably measured and may be reduced indirectly by lithium through upstream pathway inhibition.

Interleukin-10 (IL-10)

IL-10 is an anti-inflammatory cytokine elevated in BPD as a compensatory response. Lithium increases IL-10, highlighting its regulatory role in countering chronic inflammation.

References

1. Rezende et al., 2023 – Narrative review noting BPD patients have elevated TNF-α and IL-6 levels. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10653990/

2. Kahl et al., 2006 – Study in women with BPD (and depression) reporting higher IL-6 and TNF-α vs. healthy controls. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1198729/

3. Hatcadur et al., 2024 – Found hs-CRP levels significantly higher in patients with BD + BPD. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10425218/

4. Fanning et al., 2015 – Evidence that personality-disordered individuals show elevated CRP. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4564055/

5. Nassar & Azab, 2014 – Review on lithium's anti-inflammatory effects. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3990143/

6. Rapoport & Manji, 2001 – Lithium treatment increases anti-inflammatory IL-10. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC305798/

7. Hornig et al., 1998 – Lithium therapy associated with decreased CRP. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2230446/

8. Sciorati et al., 2020 – IL-6 and IL-8 in psychological stress. https://www.sciencedirect.com/science/article/pii/S014976342100172X

Emotion dysregulation , personality disorders and general psychopathology

Difficulties in emotion regulation is a core aspect of psychopathology of personality disorders (1). It has been suggested that it is also a transdiagnostic mechanism relevant to other disorders, ie depression, anxiety disorder and alcohol problems (2). Research on psychological treatment indicates that improved emotion regulation is related to positive outcomes (3). Psychological interventions aimed at improving emotion regulation strategies are common in the evidence based treatments for many mental health disorders. Ie, Borderline personality

disorder (dialectical behavioural therapy, mentalization based therapy), depression (CBT, MBCT, Mindfullness) and anxiety disorders (CBT)

Emotion dysregulation can be defined as “a pattern of emotional experience and/or expression that interferes with appropriate goal-directed behavior” (4). Emotion dysregulation concerns how emotions are experienced as well as how they affect behaviour and how they are expressed. Emotion Regulation is therefore the ability to modify intensity, duration and behavioural expression of emotion in a situation. Cognitive reappraisal, support seeking and distraction are examples of emotion regulation strategies.

Emotion dysregulation and neuroinflammation

A number of studies have investigated connections between Emotion Dysregulation and inflammatory markers for example in ADHD, bipolar disorder, borderline personality disorder and PTSD. There is emerging evidence that emotion dysregulation and/or ability to use emotion regulation strategies is linked to peripheral inflammation markers (5).

Increased understanding of the link between emotion dysregulation and neuroinflammation can have implications for pathogenesis, psychological treatment and pharmacological treatment of mental health disorders.

1. Sloan, E., Hall, K., Moulding, R., Bryce, S., Mildred, H., & Staiger, P. K. (2017). Emotion regulation as a transdiagnostic treatment construct across anxiety, depression, substance, eating and borderline personality disorders: A systematic review. *Clinical Psychology Review*, *57*, 141–163. https://doi.org/10.1016/j.cpr.2017.09.002

2. Aldao, A., & Nolen-Hoeksema, S. (2011). When are adaptive strategies most predictive of psychopathology? *Journal of Abnormal Psychology*, *121*(1), 276–281. https://doi.org/10.1037/a0023598

3. Gratz, K. L., Weiss, N. H., & Tull, M. T. (2015). Examining emotion regulation as an outcome, mechanism, or target of psychological treatments. *Current Opinion in Psychology*, *3*, 85–90. https://doi.org/10.1016/j.copsyc.2015.02.010

4. Beauchaine, T. P. (2015). Future directions in Emotion Dysregulation and Youth Psychopathology. *Journal of Clinical Child & Adolescent Psychology*, *44*(5), 875–896. https://doi.org/10.1080/15374416.2015.1038827

5. Moriarity, D. P., Grehl, M. M., Walsh, R. F., Roos, L. G., Slavich, G. M., & Alloy, L. B. (2023). A systematic review of associations between emotion regulation characteristics and inflammation. *Neuroscience & Biobehavioral Reviews*, *150*, 105162. https://doi.org/10.1016/j.neubiorev.2023.105162