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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-060522
Article Type:	Protocol
Date Submitted by the Author:	23-Dec-2021
Complete List of Authors:	Fan, Jaimie; Cooper Medical School of Rowan University Miller, Hillary; Rutgers School of Nursing Adams, Amanda; Cooper Medical School of Rowan University, Medical Library Bryan, Rebecca; Rutgers School of Nursing Salzman, Matthew; Cooper Medical School of Rowan University, Emergency Medicine
Keywords:	Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Physiology < NATURAL SCIENCE DISCIPLINES, PUBLIC HEALTH, Substance misuse < PSYCHIATRY, SOCIAL MEDICINE, TOXICOLOGY

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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 United States, causing more than 100,000 overdose-related deaths annually. While the neurobiologic 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 summarizing 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 outlined in PRISMA-ScR guidelines. 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 gray literature. We will then group, analyze, and present the data in narrative, tabular, and diagrammatic format according to themes identified in the scoping review.

Ethics and Dissemination: This paper presents the protocol for a scoping review that aims to advance understanding and identify knowledge gaps on the topic of allostatic load in the management of opioid use disorder. The results will be disseminated through a peer-reviewed journal and reported at conferences related to addiction medicine. Ethics approval is not necessary, as data is gathered from publicly accessible sources.

Registration Details: Open science framework, registration DOI: 10.17605/OSF.IO/4J6DQ

Keywords: Substance misuse, Toxicology, Physiology, Quality in health care, Public health, Social medicine

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Strengths and limitations of this study:

- To our knowledge, this scoping review protocol is the first to describe rationale and steps for summarizing existing evidence on allostatic load in the context of opioid use disorder.
- Evidence synthesis will follow the comprehensive and validated guidelines presented in PRISMA-scR.
- The extent of this scoping review will be limited by the small number of existing studies on this topic, and breadth of discussion will be broad.
- This scoping review will illuminate knowledge gaps to investigate in future prospective research.

Introduction:

Epidemiological context

Opioid use disorder (OUD) is associated with high mortality and morbidity rates. Opioid-related causes of mortality include overdose[1], increased risk of accidental trauma such as motor vehicle accidents[2], and infectious complications of injection drug use[3–5]. In fact, untreated individuals with opioid use disorder have a mortality rate 63 times higher than others of the same age and sex distribution[6]. Furthermore, chronic opioid use is frequently associated with the morbidity of hyperalgesia as well as constipation and abdominal pain[7,8]. As well, individuals are 4 times more likely to sustain a fracture while using opioids[9]. The euphoric effect and addictive potential of opioids make it difficult for individuals to rationally assess these risks[10].

Worldwide, an estimated 26.8 million people struggle with OUD[11]. In the United States alone, approximately 2.1 million people have been diagnosed with OUD[12], only 10 percent of whom have access to evidence-based treatment[13]. Overdose rates continue to rise, with over 100,000 opioid overdose fatalities in the US reported in the last year[1,12]. 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[14,15].

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 (MELD) score assesses prognosis in individuals with liver cirrhosis and helps determine the need for orthotopic liver transplant, as well as mortality risk without transplant[16]. The Thrombolysis in Myocardial Infarction (TIMI) score assesses risk of

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mortality or recurrent myocardial infarction in patients with unstable angina or non-ST elevation myocardial infarction (NSTEMI)[17]. The CHA2DS2-VASc assesses risk for stroke in patients with atrial fibrillation, guiding the healthcare professional on whether to prescribe anticoagulants[18]. 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 physiologic responses described in detail below, 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[19–21]. Specifically, the body keeps blood pH, blood oxygen tension, blood glucose, and body temperature within a narrow range known as homeostasis[19]. 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[19,22]. The behavioral and physiological mechanisms of adapting to stressors are collectively known as allostasis. Shifting setpoints within these allostatic systems contribute to internal homeostasis[19]. Allostatic mechanisms have been studied within the neuroendocrine, inflammatory, cardiometabolic, and genetic systems (Table 1), and setpoints within these systems should return to a pre-stress range after the stressor has passed[19–22]. However, if an individual is chronically exposed to prolonged stressful events, the setpoint may permanently change in such a way that predisposes to stress-related diseases such as obesity, diabetes, or hypertension[20,21]. This cumulative consequence of chronic stress is termed “allostatic load,” a maladaptive state leading to chronic physiologic changes[21].

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 favorable 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[23]. Counts are mathematically combined to determine allostatic load index[23–26].

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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., 2018[26]
Inflammatory System	Interleukin (IL)-6 C-Reactive Protein Tumor Necrosis Factor (TNF)-alpha	Deighton et al., 2018[26]
Cardiometabolic System	Body Mass Index (BMI) Waist circumference Blood pressure Triglycerides Glycated hemoglobin HDL Total Cholesterol Oxygen Combustion	Deighton et al., 2018[26]
Genetic System	Telomere Length DNA Methylation of the 5HTT promoter region	Beach et al., 2011[27] Deighton et al., 2018[26]

The allostatic load index is associated with morbidity and mortality in a variety of cohorts. A study by Guidi and colleagues found that high allostatic load index is associated with higher risk of cardiovascular, musculoskeletal, periodontal, and neurological disease, as well as cancer and diabetes[28]. Additionally, allostatic load index has been found to predict depressive symptoms in a prospective, longitudinal study[29]. Furthermore, Seeman and colleagues demonstrated that allostatic load index was a better predictor of 7-year mortality than the components of metabolic syndrome (e.g. elevated fasting glucose, hypertension, hypercholesterolemia, etc) alone[30]. Other studies have found associations between higher allostatic load and increased morbidity and mortality in a variety of populations, including black individuals[31] and specifically black women living in the United States[32].

Additionally, studies have investigated allostatic load's potential to serve as a tool for treatment stratification in psychiatric illness. Berger and colleagues demonstrated in a randomized control trial that baseline allostatic load index predicts symptom severity and level of function in patients who develop psychosis 6 months after initial diagnosis[23]. Similarly, Bizik and colleagues

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discussed allostatic load index as a tool for longitudinal monitoring of severe psychiatric illness[24].

Addiction and biomarkers of allostatic load

Addiction exerts chronic stress on the brain and body, which, over time, contributes to elevated allostatic load index[33–37]. 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[35]. An exploratory study of metabolic biomarkers in opioid and psychostimulant addiction also found elevated cardiometabolic biomarkers such as cholesterol[38]. In vitro experiments have demonstrated that morphine, a natural opiate, binds to immune receptors, leading to downstream elevation of proinflammatory cytokines such as tumor necrosis factor (TNF) and Interleukin (IL)-6[39–41]**.** 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 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. 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 utilizing 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:

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, (5) collating, summarizing and with guidance from the Joanna Briggs Institute (JBI) methodology for scoping reviews[42]. 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[42].

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

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these guidelines[43]. 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 keywords (Table 2). We created the initial search strategy in PubMed Medline, and then translated to Embase, PsycINFO, CINAHL, and Google Scholar.

To identify grey literature as well as works published outside of traditional academic publishing (e.g. theses and conference abstracts), we will conduct keyword searches in the Web of Science database for conference proceedings, and we will conduct a manual review of Google Scholar results. 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.

Table 2: Search terms for databases

Concept	Search terms
Opioids	"heroin" OR "diacetylmorphine" OR "diamorphine" OR "fentanyl" OR "fentanyl" OR "fentanyls" OR "morphine derivatives" OR morphin* OR "oxycodone" OR "hydrocodone" OR "codein*" OR narcotic* OR "Narcotics" OR opioid* OR opiate* OR "Narcotic-Related Disorders"
Allostasis	"allostatic" OR "allostasis" OR "allostatic

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	load" OR “allostatic load index”

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 and 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.

Phase 2 screening 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. 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.
2) *Outcomes:* outcomes 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 which meet the above criteria.
5) *Intervention:* we will include all intervention types as long as the study meets the above criteria.

Stage 4: Data Extraction

Two reviewers will independently extract data from each of the articles which 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

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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 (e.g. prospective cohort, randomized control trial, editorial, etc), subject of study (human, animal, subcellular components, etc), aspects of study design: i) Aim/purpose ii) Research question iii) Intervention iv) Comparison/control v) Description of primary outcome(s) vi) Description of secondary outcome(s) vii) Descriptive statistics of outcome measures (e.g. central tendency, variability, range) viii) Measures of significance conducted; and results of the study: i) Primary outcome results ii) Secondary outcome results iii) Conclusion(s) of study iv) 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: i) Number of biomarkers used to calculate allostatic load index ii) Specific biomarkers used to calculate allostatic load index iii) Discrete categories into which biomarkers were grouped iv) Allostatic load calculation method v) Cutoff values for biomarkers used in calculation vi) Descriptive statistics of biomarkers collected (e.g. central tendency, variability, range) vii) Descriptive statistics of allostatic indices calculated (e.g. central tendency, variability, range) viii) Measure of association between individual biomarkers and opioid use ix) Measure of association between allostatic load index and opioid use.

In articles with human subjects, we will collect the following items when applicable: setting of study (eg hospital, community health center, rural, urban, etc.), type(s) of opioids studied, screening tool used to diagnose opioid use disorder, health outcomes discussed (e.g. relapse following treatment, mortality, etc), ways allostatic load has been used to guide managment, number of participants enrolled, number of participants analyzed, reasons for attrition, demographics of participants: i) Age (mean, range, standard deviation) ii) Sex of participants (percent in each category) iii) Prior medical/psychiatric conditions in intervention group iv) Prior medical/psychiatric conditions in control group.

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 analyzed, 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, sample size.

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Stage 5: Analysis and presentation of results

We will report data in narrative, tabular, and diagrammatic form. Specifically, to summarize 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 summarize 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 summarize 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: We did not involve patients or the public in study design or dissemination of this protocol.

Ethics and Dissemination: This paper presents the protocol for a scoping review that aims to advance understanding and identify knowledge gaps on the topic of allostatic load in the management of opioid use disorder. The results will be disseminated through a peer-reviewed journal and reported at conferences related to addiction medicine. Ethics approval is not necessary, as data is gathered from publicly accessible sources.

Funding Statement: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing Interests: None declared.

Contributions: JF conducted the background literature search, drafted the initial manuscript, made subsequent edits, and finalized the manuscript based on team members' suggestions. HM created the figures and edited the manuscript. AA identified the kind of study most suitable for our research goals, designed the search strategy, created the Open Science Framework registration, and edited the manuscript. JF and AA designed the study methods. RB edited the manuscript and contributed her expertise on allostatic load. MS initiated the project, provided critical insights and supervision in writing the protocol, and edited the manuscript.

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Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	

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SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	
Limitations	20	Discuss the limitations of the scoping review process.	
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

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BMJ Open

Allostatic load in opioid use disorder: a scoping review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-060522.R1
Article Type:	Protocol
Date Submitted by the Author:	13-Jul-2022
Complete List of Authors:	Fan, Jaimie; Cooper Medical School of Rowan University Miller, Hillary; Rutgers School of Nursing Adams, Amanda; Cooper Medical School of Rowan University, Medical Library Bryan, Rebecca; Rutgers School of Nursing Salzman, Matthew; Cooper Medical School of Rowan University, Emergency Medicine
Primary Subject Heading:	Addiction
Secondary Subject Heading:	Addiction
Keywords:	Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Physiology < NATURAL SCIENCE DISCIPLINES, PUBLIC HEALTH, Substance misuse < PSYCHIATRY, SOCIAL MEDICINE, TOXICOLOGY

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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 United States, causing more than 100,000 overdose-related deaths annually. While the neurobiologic 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 summarizing 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 gray literature. We will then group, analyze, and present the data in narrative, tabular, and diagrammatic format according to themes identified in the scoping review.

Ethics and Dissemination: This paper presents the protocol for a scoping review that aims to advance understanding and identify knowledge gaps on the topic of allostatic load in the management of opioid use disorder. The results will be disseminated through a peer-reviewed journal and reported at conferences related to addiction medicine. Ethics approval is not necessary, as data is gathered from publicly accessible sources.

Registration Details: Open science framework, registration DOI: 10.17605/OSF.IO/4J6DQ

Keywords: Substance misuse, Allostatic load, Physiology, Quality in health care, Public health, Social medicine

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Strengths and limitations of this study:

- To our knowledge, this scoping review protocol is the first to describe rationale and steps for summarizing existing evidence on allostatic load in the context of opioid use disorder.
- Evidence synthesis will follow the comprehensive reporting guidelines presented in PRISMA-scR.
- The extent of this scoping review will be limited by the small number of existing studies on this topic, and breadth of discussion will be broad.
- This scoping review will illuminate knowledge gaps to investigate in future prospective research.

Introduction:

Epidemiological context

Opioid use disorder (OUD) is associated with high mortality and morbidity rates. Opioid-related causes of mortality include overdose[1], increased risk of accidental trauma such as motor vehicle accidents[2], and infectious complications of injection drug use[3–5]. In fact, untreated individuals with opioid use disorder have a mortality rate 63 times higher than others of the same age and sex distribution[6]. Furthermore, chronic opioid use is frequently associated with the morbidity of hyperalgesia as well as constipation and abdominal pain[7,8]. As well, individuals are 4 times more likely to sustain a fracture while using opioids[9]. The euphoric effect and addictive potential of opioids make it difficult for individuals to rationally assess these risks[10].

Worldwide, an estimated 26.8 million people struggle with OUD[11]. In the United States alone, approximately 2.1 million people have been diagnosed with OUD[12], only 10 percent of whom have access to evidence-based treatment[13]. Overdose rates continue to rise, with over 100,000 opioid overdose fatalities in the US reported in the last year[1,12]. 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[14,15].

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 (MELD) score assesses prognosis in individuals with liver cirrhosis and helps determine the need for orthotopic liver transplant, as well as mortality risk without transplant[16]. The Thrombolysis in Myocardial Infarction (TIMI) score assesses risk of

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mortality or recurrent myocardial infarction in patients with unstable angina or non-ST elevation myocardial infarction (NSTEMI)[17]. The CHA2DS2-VASc assesses risk for stroke in patients with atrial fibrillation, guiding the healthcare professional on whether to prescribe anticoagulants[18]. 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 physiologic responses described in detail below, 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[19–21]. Specifically, the body keeps blood pH, blood oxygen tension, blood glucose, and body temperature within a narrow range, maintaining homeostasis[19]. 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[19,23]. The behavioral and physiological mechanisms of adapting to stressors are collectively known as allostasis. Shifting setpoints within these allostatic systems contribute to internal homeostasis[19]. Allostatic mechanisms have been studied within the neuroendocrine, inflammatory, cardiometabolic, and genetic systems (Table 1), and setpoints within these systems should return to a pre-stress range after the stressor has passed[19–23]. However, if an individual is chronically exposed to prolonged stressful events, the setpoint may permanently change in such a way that predisposes to stress-related diseases such as obesity, diabetes, or hypertension[20,21]. This cumulative consequence of chronic stress is termed “allostatic load,” a maladaptive state leading to chronic physiologic changes[21].

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, allostatic process. However, if an individual is exposed to chronic psychological stressors, cortisol release may become upregulated[22]. 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[20]

Quantifying risk of morbidity and mortality through allostatic load index

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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 favorable 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[24]. Counts are mathematically combined to determine allostatic load index[24–27].

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., 2018[27]
Inflammatory System	Interleukin (IL)-6 C-Reactive Protein Tumor Necrosis Factor (TNF)-alpha	Deighton et al., 2018[27]
Cardiometabolic System	Body Mass Index (BMI) Waist circumference Blood pressure Triglycerides Glycated hemoglobin HDL Total Cholesterol Oxygen Combustion	Deighton et al., 2018[27]
Genetic System	Telomere Length DNA Methylation of the 5HTT promoter region	Beach et al., 2011[28] Deighton et al., 2018[27]

The allostatic load index is associated with morbidity and mortality in a variety of cohorts. A study by Guidi and colleagues found that high allostatic load index is associated with higher risk of cardiovascular, musculoskeletal, periodontal, and neurological disease, as well as cancer and diabetes[29]. Additionally, allostatic load index has been found to predict depressive symptoms in a prospective, longitudinal study[30]. Furthermore, Seeman and colleagues demonstrated that allostatic load index was a better predictor of 7-year mortality than the components of metabolic

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syndrome (e.g. elevated fasting glucose, hypertension, hypercholesterolemia, etc) alone[31]. Other studies have found associations between higher allostatic load and increased morbidity and mortality in a variety of populations, including black individuals[32] and specifically black women living in the United States[33].

Additionally, studies have investigated allostatic load's potential to serve as a tool for treatment stratification in psychiatric illness. Berger and colleagues demonstrated in a randomized control trial that baseline allostatic load index predicts symptom severity and level of function in patients who develop psychosis 6 months after initial diagnosis[24]. Similarly, Bizik and colleagues discussed allostatic load index as a tool for longitudinal monitoring of severe psychiatric illness[25].

Addiction and biomarkers of allostatic load

Addiction exerts chronic stress on the brain and body, which, over time, contributes to elevated allostatic load index[34–38]. 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[36]. An exploratory study of metabolic biomarkers in opioid and psychostimulant addiction also found elevated cardiometabolic biomarkers such as cholesterol[39]. In vitro experiments have demonstrated that morphine, a natural opiate, binds to immune receptors, leading to downstream elevation of proinflammatory cytokines such as tumor necrosis factor (TNF) and Interleukin (IL)-6[40–42]**.** 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 utilizing 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:

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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, (5) collating, summarizing and with guidance from the Joanna Briggs Institute (JBI) methodology for scoping reviews[43]. 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[43].

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[44]. 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, PsycINFO, CINAHL, and Google Scholar.

To identify grey literature as well as works published outside of traditional academic publishing (e.g. theses and conference abstracts), we will conduct keyword searches in the Web of Science database for conference proceedings, and we will conduct a manual review of Google Scholar results. 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.

Table 2: Search terms for PubMed Medline

Concept	Search terms

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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]

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 interrater 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[45].

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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 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 which meet the above criteria.
5) *Intervention:* we will include all intervention types as long as the study meets the above criteria.

Stage 4: Data Extraction

Two reviewers will independently extract data from each of the articles which 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 (e.g. prospective cohort, randomized control trial, editorial, etc), subject of study (human, animal, subcellular components, etc), aspects of study design: i) Aim/purpose ii) Research question iii) Intervention iv) Comparison/control v) Description of primary outcome(s) vi) Description of secondary outcome(s) vii) Descriptive statistics of outcome measures (e.g. central tendency, variability, range) viii) Measures of significance conducted; and results of the study: i) Primary outcome results ii) Secondary outcome results iii) Conclusion(s) of study iv) 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: i) Number of biomarkers used to calculate allostatic load index ii) Specific biomarkers used to calculate allostatic load index iii) Discrete categories into which biomarkers were grouped iv) Allostatic load calculation method v) Cutoff values for

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biomarkers used in calculation vi) Descriptive statistics of biomarkers collected (e.g. central tendency, variability, range) vii) Descriptive statistics of allostatic indices calculated (e.g. central tendency, variability, range) viii) Measure of association between individual biomarkers and opioid use ix) Measure of association between allostatic load index and opioid use x) 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 center, rural, urban, etc.), type(s) of opioids studied, screening tool used to diagnose opioid use disorder, health outcomes discussed (e.g. relapse following treatment, mortality, etc), ways allostatic load has been used to guide management, number of participants enrolled, number of participants analyzed, reasons for attrition, demographics of participants: i) Age (mean, range, standard deviation) ii) Sex of participants (percent in each category) iii) Prior medical/psychiatric conditions in intervention group iv) Prior medical/psychiatric conditions in control group v) current medications used by participants vi) current non-pharmacological treatments used by participants vii) current medical andpsychiatric 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 analyzed, 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, sample size.

Stage 5: Analysis and presentation of results

We will report data in narrative, tabular, and diagrammatic form. Specifically, to summarize 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 summarize 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 summarize 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.

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Patient and Public Involvement: We did not involve patients or the public in study design or dissemination of this protocol.

Ethics and Dissemination: This paper presents the protocol for a scoping review that aims to advance understanding and identify knowledge gaps on the topic of allostatic load in the management of opioid use disorder. The results will be disseminated through a peer-reviewed journal and reported at conferences related to addiction medicine. Ethics approval is not necessary, as data is gathered from publicly accessible sources.

Funding Statement: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing Interests: None declared.

Contributions: JF conducted the background literature search, drafted the initial manuscript, made subsequent edits, and finalized the manuscript based on team members' suggestions. HM created the figures and edited the manuscript. AA identified the kind of study most suitable for our research goals, designed the search strategy, created the Open Science Framework registration, and edited the manuscript. JF and AA designed the study methods. RB edited the manuscript and contributed her expertise on allostatic load. MS initiated the project, provided critical insights and supervision in writing the protocol, and edited the manuscript.

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Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	

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SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	
Limitations	20	Discuss the limitations of the scoping review process.	
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

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BMJ Open

Allostatic load in opioid use disorder: a scoping review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-060522.R2
Article Type:	Protocol
Date Submitted by the Author:	09-Feb-2023
Complete List of Authors:	Fan, Jaimie; Cooper Medical School of Rowan University Miller, Hillary; Rutgers School of Nursing Adams, Amanda; Cooper Medical School of Rowan University, Medical Library Bryan, Rebecca; Rutgers School of Nursing Salzman, Matthew; Cooper Medical School of Rowan University, Emergency Medicine
Primary Subject Heading:	Addiction
Secondary Subject Heading:	Addiction
Keywords:	Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Physiology < NATURAL SCIENCE DISCIPLINES, PUBLIC HEALTH, Substance misuse < PSYCHIATRY, SOCIAL MEDICINE, TOXICOLOGY

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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 United States, causing more than 100,000 overdose-related deaths annually. While the neurobiologic 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 summarizing 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 gray literature. We will then group, analyze, 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 is gathered from publicly accessible sources. The results will be disseminated through a peer-reviewed journal and reported at conferences related to addiction medicine.

Study registration: Open Science Framework, registration DOI: 10.17605/OSF.IO/4J6DQ.

Keywords: Substance misuse, Allostatic load, Physiology, Quality in health care, Public health, Social medicine

Strengths and limitations of this study

- Evidence synthesis will follow the comprehensive reporting guidelines presented in PRISMA-ScR.
- 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.

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Introduction

Epidemiological context

Opioid use disorder (OUD), previously referred to as addiction, is characterized 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 physiologic 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, 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 4 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 United States alone, approximately 2.1 million people have been diagnosed with OUD[14], only 10 percent of whom have access to evidence-based treatment[15]. Overdose rates continue to rise, with over 100,000 opioid overdose fatalities in the US 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 (MELD) 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 (TIMI) score assesses risk of mortality or recurrent myocardial infarction in patients with unstable angina or non-ST elevation myocardial infarction (NSTEMI)[19]. The 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.

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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 physiologic responses described in detail below, 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 behavioral 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 pre-stress 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 physiologic 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, 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

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is in the least favorable 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].

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., 2018[29]
Inflammatory System	Interleukin (IL)-6 C-Reactive Protein Tumor Necrosis Factor (TNF)-alpha	Deighton et al., 2018[29]
Cardiometabolic System	Body Mass Index (BMI) Waist circumference Blood pressure Triglycerides Glycated hemoglobin HDL Total Cholesterol Oxygen Combustion	Deighton et al., 2018[29]
Genetic System	Telomere Length DNA Methylation of the 5HTT promoter region	Beach et al., 2011[30] Deighton et al., 2018[29]

The allostatic load index is associated with morbidity and mortality in a variety of cohorts. A study by Guidi and colleagues found that high allostatic load index is associated with higher risk of cardiovascular, musculoskeletal, periodontal, and neurological disease, as well as cancer and diabetes[31]. Additionally, allostatic load index has been found to predict depressive symptoms in a prospective, longitudinal study[32]. Furthermore, Seeman and colleagues demonstrated that allostatic load index was a better predictor of 7-year mortality than the components of metabolic syndrome (e.g. elevated fasting glucose, hypertension, hypercholesterolemia, etc) alone[33]. Other studies have found associations between higher allostatic load and increased morbidity and

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mortality in a variety of populations, including black individuals[34] and specifically black women living in the United States[35].

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

Addiction and biomarkers of allostatic load

Addiction exerts chronic stress on the brain and body, which, over time, contributes to elevated allostatic load index[36–40]. 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[38]. An exploratory study of metabolic biomarkers in opioid and psychostimulant addiction also found elevated cardiometabolic biomarkers such as cholesterol[41]. In vitro experiments have demonstrated that morphine, a natural opiate, binds to immune receptors, leading to downstream elevation of proinflammatory cytokines such as tumor necrosis factor (TNF) and Interleukin (IL)-6[42–44]**.** 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 utilizing 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

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studies, (3) study selection, (4) charting the data, (5) collating, summarizing and with guidance from the Joanna Briggs Institute (JBI) methodology for scoping reviews[45]. 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[45].

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[46]. 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 Supplemental Table 1.

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

Table 2. Search terms for PubMed Medline

Concept	Search terms

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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]

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 interrater 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[47].

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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 which meet the above criteria.
5) *Intervention:* we will include all intervention types as long as the study meets the above criteria.

Stage 4: Data extraction

Two reviewers will independently extract data from each of the articles which 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 (e.g. prospective cohort, randomized control trial, editorial, etc), subject of study (human, animal, subcellular components, etc), aspects of study design: i) Aim/purpose ii) Research question iii) Intervention iv) Comparison/control v) Description of primary outcome(s) vi) Description of secondary outcome(s) vii) Descriptive statistics of outcome measures (e.g. central tendency, variability, range) viii) Measures of significance conducted; and results of the study: i) Primary outcome results ii) Secondary outcome results iii) Conclusion(s) of study iv) 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: i) Number of biomarkers used to calculate allostatic load index ii) Specific biomarkers used to calculate allostatic load index iii) Discrete categories into which biomarkers were grouped iv) Allostatic load calculation method v) Cutoff values for

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biomarkers used in calculation vi) Descriptive statistics of biomarkers collected (e.g. central tendency, variability, range) vii) Descriptive statistics of allostatic indices calculated (e.g. central tendency, variability, range) viii) Measure of association between individual biomarkers and opioid use ix) Measure of association between allostatic load index and opioid use x) 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 center, rural, urban, etc.), type(s) of opioids studied, screening tool used to diagnose opioid use disorder, health outcomes discussed (e.g. relapse following treatment, mortality, etc), ways allostatic load has been used to guide management, number of participants enrolled, number of participants analyzed, reasons for attrition, demographics of participants: i) Age (mean, range, standard deviation) ii) Sex of participants (percent in each category) iii) Prior medical/psychiatric conditions in intervention group iv) Prior medical/psychiatric conditions in control group v) current medications used by participants vi) current non-pharmacological treatments used by participants vii) 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 analyzed, 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, sample size.

Stage 5: Analysis and presentation of results

We will report data in narrative, tabular, and diagrammatic form. Specifically, to summarize 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 summarize 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 summarize 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.

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Patient and public involvement
None.

Ethics and dissemination

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

*** ***

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: None declared.

Contributors: JF conducted the background literature search, drafted the initial manuscript, made subsequent edits, and finalized the manuscript based on team members' suggestions. HM edited the manuscript. AA identified the kind of study most suitable for our research goals, designed the search strategy, created the Open Science Framework registration, and edited the manuscript. JF and AA designed the study methods. RB edited the manuscript and contributed her expertise on allostatic load. MS initiated the project, provided critical insights and supervision in writing the protocol, and edited the manuscript.

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Supplemental Table 1: Search Strategies for all Databases	
Database	**Search Strategy**
PubMed MEDLINE	1. "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] 2. "allostatic"[All Fields] OR "allostasis"[MeSH Terms] OR "allostasis"[All Fields] 3. 1 AND 2
Embase	1. heroin OR diacetylmorphine OR diamorphine OR fentanyl* OR 'morphine derivative'/exp OR morphin* OR oxycodone OR hydrocodone OR codein* OR 'narcotic analgesic agent'/exp OR 'narcotic agent'/exp OR narcotic* OR opioid* OR 'opiate agonist'/exp OR opiate* OR 'narcotic dependence'/exp 2. 'allostatic load'/exp OR 'allostasis'/exp OR allostasis OR allostatic 3. 1 AND 2
PsycARTICLES	1. MAINSUBJECT.EXACT.EXPLODE("Narcotic Drugs") OR heroin OR diacetylmorphine OR diamorphine OR fentanyl* OR morphin* OR

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	oxycodone OR hydrocodone OR codein* OR narcotic* OR opioid* OR opiate* OR MAINSUBJECT.EXACT.EXPLODE("Opioid Use Disorder") 2. allostatic OR allostasis 3. 1 AND 2
CINAHL	1. (MH "Narcotics+") OR heroin OR diacetylmorphine OR diamorphine OR fentanyl OR morphin* OR oxycodone OR hydrocodone OR codeine OR (MH "Analgesics, Opioid+") OR narcotic OR opioid* OR opiate* OR (MH "Substance Abuse+") OR opioid use disorder 2. allostatic OR allostasis 3. 1 AND 2
ProQuest Central	1. MAINSUBJECT.EXACT("Narcotics") OR heroin OR diacetylmorphine OR diamorphine OR fentanyl* OR morphin* OR oxycodone OR hydrocodone OR codein* OR narcotic* OR opioid* OR opiate* OR MAINSUBJECT.EXACT("Drug abuse") OR MAINSUBJECT.EXACT("Drug addiction") 2. noft(allostatic OR allostasis) 3. 1 AND 2
Cochrane Central	1. heroin OR diacetylmorphine OR diamorphine OR fentanyl OR morphine OR oxycodone OR

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	hydrocodone OR codeine OR narcotic OR opioid OR opiate OR opioid use disorder 2. allostasis OR allostatic 3. 1 AND 2
Web of Science	(ALL=(heroin OR diacetylmorphine OR diamorphine OR fentanyl OR morphine OR oxycodone OR hydrocodone OR codeine OR narcotic OR opioid OR opiate OR “opioid use disorder”)) AND ALL=(allostatic OR allostasis)
Google Scholar	1. heroin OR diacetylmorphine OR diamorphine OR fentanyl OR morphine OR oxycodone OR hydrocodone OR codeine OR narcotic OR opioid OR opiate OR "opioid use disorder" "allostatic load" 2. heroin OR diacetylmorphine OR diamorphine OR fentanyl OR morphine OR oxycodone OR hydrocodone OR codeine OR narcotic OR opioid OR opiate OR "opioid use disorder" "allostasis" 3. 1 OR 2

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Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	

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SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	
Limitations	20	Discuss the limitations of the scoping review process.	
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.
* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).
‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-060522 on 17 March 2023. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.