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# Allostatic load in opioid use disorder: a scoping review protocol.

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# Allostatic load in opioid use disorder: a scoping review protocol

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## ABSTRACT

**Introduction** Opioid use disorder affects 2.1 million individuals in the USA, causing more than 100 000 overdose-related deaths annually. While the neurobiological model of addiction is well described and accepted, there is a lack of morbidity and mortality prognosticators for patients struggling with opioid use disorder. Allostatic load index is a promising candidate for the basis of a prognostication tool. Previous studies show that allostatic load predicts both morbidity and mortality in a variety of cohorts. This scoping review protocol provides the rationale and steps for summarising and presenting existing evidence surrounding allostatic load in the context of opioid use disorder. Identification of current knowledge gaps will pave the way for subsequent prospective studies.

**Methods and analysis** This scoping review protocol will follow the five-step method designed by Arksey and O'Malley. All studies written in English on allostatic load in the context of opioid use disorder, as defined in our inclusion criteria, will be included. There will be no limit on the year of publication. We will search PubMed, Embase, CINAHL, PsycINFO and Google Scholar. We will hand-review reference lists of included articles, and we will hand search grey literature. We will then group, analyse and present the data in narrative, tabular and diagrammatic format according to themes identified in the scoping review.

**Ethics and dissemination** Ethics approval is not necessary, as data are gathered from publicly accessible sources. The results will be disseminated through a peer-reviewed journal and reported at conferences related to addiction medicine.

**Trial registration number** 10.17605/OSF.IO/4J6DQ.

## INTRODUCTION
### Epidemiological context

Opioid use disorder (OUD), previously referred to as addiction, is characterised by a compulsion to use opioids, cravings for opioids, ongoing opioid use despite negative consequences and loss of control over opioid use. This phenomenon is distinguished from opioid dependence, a condition by which an individual who is chronically exposed to opioids experiences physiological withdrawal with abrupt cessation.[1] The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders provides the 12 clinical criteria to distinguish dependence and use disorder

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Evidence synthesis will follow the comprehensive reporting guidelines presented in Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews.
⇒ By design, this scoping review will encompass a wide breadth within the topic of interest.
⇒ The extent of this scoping review will be limited by the small number of existing studies on this topic.

and distinguishes mild, moderate and severe use disorder based on the number of criteria met.[2]

OUD is associated with high mortality and morbidity rates. Opioid-related causes of mortality include overdose,[3] increased risk of accidental trauma such as motor vehicle accidents,[4] and infectious complications of injection drug use.[5–7] In fact, untreated individuals with opioid use disorder have a mortality rate 63 times higher than others of the same age and sex distribution.[8] Furthermore, chronic opioid use is frequently associated with the morbidity of hyperalgesia as well as constipation and abdominal pain.[9 10] As well, individuals are four times more likely to sustain a fracture while using opioids.[11] The euphoric effect and addictive potential of opioids make it difficult for individuals to rationally assess these risks.[12]

Worldwide, an estimated 26.8 million people struggle with OUD.[13] In the USA alone, approximately 2.1 million people have been diagnosed with OUD,[14] only 10% of whom have access to evidence-based treatment.[15] Overdose rates continue to rise, with over 100 000 opioid overdose fatalities in the USA reported in the last year.[3 14] Additionally, the financial cost to society directly attributable to OUD is over $141 billion annually, with $35 billion spent on healthcare and $92 billion lost on work productivity.[16 17]

### Prognosis and treatment stratification
Many chronic conditions with high morbidity and mortality have studied and validated

prognostic and risk stratification tools to guide treatment. For example, the Model for End-Stage Liver Disease score assesses prognosis in individuals with liver cirrhosis and helps determine the need for liver transplant, as well as mortality risk without transplant.[18] The Thrombolysis in Myocardial Infarction score assesses risk of mortality or recurrent myocardial infarction in patients with unstable angina or non-ST elevation myocardial infarction.[19] The Congestive heart failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74, and sex category (CHA2DS2-VASc) assesses risk for stroke in patients with atrial fibrillation, guiding the healthcare professional on whether to prescribe anticoagulants.[20] Each of these tools uses biomarkers or elements of the patient history as predictive elements, guiding clinical decision making.

Given the high morbidity and mortality associated with opioid use disorder, a similar risk stratification tool may be beneficial. However, such a tool does not currently exist. In developing such a tool, one may consider searching for biomarkers predictive of opioid use-related outcomes. Allostatic load, a marker of stress and associated physiological responses described in detail further, offers promise as such a risk stratification tool.

## Allostatic load

Homeostasis is the state of internal stability at certain setpoints that are critical for maintaining life.[21–23] Specifically, the body keeps blood pH, blood oxygen tension, blood glucose and body temperature within a narrow range, maintaining homeostasis.[21] However, Sterling and colleagues have proposed that other stress-related systems within the body have setpoints that fluctuate throughout the course of a lifespan in response to expected and unexpected stressors.[21 24] The behavioural and physiological mechanisms of adapting to stressors are collectively known as allostasis. Shifting setpoints within these allostatic systems contribute to internal homeostasis.[21] Allostatic mechanisms have been studied within the neuroendocrine, inflammatory, cardiometabolic and genetic systems (table 1), and setpoints within these systems should return to a prestress range after the stressor has passed.[21–25] However, if an individual is chronically exposed to stressful life circumstances or if the individual repeatedly experiences stressful life events, the setpoint may permanently change in such a way that predisposes to stress-related diseases such as obesity, diabetes or hypertension.[22 23] For example, chronic sleep deprivation may lead to a changed cortisol rhythm.[21] This cumulative consequence of chronic stress is termed 'allostatic load', a maladaptive state leading to chronic physiologic changes.[23] In summary, allostatic load is the cumulative, maladaptive physiological change that results from chronic life stressors.

For example, the neuroendocrine system releases cortisol in response to psychological stress to promote glucose release such that the body can respond appropriately to threatening stimuli. This is an adaptive,

**Table 1** Biomarkers associated with allostatic load

| System: | Marker: | Source: |
|---|---|---|
| Neuroendocrine system | Skin conductance Eyeblink electromyogram Urinary cortisol Salivary cortisol Urinary norepinephrine Urinary dopamine | Deighton et al[29] 2018 |
| Inflammatory system | Interleukin (IL)-6 C reactive protein Tumour necrosis factor (TNF)-alpha | Deighton et al[29] 2018 |
| Cardiometabolic system | Body mass index (BMI) Waist circumference Blood pressure Triglycerides Glycated haemoglobin HDL Total cholesterol Oxygen combustion | Deighton et al[29] 2018 |
| Genetic system | Telomere Length DNA methylation of the Human Serotonin Transporter (5HTT) promoter region | Beach et al[47] 2011 Deighton et al[29] 2018 |

allostatic process. However, if an individual is exposed to chronic psychological stressors, cortisol release may become upregulated.[25] Cortisol upregulation, leads to increased insulin secretion in response to elevated blood glucose. Persistent stress leads to continued, maladaptive physiologic responses, including increased cortisol and increased insulin secretion, which in turn may accelerate atherosclerosis, contributing to premature morbidity and mortality.[22]

## Quantifying risk of morbidity and mortality through allostatic load index

Researchers have developed count-based methods of calculating allostatic load index, a quantification of allostatic load, based on a set of stress-related biomarkers within several physiological systems (table 1). For example, in an individual, for each biomarker whose value is in the least favourable 75th percentile, that biomarker receives a score of '1'. For example, heart rates above 76.5 will receive a score of '1', as these are above the 75th percentile of the population's heart rates.[26] Counts are mathematically combined to determine allostatic load index.[26–29]

The allostatic load index is associated with morbidity and mortality in a variety of cohorts. A study by Guidi and colleagues[30] found that high allostatic load index is associated with higher risk of cardiovascular, musculoskeletal, periodontal and neurological disease, as well as cancer and diabetes. Additionally, allostatic load index has been found to predict depressive symptoms in a prospective, longitudinal study.[31] Furthermore, Seeman and colleagues[32] demonstrated that allostatic load index was a

better predictor of 7-year mortality than the components of metabolic syndrome (eg, elevated fasting glucose, hypertension, hypercholesterolemia, etc) alone. Other studies have found associations between higher allostatic load and increased morbidity and mortality in a variety of populations, including black individuals[33] and specifically black women living in the USA.[34]

Additionally, studies have investigated allostatic load's potential to serve as a tool for treatment stratification in psychiatric illness. Berger and colleagues[26] demonstrated in a randomised control trial that baseline allostatic load index predicts symptom severity and level of function in patients who develop psychosis 6 months after initial diagnosis. Similarly, Bizik and colleagues[27] discussed allostatic load index as a tool for longitudinal monitoring of severe psychiatric illness.

### Addiction and biomarkers of allostatic load
Addiction exerts chronic stress on the brain and body which, over time, contributes to elevated allostatic load index.[35–39] Researchers have found that several markers of the chronic stress response are elevated in individuals struggling with drug addiction. For example, a prolonged increase in neuroendocrine markers such as glucocorticoids in response to stress was found in animal models of addiction.[37] An exploratory study of metabolic biomarkers in opioid and psychostimulant addiction also found elevated cardiometabolic biomarkers such as cholesterol.[40] In vitro experiments have demonstrated that morphine, a natural opiate, binds to immune receptors, leading to downstream elevation of proinflammatory cytokines such as tumour necrosis factor and interleukin-6.[41–43] These biomarkers match the ones that comprise allostatic load index. Thus, it is reasonable to suggest that the quantifiers of allostatic load, a stress-induced state, be used to quantify mortality and morbidity risk in OUD.

### Rationale for this scoping review
The purpose of this scoping review is to thoroughly map the existing body of evidence on the intersection between allostatic load and opioid use disorder. In doing this, we will capture data on dysregulated allostatic mechanisms related to opioid use disorder. This paper aims to present a comprehensive mapping of the current state of evidence on our topic. This information will serve to illuminate gaps in the literature that warrant further exploration in subsequent prospective studies. Ultimately, we hope that this study will serve as a step towards using allostatic load index to predict and quantify morbidity and mortality, as well as response to different treatment modalities for patients with opioid use disorder, potentially opening the door to development of more effective treatment algorithms for this high risk patient population.

### METHODS AND ANALYSIS
Arksey and O'Malley's framework for scoping reviews guided the development of our methods, which involves five main stages: (1) identifying the research question, (2) identifying relevant studies, (3) study selection, (4) charting the data and (5) collating, summarising and with guidance from the Joanna Briggs Institute methodology for scoping reviews.[44] The Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR), a 22-item checklist, will further guide our study selection process. PRISMA-ScR was published in 2018 to facilitate a systematic approach to conducting scoping reviews.[44]

The Joanna Briggs chapter on scoping reviews provides additional detailed guidance for the completion of each item in the PRISMA-ScR checklist, and this scoping review will adhere to these guidelines.[45] In addition, we registered this protocol through Open Science Framework (DOI: 10.17605/OSF.IO/4J6DQ) to further ensure transparency in research methodology.

### Stage 1: defining the research question
Current research on allostatic load in the context of opioid use disorder is limited. Thus, we define a broad research question in order to capture the most comprehensive set of data and ideas that currently exist within this subfield. This scoping review answers the question: what data, ideas and questions have been presented on the topic of how allostatic load manifests in the context of opioid use or opioid use disorder?

### Stage 2: identifying relevant studies (search strategy)
With the assistance of an experienced medical librarian, we developed a comprehensive search strategy, approved by medical professionals in the field of addiction medicine. Search strategies use opioid drug terms combined with terms related to allostatic load as both keywords and corresponding medical subject headings. We created the initial search strategy in PubMed MEDLINE (table 2), and then translated to Embase, PsycARTICLES, CINAHL, ProQuest Central, Cochrane Central, Web of Science and Google Scholar. Search strategies for these databases can be found in online supplemental table 1).

To identify grey literature as well as works published outside of traditional academic publishing (eg, theses and conference abstracts), we will conduct keyword

**Table 2** Search terms for PubMed MEDLINE

| Concept | Search terms |
| --- | --- |
| Opioids | "heroin"(All Fields] OR "diacetylmorphine"(All Fields] OR "diamorphine"(All Fields] OR "fentanyl"(MeSH Terms] OR fentanyl*(All Fields] OR "morphine derivatives"(MeSH Terms] OR morphin*(All Fields] OR "oxycodone"(All Fields] OR "hydrocodone"(All Fields] OR codein*(All Fields] OR narcotic*(All Fields] OR "Narcotics"(Mesh) OR opioid*(All Fields] OR opiate* OR "Narcotic-Related Disorders"(Mesh) |
| Allostasis | "allostatic"(All Fields] OR "allostasis"(MeSH Terms] OR "allostasis"(All Fields] |

searches in the Web of Science database for conference proceedings. As well, we will review the reference lists of included papers to identify additional relevant articles. We will exclude studies that are not published in English.

## Stage 3: screening studies for inclusion

We will export articles obtained through the search strategy to EndNote. We will remove duplicate articles using EndNote's 'Find Duplicates' capability, and researchers will manually identify any remaining duplicates. We will note the number of records at each stage. After deduplication, we will use Rayyan QCRI article screening software to complete the blinded screening process. Two reviewers will determine inclusion of each study, with a third reviewer will make the final decision in the case of discrepancy between the first two reviewers.

Stage 1 screening will be based on the title and abstract of each study. Reviewers will independently determine eligibility of the study based on adherence to inclusion criteria demonstrated by these two components. Specifically, the title or abstract must mention opioid use as well as allostatic load (or: allostatic load index, allostasis, allostatic) in order to pass this stage. Only articles written in English will be considered. All articles that are marked as eligible by either of the reviewers in phase 1 will be reviewed in phase 2.

We will use the first 10% of the articles that pass phase 1 (alphabetically) to evaluate the inter-rater agreement using Cohen's kappa statistic. If the kappa statistic is below 0.5, the reviewers will meet to evaluate reasons for disagreement. We will continue to pilot an additional 10% of the articles until the Cohen's kappa rises above 0.8, which represents a strong level of agreement.[46]

Phase 2 will be based on the article's full text. Reviewers will independently determine eligibility of the study based on a reading of the article in its entirety. Any disagreements in the stage 2 process will be resolved by consensus with a third reviewer. Inclusion criteria for full-text review will include the following:

1. *Population:* the article involves humans, animals or in vitro models that are exposed to opioids. There will be no restriction on age range of human subjects.
2. *Outcomes:* outcomes or independent variables (predictors) involve allostatic load or allostasis.
3. *Context:* there will be no limitation on year of publication or type of institution that conducted the study.
4. *Study design:* we will include all empirical study types, review articles or editorials that meet the above criteria.
5. *Intervention:* we will include all intervention types as long as the study meets the previous criteria.

## Stage 4: data extraction

Two reviewers will independently extract data from each of the articles that passed phase 2 review, recording data in an Excel data extraction form. Due to the broad nature of our research question, we do not anticipate that each of these items will pertain to each article. Similarly, as we

are working on the frontier of our topic, we expect to encounter data points not previously anticipated, and we will record these data points from included publications as necessary.

We will extract the following data points from each article: author(s), year of publication, duration of study, country of study, type of study (eg, prospective cohort, randomised control trial, editorial, etc), subject of study (human, animal, subcellular components, etc), aspects of study design: (1) aim/purpose; (2) research question; (3) intervention; (4) comparison/control; (5) description of primary outcome(s); (6) description of secondary outcome(s); (7) descriptive statistics of outcome measures (eg, central tendency, variability, range); and (8) measures of significance conducted, and results of the study: (1) primary outcome results; (2) secondary outcome results; (3) conclusion(s) of study; and (4) limitations disclosed.

Additionally, we will extract from each article information about allostatic load, including the following items when applicable: allostatic changes described (eg, summary of mechanisms), items related to allostatic load index: (1) number of biomarkers used to calculate allostatic load index; (2) specific biomarkers used to calculate allostatic load index; (3) discrete categories into which biomarkers were grouped; (4) allostatic load calculation method; (5) cut-off values for biomarkers used in calculation; (6) descriptive statistics of biomarkers collected (eg, central tendency, variability, range); (7) descriptive statistics of allostatic indices calculated (eg, central tendency, variability, range); (8) measure of association between individual biomarkers and opioid use; (9) measure of association between allostatic load index and opioid use; and (10) a dichotomous indicator of whether or not the index included any biomarker with experimental evidence linked to opioid use.

In articles with human subjects, we will collect the following items when applicable: setting of study (eg, hospital, community health centre, rural, urban, etc), type(s) of opioids studied, screening tool used to diagnose opioid use disorder, health outcomes discussed (eg, relapse following treatment, mortality, etc), ways allostatic load has been used to guide management, number of participants enrolled, number of participants analysed, reasons for attrition, demographics of participants: (1) age (mean, range, SD); (2) sex of participants (percent in each category); (3) prior medical/psychiatric conditions in intervention group; (4) prior medical/psychiatric conditions in control group; (5) current medications used by participants; (6) current non-pharmacological treatments used by participants; and (7) current medical and psychiatric comorbidities of participants.

In articles with animal models, we will collect the following items when applicable: type of animal model involved, how animal model was created, opioid used, definition of opioid use disorder in animal model, number of subjects at start of study, number of subjects analysed and reasons for attrition.

In articles with in vitro models, we will collect the following items when applicable: description of model, how model was created, how model is related to opioid use disorder, type(s) of opioids used and sample size.

## Stage 5: analysis and presentation of results

We will report data in narrative, tabular and diagrammatic form. Specifically, to summarise the biomarkers that have been used for calculation of allostatic load index, we will create a histogram: one for individual biomarkers and one for unique combinations of biomarkers. We will summarise methods for calculating allostatic load index in tabular form.

Further themes will be identified during the scoping review process. We will group articles that address a similar theme, and we will summarise results in narrative, tabular and diagrammatic format.

We will then present overall conclusions from the scoping review as well as limitations encountered. We will discuss opportunities and implications for future research.

## Patient and public involvement
None.

## ETHICS AND DISSEMINATION

Ethics approval is not necessary, as data are gathered from publicly accessible sources. The results will be disseminated through a peer-reviewed journal and reported at conferences related to addiction medicine.

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## REFERENCES

1 Preuss CV, Kalava A, King KC. Prescription of controlled substances: benefits and risks. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing, 2022.
2 Diagnostic and statistical manual of mental disorders. Available: https://dsm-psychiatryonline-org.ezproxy.rowan.edu/doi/epdf/10.1176/appi.books.9780890425596 [Accessed 23 Nov 2022].
3 Top 100,000 annually. 2021. Available: www.cdc.gov/nchs/pressroom/nchs_press_releases/2021/20211117.htm [Accessed 10 Dec 2021].
4 Chihuri S, Li G. Use of prescription opioids and motor vehicle crashes: a meta analysis. *Accid Anal Prev* 2017;109:S0001-4575(17)30360-3:123–31.:.
5 Tung MKY, Light M, Giri R, *et al*. Evolving epidemiology of injecting drug use-associated infective endocarditis: a regional centre experience. *Drug Alcohol Rev* 2015;34:412–7.
6 Iskandar S, Basar D, Hidayat T, *et al*. High risk behavior for HIV transmission among former injecting drug users: a survey from Indonesia. *BMC Public Health* 2010;10:472.
7 Backmund M, Reimer J, Meyer K, *et al*. Hepatitis C virus infection and injection drug users: prevention, risk factors, and treatment. *Clin Infect Dis* 2005;40 Suppl 5:S330–5.
8 Grönbladh L, Ohlund LS, Gunne LM. Mortality in heroin addiction: impact of methadone treatment. *Acta Psychiatr Scand* 1990;82:223–7.
9 Mercadante S, Arcuri E, Santoni A. Opioid-Induced tolerance and hyperalgesia. *CNS Drugs* 2019;33:943–55.
10 Farmer AD, Holt CB, Downes TJ, *et al*. Pathophysiology, diagnosis, and management of opioid-induced constipation. *Lancet Gastroenterol Hepatol* 2018;3:S2468-1253(18)30008-6:203–12.:.
11 Peach EJ, Pearce FA, Gibson J, *et al*. Opioids and the risk of fracture: a self-controlled case series study in the clinical practice research Datalink. *Am J Epidemiol* 2021;190:1324–31.
12 Bhatia D, Mikulich-Gilbertson SK, Sakai JT. Prescription opioid misuse and risky adolescent behavior. *Pediatrics* 2020;145:e20192470.
13 Strang J, Volkow ND, Degenhardt L, *et al*. Opioid use disorder. *Nat Rev Dis Primers* 2020;6:3.
14 Dydyk AM, Jain NK, Gupta M. Opioid use disorder. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing, 2021. Available: www.ncbi.nlm.nih.gov/books/NBK553166
15 Nosyk B, Anglin MD, Brissette S, *et al*. A call for evidence-based medical treatment of opioid dependence in the United States and Canada. *Health Aff (Millwood)* 2013;32:1462–9.
16 Florence C, Luo F, Rice K. The economic burden of opioid use disorder and fatal opioid overdose in the United States, 2017. *Drug Alcohol Depend* 2021;218:S0376-8716(20)30515-9:108350.:.
17 The high price of the opioid crisis. 2021. Available: https://pew.org/2XZEFhY [Accessed 13 Dec 2021].
18 Peng Y, Qi X, Guo X. Child-Pugh versus MELD score for the assessment of prognosis in liver cirrhosis: a systematic review and meta-analysis of observational studies. *Medicine (Baltimore)* 2016;95:e2877.
19 Antman EM, Cohen M, Bernink PJ, *et al*. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;284:835–42.
20 Shariff N, Aleem A, Singh M, *et al*. Af and venous thromboembolism- pathophysiology, risk assessment and CHADS-vasc score. *J Atr Fibrillation* 2012;5:649:649.:.
21 McEwen BS, Wingfield JC. The concept of allostasis in biology and biomedicine. *Horm Behav* 2003;43:2–15.
22 McEwen BS, Stellar E. Stress and the individual. mechanisms leading to disease. *Arch Intern Med* 1993;153:2093–101.
23 McEwen BS. Stress, adaptation, and disease. allostasis and allostatic load. *Ann N Y Acad Sci* 1998;840:33–44.
24 Sterling P, Eyer J. Allostasis: A new paradigm to explain arousal pathology. *Handb Life Stress Cogn Health* 1988.
25 Hannibal KE, Bishop MD. Chronic stress, cortisol dysfunction, and pain: a psychoneuroendocrine rationale for stress management in pain rehabilitation. *Phys Ther* 2014;94:1816–25.
26 Berger M, Lavoie S, McGorry PD, *et al*. Relationship between allostatic load and clinical outcomes in youth at ultra-high risk for psychosis in the NEURAPRO study. *Schizophr Res* 2020;226:S0920-9964(18)30604-2:38–43.:.

27 Bizik G, Picard M, Nijjar R, *et al*. Allostatic load as a tool for monitoring physiological dysregulations and comorbidities in patients with severe mental illnesses. *Harv Rev Psychiatry* 2013;21:296–313.

28 Seeman TE, Singer BH, Rowe JW, *et al*. Price of adaptation -- allostatic load and its health consequences. MacArthur studies of successful aging. *Arch Intern Med* 1997;157:2259–68.

29 Deighton S, Neville A, Pusch D, *et al*. Biomarkers of adverse childhood experiences: a scoping review. *Psychiatry Res* 2018;269:S0165-1781(18)30040-4:719–32.:.

30 Guidi J, Lucente M, Sonino N, *et al*. Allostatic load and its impact on health: a systematic review. *Psychother Psychosom* 2021;90:11–27.

31 Juster R-P, Marin M-F, Sindi S, *et al*. Allostatic load associations to acute, 3-year and 6-year prospective depressive symptoms in healthy older adults. *Physiol Behav* 2011;104:360–4.

32 Seeman TE, McEwen BS, Rowe JW, *et al*. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. *Proc Natl Acad Sci U S A* 2001;98:4770–5.

33 Duru OK, Harawa NT, Kermah D, *et al*. Allostatic load burden and racial disparities in mortality. *J Natl Med Assoc* 2012;104:89–95.

34 Seeman T, Gruenewald T, Karlamangla A, *et al*. Modeling multisystem biological risk in young adults: the coronary artery risk development in young adults study. *Am J Hum Biol* 2010;22:463–72.

35 Koob GF. Alcoholism: allostasis and beyond. *Alcohol Clin Exp Res* 2003;27:232–43.

36 Koob GF, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology* 2001;24:97–129.

37 Fagen ZM, Mitchum R, Vezina P, *et al*. Enhanced nicotinic receptor function and drug abuse vulnerability. *J Neurosci* 2007;27:8771–8.

38 Koob GF, Ahmed SH, Boutrel B, *et al*. Neurobiological mechanisms in the transition from drug use to drug dependence. *Neurosci Biobehav Rev* 2004;27:739–49.

39 George O, Le Moal M, Koob GF. Allostasis and addiction: role of the dopamine and corticotropin-releasing factor systems. *Physiol Behav* 2012;106:58–64.

40 Caspani G, Sebők V, Sultana N, *et al*. Metabolic phenotyping of opioid and psychostimulant addiction: a novel approach for biomarker discovery and biochemical understanding of the disorder. *Br J Pharmacol* 2022;179:1578–606.

41 Hofford RS, Russo SJ, Kiraly DD. Neuroimmune mechanisms of psychostimulant and opioid use disorders. *Eur J Neurosci* 2019;50:2562–73.

42 Eidson LN, Murphy AZ. Inflammatory mediators of opioid tolerance: implications for dependency and addiction. *Peptides* 2019;115:S0196-9781(19)30009-9:51–8.:.

43 Wang X, Loram LC, Ramos K, *et al*. Morphine activates neuroinflammation in a manner parallel to endotoxin. *Proc Natl Acad Sci U S A* 2012;109:6325–30.

44 Tricco AC, Lillie E, Zarin W, *et al*. PRISMA extension for scoping reviews (PRISMA-scr): checklist and explanation. *Ann Intern Med* 2018;169:467–73.

45 Peters MDJ, Marnie C, Tricco AC, *et al*. Updated methodological guidance for the conduct of scoping reviews. *JBI Evid Synth* 2020;18:2119–26.

46 McHugh ML. Interrater reliability: the kappa statistic. *Biochem Med* 2012:276–82.

47 Beach SRH, Brody GH, Todorov AA, *et al*. Methylation at 5HTT mediates the impact of child sex abuse on women's antisocial behavior: an examination of the Iowa adoptee sample. *Psychosom Med* 2011;73:83–7.