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Commentary

# Inflammation as a driver and consequence of addiction: translating Mendelian randomization findings into psychiatric practice and research

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## Abstract

Substance use disorders (SUD) have long been diagnosed and monitored through subjective self-report, leaving a critical gap in objective biomarkers for subtyping, treatment response, and relapse prediction. Cao *et al.* provided pivotal genetic evidence for bidirectional causal relationships between addiction phenotypes and systemic inflammation using Mendelian Randomization (MR), a methodological breakthrough that opens a tangible path toward closing this gap. Building upon these genetic insights, this commentary evaluates their implications for psychiatric practice and mechanistic research. We assess cytokines such as HGF, IL-10, and M-CSF as potential biomarkers for addiction subtyping, treatment response, and relapse monitoring, and emphasize the need to shift from peripheral measures to central neuroimmune mechanisms. By incorporating the key bibliometric theme of "oxidative stress," we outline an integrative pathology framework connecting oxidative stress, inflammation, and neuroplasticity in addiction. Methodological considerations of the MR design, including population generalizability, are discussed. We conclude that addiction is not solely a brain disorder but an immunologically embedded condition, and call for trans-ethnic, longitudinal, and multi-omics studies to translate these causal clues into precision diagnostics and immunomodulatory therapies for SUD.

**Keywords:** Substance use disorders, Addiction, Inflammation, Biomarkers, Mendelian randomization, Oxidative stress

**Abbreviations:** MR: Mendelian Randomization; TUD: Tobacco Use Disorders; AUD: Alcohol Use Disorders; SUD: Substance Use Disorders; IVs: Instrumental Variables; HGF: Hepatocyte Growth Factor; IL-10: Interleukin-10; SDF-1α: Stromal Cell-Derived Factor-1α; G-CSF: Granulocyte Colony-Stimulating Factor; M-CSF: Macrophage Colony-Stimulating Factor; IFN-γ: Interferon-γ; CNS: Central Nervous System; BBB: Blood-Brain Barrier; Sirt1: Sirtuin 1

## Introduction

Tobacco and alcohol use disorders (TUD and AUD) represent a significant global public health and psychiatric challenge, contributing to immense morbidity and mortality [1,2]. Current diagnostic assessments for these SUD predominantly rely on subjective self-reporting [3], underscoring a critical need for objective biomarkers to enhance diagnostic precision, phenotyping, and disease management. Inflammatory cytokines have emerged as promising candidate biomarkers, implicated in the pathology, withdrawal, and relapse processes of both AUD and TUD [4]. However, establishing causal links in humans remains challenging, not only due to confounding and reverse causation, but also because of the predominant reliance on preclinical models and observational studies with constrained samples [5–7].

To address this pivotal gap, the study by Cao *et al.* [8] employs a bidirectional MR framework to systematically investigate genetic evidence for causal relationships between 41 inflammatory cytokines and five key addiction phenotypes. This approach represents a significant methodological advance, offering a powerful means to infer causality by leveraging genetic variants as instrumental variables (IVs), thereby mitigating issues prevalent in observational research [9]. Consequently, their work provides a novel, population-level mapping of the genetic causal network linking inflammatory pathways with addiction severity and behaviors.

Building on this methodological rigor, this commentary takes Cao *et al.*'s genetic map as a departure point to advance a translational framework interrogating the clinical and mechanistic relevance of their findings. We critically examine three questions: How does this evidence refine our understanding of addiction as a biologically heterogeneous condition? Which cytokines are most promising as biomarkers or therapeutic targets? And what methodological steps are needed to bridge population-level genetic estimates and individual treatment decisions?

While their study established population-level causal links between inflammatory cytokines and addiction phenotypes, we extend these findings by: (i) evaluating their implications for biomarker-guided subtyping and treatment monitoring; (ii) integrating the emerging bibliometric theme of "oxidative stress" to propose a unified pathological axis linking peripheral inflammation, central neuroimmune dysfunction, and neuroplasticity; and (iii) critically assessing the methodological steps required to translate MR findings into individualized psychiatric care. In doing so, we draw upon very recent literature, including 2026 studies on TSPO neuroimaging [10], HGF immunoregulatory mechanisms [11], and multi-omics MR frameworks [12], to contextualize Cao *et al.*'s findings within the evolving evidence landscape. This integrative effort is structured across four domains, methodological implications, biomarker potential, mechanistic translation, and a forward-looking research roadmap, with the overarching goal of transforming correlational legacy into causal, clinically actionable knowledge.

## Methodological Implications: Refining Causal Inference in Addiction Heterogeneity

Building on the methodological rigor of Cao *et al.*, this section examines how MR approaches refine our understanding of addiction as a biologically heterogeneous condition. We critically evaluate the methodological steps required to translate population-level genetic estimates into insights that could inform individual-level treatment decisions.

MR offers a valuable epidemiological framework for strengthening causal inference, which is particularly relevant in psychiatric research where phenotypes such as addiction are often confounded by environmental and psychosocial factors [13]. By utilizing genetic variants such as IVs, MR mimics randomization in controlled trials to isolate the effect of an exposure on an outcome [14]. In the study, weak instrument bias was appropriately mitigated through the selection of IVs with F-statistics >10 [15]. It should be noted, however, that the adoption of suggestive p-value thresholds ($p<5\times10^{-6}$ / $1\times10^{-5}$) for IV selection rather than the conventional genome-wide significance threshold of $5\times10^{-8}$ represents a deliberate methodological trade-off [15,16]. While this strategy increases statistical power by incorporating a broader set of genetic variants, it concurrently raises the potential risk of including SNPs with horizontal pleiotropic effects [16].

Understanding addiction as a biologically heterogeneous condition requires careful consideration of such methodological nuances. A fundamental assumption of MR is the absence of horizontal pleiotropy, whereby genetic variants influence the outcome through pathways independent of the exposure [17]. Although sensitivity analyses, including MR-PRESSO and MR-Egger, indicated no significant horizontal pleiotropy ($p>0.1$) [18], it is important to acknowledge that biological pleiotropy remains pervasive for complex traits [19]. Consequently, undetected or "hidden" pleiotropy, where genetic variants affect addictive behaviors via pathways separate from inflammatory cytokine levels, may still pose a limitation that could bias causal estimates [20,21]. Such biases could obscure the true heterogeneity underlying addiction subtypes, potentially masking distinct immunological profiles that characterize different patient populations. Moreover, the systematic impact of such pleiotropy on MR inferences in psychiatry has yet to be fully quantified [21].

A further limitation is the study's exclusive reliance on genetic data from European-ancestry populations [15]. Genetic architectures (e.g., allele frequencies, linkage disequilibrium) vary substantially across populations due to distinct evolutionary histories and environmental exposures [22]; thus, an IV valid in one population may not hold in another [23]. This restricts generalizability of causal estimates and potential biomarkers to non-European groups, underscoring the need for more diverse genetic studies in psychiatric research [22,24]. Emerging methods such as MR-EILLS offer a potential solution by integrating heterogeneous GWAS datasets to infer robust causal relationships [23].

Beyond these study-specific considerations, two fundamental limitations of the MR framework itself hinder translation to individual treatment decisions. First, genetic instruments reflect lifelong average predispositions rather than dynamic, state-dependent changes in cytokine levels across addiction stages [25]; thus, MR estimates cannot capture the fluctuating inflammatory milieu relevant to individual treatment response. Second, MR cannot resolve cellular source specificity, circulating cytokines originate from diverse tissues, and identifying their origins is essential for mechanistic insight and targeted intervention. Without such resolution, translating population-level estimates into individualized therapeutic strategies remains challenging.

## Biomarker Potential: Cytokines as Tools for Subtyping and Prognosis

This section addresses the second question posed in our Introduction, which cytokines are most promising as biomarkers or therapeutic targets, by evaluating a panel of circulating cytokines causally linked to smoking and alcohol use phenotypes in the study by Cao *et al.* [26]. These molecules appear not merely as consequences or drivers of addictive behaviors but active participants in their pathophysiology, holding translational potential for subtyping addiction, prognostic evaluation, and therapeutic targeting.

Among these, certain cytokines may function protectively by mitigating tissue damage, promoting repair, and suppressing detrimental inflammation, features that could define a "low-risk" or "resilient" immunological subtype. For instance, hepatocyte growth factor (HGF) exhibits immunoregulatory and cytoprotective effects

by promoting epithelial regeneration and shifting macrophages from a pro-inflammatory M1 toward an anti-inflammatory M2-like phenotype, thereby facilitating tissue repair [11]. The observed reduction in circulating HGF with increased alcohol consumption [27] and its suppression by smoking [28] suggest a diminished tissue repair capacity in individuals with substance use. Consequently, monitoring HGF could serve as a dynamic indicator of somatic health risk in addiction [29] and as a potential biomarker of recovery during abstinence. Similarly, interleukin-10 (IL-10), an anti-inflammatory cytokine, was positively associated with smoking cessation in the present study [26] and elevated during nicotine withdrawal in animal models [30]. This suggests that IL-10 may alleviate neuroinflammation mediated negative affect and craving, positioning it as a candidate biomarker for assessing withdrawal severity and response to anti-inflammatory interventions.

Conversely, elevated levels of other cytokines may contribute to addiction related complications or mark a "high-risk" clinical subtype characterized by heightened systemic inflammation and susceptibility to comorbid conditions. Stromal cell-derived factor-1α (SDF-1α) was positively influenced by daily cigarette consumption [26]. Although *in vitro* findings remain inconsistent, higher SDF-1α levels are linked to increased heart failure risk, implying its role as a mediator of smoking associated cardiovascular pathology [31,32]. Likewise, granulocyte colony stimulating factor (G-CSF) elevation upon smoke exposure reflects neutrophil activation and depletion, potentially serving as an indicator of systemic inflammation and respiratory complication risk [33–35]. Notably, macrophage colony stimulating factor (M-CSF) was inversely associated with the age of smoking initiation and positively with weekly alcohol consumption [26], implying a novel role in predisposing individuals to addictive behaviors, a finding that could inform early-risk stratification.

Importantly, the functions of these cytokines are context-dependent, underscoring the complexity of biomarker interpretation for prognostic purposes. While most evidence supports a positive correlation between smoking severity and interferon-γ (IFN-γ), indicating aggravated lung inflammation [36], tobacco exposure has also been reported to suppress IFN-γ secretion in certain clinical settings, such as during tuberculosis diagnosis [37]. This discrepancy highlights that IFN-γ dynamics may vary with disease state or tissue microenvironment, suggesting that its utility as a prognostic marker may require careful contextualization.

Collectively, these findings advocate integrating protective (HGF, IL-10) and risk-indicating (SDF-1α, G-CSF, M-CSF) cytokines into a multi-parameter panel for clinical translation. Such a panel could enable subtyping into distinct pathophysiological profiles, inform personalized risk stratification for complications and relapse, and identify novel therapeutic targets. Given the context-dependent roles of factors like IFN-γ, biomarker interpretation must account for specific clinical scenarios. Future research should validate these markers in longitudinal studies and integrate multi-omics data to build dynamic models for precision addiction management.

## Mechanistic Translation: From Peripheral Inflammation to Central Neuroimmune Pathways

This section deepens our understanding of addiction as a biologically heterogeneous condition by exploring the mechanistic pathways that link peripheral inflammatory markers to central neuroimmune processes. Understanding these mechanisms is essential for explaining why individuals with similar substance use patterns may exhibit different clinical trajectories and treatment responses.

The investigation by Cao *et al.* utilizes MR to establish genetic evidence for causal links between addiction phenotypes and peripheral inflammatory states [38]. However, while circulating cytokines serve as important indicators of systemic immune activation [39], the core pathology of SUD is fundamentally rooted in the central nervous system (CNS) [40,41]. Addictive substances may drive neuroinflammatory processes, either directly or via peripheral inflammation [42–44], leading to functional disturbances in key brain regions such as the prefrontal cortex and striatum, circuits critically involved in impaired cognitive control, habit formation, and relapse [40,41,45]. This peripheral-central connection may represent one source of biological heterogeneity: individuals may differ in the extent to which their peripheral inflammation translates into central neuroimmune dysfunction.

This context raises a pivotal question: can peripheral biomarkers accurately reflect these central pathological processes? Findings based on genetic variants associated with circulating cytokines [38] may not fully capture cytokine dynamics in the cerebrospinal fluid or neuroinflammation confined to brain circuits underlying addiction [40,46]. The blood-brain barrier (BBB) plays a crucial regulatory role in peripheral-central immune communication [42], and it remains to be determined whether substance-induced peripheral inflammation affects the CNS milieu by disrupting BBB integrity [42]. Interindividual variability in BBB integrity or function could therefore contribute to differential vulnerability to substance-induced neuroinflammation, further underpinning the heterogeneous nature of addiction.

Notably, recent neuroimaging advances provide direct evidence of central neuroimmune activation in humans. Beyond classical cytokines, alcohol induces neuroinflammatory effectors such as inducible nitric oxide synthase and cyclooxygenase-2 within the CNS [47]. TSPO PET studies demonstrate that acute alcohol challenge rapidly increases global brain TSPO signal (9–16%) alongside peripheral cytokine alterations, confirming rapid bidirectional immune crosstalk [48]. Chronic adaptation is also evident: women with mild-to-moderate alcohol use disorder show a pronounced reduction (~21%) in brain TSPO availability, associated with executive function impairments, indicating clinically relevant neuroimmune dysregulation [10]. These sex-specific differences further illustrate the biological heterogeneity underlying addiction phenotypes.

The identification of oxidative stress as a central research hotspot in substance abuse [38] supports the notion that oxidative stress pathways may mediate the link between peripheral and central inflammation. Both alcohol and tobacco exposure induce oxidative stress, which activates transcription factors such as NF-κB and upregulates pro-inflammatory signaling molecules like TNF-α, leading to inflammatory responses, cellular damage, and mitochondrial dysfunction [49,50]. This cascade contributes to related diseases and neuropsychiatric disorders [51]. An integrative pathological framework thus emerges: substance use promotes oxidative stress, driving inflammatory activation and neuronal damage that reinforce addictive behaviors. Conversely, genetically influenced baseline levels of oxidative stress and inflammation may

increase individual susceptibility to substance-induced neurotoxicity, offering a potential explanation for differential vulnerability across individuals.

This oxidative stress-inflammation axis may be critically modulated by the anti-aging gene Sirtuin 1 (Sirt1), which regulates appetite, nuclear-mitochondria interaction, synaptic plasticity, and neuronal proliferation [52]. Its repression, driven by overnutrition, environmental factors, or bacterial lipopolysaccharides, has been linked to immune alterations, mitochondrial apoptosis, and chronic disease [53]. Given Sirt1's regulation of FOXO and other anti-aging genes [54], investigating its dysregulation in SUD could reveal an early biomarker for addiction vulnerability and multi-organ complications. Interindividual variation in Sirt1 expression or activity may therefore represent another layer of biological heterogeneity influencing addiction susceptibility and progression.

Future studies could employ a multi-omics MR framework to examine causal pathways linking oxidative stress and inflammation in addiction. Genetic variants associated with oxidative stress biomarkers (e.g., lipid peroxidation products, DNA damage [55]) and inflammatory cytokines could be integrated using bidirectional or mediation analyses to clarify their interplay. A recent multi-omics MR study in Crohn's disease successfully dissected such mechanisms by combining oxidative stress-related gene expression, DNA methylation, and gut microbiota data [12]. Adopting a similar strategy could systematically elucidate dynamic interactions between oxidative stress and inflammation in addiction, clarifying the mechanistic basis of its biological heterogeneity.

## A Forward-Looking Research Roadmap: From Population Estimates to Personalized Intervention

Building on the bidirectional causal relationships identified by Cao *et al.*, this section outlines a roadmap for translating population-level genetic estimates into clinically actionable strategies for personalized intervention.

The bidirectional MR analyses reveal that addictive behaviors and inflammatory states exert mutual causal influences: forward-direction analysis establishes substance use as a direct contributor to immune dysregulation, while reverse-direction analysis indicates that an individual's immune profile may predispose them to addiction vulnerability, greater severity, and differential treatment responses [38]. These findings position specific cytokines as active modulators of addiction-related outcomes and inform two strategic clinical approaches. In preventive settings, baseline inflammatory profiling (e.g., M-CSF) may identify high-risk individuals for targeted early intervention. During active treatment, efforts can focus on reducing pro-inflammatory cytokines linked to consumption severity or supporting protective factors like HGF as dynamic biomarkers of recovery. Together, these findings offer a targeted framework for pharmacotherapy, guiding the design of inhibitors (e.g., against M-CSF) and enhancers (e.g., of IP-10 signaling) [38].

To bridge population-level estimates and individual treatment decisions, several methodological steps are required. First, cross-ethnic replication in non-European populations is needed to assess generalizability. Second, longitudinal designs with dynamic biomarker sampling should clarify cytokine trajectories in predicting addiction stages, treatment response, and relapse. Third, genetic findings should guide interventional trials targeting specific pathways (e.g., elevating HGF, inhibiting M-CSF). Fourth, multi-omics integration (immunomics, epigenomics, metabolomics, gut microbiome) will enable construction of a comprehensive biological network of addiction. Finally, linking inflammation-related genetic variants to neuroimaging phenotypes and cognitive-behavioral traits (e.g., impulsivity, reward sensitivity) is essential to bridge molecular mechanisms with clinically relevant outcomes.

Returning to the three questions posed at the outset of this commentary, we now assess the extent to which they have been addressed. First, the evidence synthesized here refines our understanding of addiction as a biologically heterogeneous condition by revealing that its heterogeneity arises from multiple sources: methodological limitations such as undetected horizontal pleiotropy may mask distinct immunological subtypes, while mechanistically, individuals vary in the translation of peripheral inflammation to central neuroimmune dysfunction, a process modulated by blood-brain barrier integrity, sex differences, and oxidative stress pathways, all of which converge to shape differential vulnerability and disease trajectories. Second, we have identified a prioritized panel of cytokines with translational potential, not only as static biomarkers but as dynamic indicators of withdrawal, relapse risk, and treatment response. Third, we have outlined a multi-step methodological roadmap, encompassing trans-ethnic replication, longitudinal sampling, multi-omics integration, and neuroimaging-immunology linkages, that is essential to bridge population-level genetic estimates with individualized clinical decision-making. Collectively, these contributions transform the causal clues from Cao *et al.* into an actionable framework for advancing precision psychiatry in SUD.

## Conclusion

In summary, the study by Cao *et al.* represents a significant step toward elucidating the immunobiology of addiction, and this commentary has sought to extend their genetic insights into a translational framework with clinical and mechanistic relevance. By addressing the three guiding questions, we have demonstrated how their findings refine our understanding of addiction as a biologically heterogeneous condition, identified a prioritized panel of cytokines with biomarker and therapeutic potential, and outlined a methodological roadmap to bridge population-level estimates with individualized care. Collectively, these contributions reposition addiction not merely as a brain disorder but as an immunologically embedded condition, wherein systemic and central immune pathways interact to shape vulnerability, disease trajectory, and treatment response. Realizing the clinical promise of this addiction-immune axis will require trans-ethnic replication, longitudinal biomarker validation, multi-omics integration, and ultimately, immunomodulatory trials guided by causal genetic evidence.

## Competing Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Authors' Contributions

Xiang Chen: Writing-review & editing, Writing–original draft. Longtao Yang: Writing-review & editing, Writing-original draft. Yihui Tang: Conceptualization. Ben Wu: Conceptualization. Jun Liu: Conceptualization, Funding acquisition. All authors have approved the final submitted version of the paper.

## References


1. Dey M, Awasthi D, Wali S. Causes of Tobacco Use and its Effects on Human Health: A Comprehensive Review. J Clin Diagn Res 2026 Mar 1;20(3):XD01–6.
2. Carr T, Kilian C, Llamosas-Falcón L, Zhu Y, Lasserre AM, Puka K, et al. The risk relationships between alcohol consumption, alcohol use disorder and alcohol use disorder mortality: A systematic review and meta-analysis. Addiction. 2024 Jul;119(7):1174–87.
3. Fang F, Andersen AM, Philibert R, Hancock DB. Epigenetic biomarkers for smoking cessation. Addict Neurosci. 2023 Jun;6:100079.
4. Ball J, Darby I. Mental health and periodontal and peri-implant diseases. Periodontol 2000. 2022 Oct;90(1):106–24.
5. Belkin S, Benthien J, Axt PN, Mohr T, Mortensen K, Weckmann M, et al. Impact of Heated Tobacco Products, E-Cigarettes, and Cigarettes on Inflammation and Endothelial Dysfunction. Int J Mol Sci. 2023 May 29;24(11):9432.
6. Effenberger M, Widjaja AA, Grabherr F, Schaefer B, Grander C, Mayr L, et al. Interleukin-11 drives human and mouse alcohol-related liver disease. Gut. 2023 Jan;72(1):168–79.
7. O'Neill J, Diaz MP, Alger JR, Pochon JB, Ghahremani D, Dean AC, et al. Smoking, tobacco dependence, and neurometabolites in the dorsal anterior cingulate cortex. Mol Psychiatry. 2023 Nov;28(11):4756–65.
8. Cao S, Yang L, Wang X, Yang W, Tang F, Tang S, et al. Unveiling causal relationships between addiction phenotypes and inflammatory cytokines: insights from bidirectional mendelian randomization and bibliometric analysis. Eur Arch Psychiatry Clin Neurosci. 2025 Mar;275(2):473–85.
9. Chen LG, Tubbs JD, Liu Z, Thach TQ, Sham PC. Mendelian randomization: causal inference leveraging genetic data. Psychol Med. 2024 Jun;54(8):1461–74.
10. Zakiniaeiz Y, Hillmer AT, Shi H, Pittman B, Nabulsi N, Huang Y, et al. Greater Neuroimmune System Deficit in Women Than Men With Alcohol Use Disorder. Biol Psychiatry. 2026 Jan 1;99(1):49–56.
11. Maeda N, Kanmura S, Morinaga Y, Mori S, Tanaka A, Maeda H et al. P0017Intestine-Targeted Delivery of Hepatocyte Growth Factor Using AccumBody® Ameliorates Colitis in a Dextran Sulfate Sodium-Induced Mouse Model. J. Crohns Colitis. 2026 Jan;20(Supplement_1):jjaf231–198.
12. Xu S, Li X, Zhang S, Qi C, Zhang Z, Ma R, et al. Oxidative stress gene expression, DNA methylation, and gut microbiota interaction trigger Crohn's disease: a multi-omics Mendelian randomization study. BMC Med. 2023 May 11;21(1):179.
13. Hu J, Grasby K, Mitchell B. Sex differences in the genetic and causal relationships between depression, smoking, and alcohol use: the role of socioeconomic status. Psychol Med. 2026;56:e58.
14. Zhang Y, Li M, Haas DM, Bairey Merz CN, Workalemahu T, Ryckman K, et al. A novel two-sample Mendelian randomization framework integrating common and rare variants: application to assess the effect of HDL-C on preeclampsia risk. Brief Bioinform. 2026 Jan 7;27(1):bbaf649.
15. Cao S, Yang L, Wang X, Yang W, Tang F, Tang S, et al. Unveiling causal relationships between addiction phenotypes and inflammatory cytokines: insights from bidirectional mendelian randomization and bibliometric analysis. Eur Arch Psychiatry Clin Neurosci. 2025 Mar;275(2):473–85.
16. Jannot AS, Ehret G, Perneger T. P < 5 × 10(-8) has emerged as a standard of statistical significance for genome-wide association studies. J Clin Epidemiol. 2015 Apr;68(4):460–5.
17. Yang Y, Lorincz-Comi N, Li M, Zhu X. A multivariable cis-Mendelian randomization method robust to weak instrument bias and horizontal pleiotropy bias. Brief Bioinform. 2025 May 1;26(3):bbaf250.
18. Minelli C, Del Greco M F, van der Plaat DA, Bowden J, Sheehan NA, Thompson J. The use of two-sample methods for Mendelian randomization analyses on single large datasets. Int J Epidemiol. 2021 Nov 10;50(5):1651–9.
19. Barbitoff YA, Bogaichuk PM, Pavlova NS, Malysheva PV, Predeus AV. Functional Determinants and Evolutionary Consequences of Pleiotropy in Complex and Mendelian Traits. Mol Biol Evol. 2025 Oct 1;42(10):msaf232.
20. Solovieff N, Cotsapas C, Lee PH, Purcell SM, Smoller JW. Pleiotropy in complex traits: challenges and strategies. Nat Rev Genet. 2013 Jul;14(7):483–95.
21. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nat Genet. 2018 May;50(5):693–8.
22. Lewis ACF, Molina SJ, Appelbaum PS, Dauda B, Di Rienzo A, Fuentes A, et al. Getting genetic ancestry right for science and society. Science. 2022 Apr 15;376(6590):250–2.
23. Hou L, Chen H, Zhou XH. MR-EILLS: an invariance-based Mendelian randomization method integrating multiple heterogeneous GWAS summary datasets. Nat Commun. 2025 Aug 18;16(1):7668.
24. Petrovski S, Goldstein DB. Unequal representation of genetic variation across ancestry groups creates healthcare inequality in the application of precision medicine. Genome Biol. 2016 Jul 14;17(1):157.
25. Labrecque JA, Swanson SA. Interpretation and Potential Biases of Mendelian Randomization Estimates With Time-Varying Exposures. Am J Epidemiol. 2019 Jan 1;188(1):231–8.
26. Cao S, Yang L, Wang X, Yang W, Tang F, Tang S, et al. Unveiling causal relationships between addiction phenotypes and inflammatory cytokines: insights from bidirectional mendelian randomization and bibliometric analysis. Eur Arch Psychiatry Clin Neurosci. 2025 Mar;275(2):473–85.
27. Chung JS, Hwang S, Hong JE, Jo M, Rhee KJ, Kim S, et al. Skeletal muscle satellite cell-derived mesenchymal stem cells ameliorate acute alcohol-induced liver injury. Int J Med Sci. 2022 Jan 24;19(2):353–63.
28. Zhang M, Zheng Y, Yao T, Wang L, Yu H, Wang Z. Impact of Smoking on the Efficacy of Human Autologous Oral Mucosal Epithelial Cell Sheet Transplantation for Treating Limbal Stem Cell Deficiency. Stem Cells Int. 2026 Jan 5;2026:3769266.
29. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020 Oct 17;396(10258):1223–49.
30. Saravia R, Ten-Blanco M, Grande MT, Maldonado R, Berrendero F. Anti-inflammatory agents for smoking cessation? Focus on cognitive deficits associated with nicotine withdrawal in male mice. Brain Behav Immun. 2019 Jan;75:228–39.
31. Subramanian S, Liu C, Aviv A, Ho JE, Courchesne P, Muntendam P, et al. Stromal cell-derived factor 1 as a biomarker of heart failure and mortality risk. Arterioscler Thromb Vasc Biol. 2014 Sep;34(9):2100–5.

32. Haybar H, Shahrabi S, Deris Zayeri Z, Pezeshki S. Strategies to increase cardioprotection through cardioprotective chemokines in chemotherapy-induced cardiotoxicity. Int J Cardiol. 2018 Oct 15;269:276–82.

33. Mehta HM, Corey SJ. G-CSF, the guardian of granulopoiesis. Semin Immunol. 2021 Apr;54:101515.

34. Milad N, Pineault M, Lechasseur A, Routhier J, Beaulieu MJ, Aubin S, et al. Neutrophils and IL-1α Regulate Surfactant Homeostasis during Cigarette Smoking. J Immunol. 2021 Apr 15;206(8):1923–31.

35. Jiang G, Liu W, Wang X, Wang Z, Song C, Chen R, et al. The causality between systemic inflammatory regulators and chronic respiratory diseases: A bidirectional Mendelian-randomization study. Cytokine. 2024 Feb;174:156470.

36. Lee SM, Shin YJ, Go RE, Bae SH, Kim CW, Kim S, et al. Inhalation exposure by cigarette smoke: Effects on the progression of bleomycin- and lipopolysaccharide-induced lung injuries in rat models. Toxicology. 2021 Mar 15;451:152695.

37. Arriaga MB, Amorim G, Figueiredo MC, Staats C, Kritski AL, Cordeiro-Santos M, et al. Effect of Smoking on Longitudinal Interferon γ Release Assay Results Among Close Contacts of People with Pulmonary Tuberculosis. J Infect Dis. 2025 Feb 4;231(1):103–8.

38. Cao S, Yang L, Wang X, Yang W, Tang F, Tang S, et al. Unveiling causal relationships between addiction phenotypes and inflammatory cytokines: insights from bidirectional mendelian randomization and bibliometric analysis. Eur Arch Psychiatry Clin Neurosci. 2025 Mar;275(2):473–85.

39. Liu C, Chu D, Kalantar-Zadeh K, George J, Young HA, Liu G. Cytokines: From Clinical Significance to Quantification. Adv Sci (Weinh). 2021 Aug;8(15):e2004433.

40. Zilverstand A, Huang AS, Alia-Klein N, Goldstein RZ. Neuroimaging Impaired Response Inhibition and Salience Attribution in Human Drug Addiction: A Systematic Review. Neuron. 2018 Jun 6;98(5):886–903.

41. Garrison KA, Sinha R, Potenza MN, Gao S, Liang Q, Lacadie C, et al. Transdiagnostic Connectome-Based Prediction of Craving. Am J Psychiatry. 2023 Jun 1;180(6):445–53.

42. Huang X, Hussain B, Chang J. Peripheral inflammation and blood-brain barrier disruption: effects and mechanisms. CNS Neurosci Ther. 2021 Jan;27(1):36–47.

43. Karatas KS, Soudkhah S, Haci S, Gioventikli T, Arslan H, Gokcen O, et al. Clinical and inflammatory profiles in substance use disorder: gender, substance type, and comorbidity in a single-center cross-sectional study in Turkey. J Addict Dis. 2026 Jan 23:1–11.

44. Acuña AM, Whittington R, Peacock E, Rodarte SE, Legg JL, Nagy EK, et al. Cyclooxygenase 2 (COX-2) expression is elevated in prefrontal cortex neurons, not microglia, following methamphetamine self-administration in male and female rats. Neuropharmacology. 2026 Feb 15;284:110778.

45. Zakiniaeiz Y, Raval NR, Riordan W, Nabulsi N, Huang Y, Pittman B, et al. Higher drinking frequency corresponds to lower synaptic density in people with alcohol use disorder. J Clin Invest. 2026 Jan 13;136(7):e199989.

46. Guo X, Tang P, He J, Li R. Dissecting the effect of blood colony-stimulating factors and receptors on Alzheimer's disease: the role of myeloid traits and inflammation. Cytokine. 2026 Jan;197:157072.

47. Mellado S, Cuesta CM, Montagud S, Rodríguez-Arias M, Moreno-Manzano V, Guerri C, et al. Therapeutic role of mesenchymal stem cell-derived extracellular vesicles in neuroinflammation and cognitive dysfunctions induced by binge-like ethanol treatment in adolescent mice. CNS Neurosci Ther. 2023 Dec;29(12):4018–31.

48. Raval NR, Angarita G, Matuskey D, Miller R, Drake LR, Kapinos M, et al. Imaging the brain's immune response to alcohol with [11C] PBR28 TSPO Positron Emission Tomography. Mol Psychiatry. 2023 Aug;28(8):3384–90.

49. Lian S, Li S, Zhu J, Xia Y, Do Jung Y. Nicotine stimulates IL-8 expression via ROS/NF-κB and ROS/MAPK/AP-1 axis in human gastric cancer cells. Toxicology. 2022 Jan 30;466:153062.

50. Tsermpini EE, Plemenitaš Ilješ A, Dolžan V. Alcohol-Induced Oxidative Stress and the Role of Antioxidants in Alcohol Use Disorder: A Systematic Review. Antioxidants (Basel). 2022 Jul 15;11(7):1374.

51. El-Azab G, Elkhouly E, Abouyoussef R, Nagdy H. Smoking and liver diseases: an updated review of pathogenesis, progression, and therapeutic implications. Clin Exp Med. 2025 Dec 3;26(1):51.

52. Martins IJ. Nutrition therapy regulates caffeine metabolism with relevance to NAFLD and induction of type 3 diabetes. J Diabetes Metab Disord. 2017;4(1):1–9.

53. Martins IJ. Single gene inactivation with implications to diabetes and multiple organ dysfunction syndrome. J Clin Epigenet. 2017 Aug 1;3(3):1–8.

54. Martins, I. (2016) Anti-Aging Genes Improve Appetite Regulation and Reverse Cell Senescence and Apoptosis in Global Populations. Adv Aging Res, 5, 9–26.

55. Lima MR, Souza IDC, Maraschi AC, Souza CM, Griboff J, Monferrán MV, et al. Antioxidant, oxidative damage and histopathological biomarkers in the gills to assess the impacts of metal/metalloid on Oreochromis niloticus inhabiting lagoons in metallurgical industrial areas. Sci Total Environ. 2026 Jan 15;1012:181200.