

INPLASY

Cardiovascular-Kidney-Liver-Metabolic (CKLM) Syndrome in the Veterans Health Administration: A Scoping Review of Populations, Therapies, and Outcomes

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ADMINISTRATIVE INFORMATION**Support** - No support.**Review Stage at time of this submission** - Preliminary searches.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2026100003**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 1 October 2026 and was last updated on 1 October 2026.**INTRODUCTION**

Review question / Objective What is the extent, nature, and distribution of the evidence on cardiovascular-kidney-liver-metabolic (CKLM) syndrome and its component conditions among United States veterans receiving care in the Veterans Health Administration (VHA), and what does that evidence show about the therapies and system-level strategies available to treat it?

Using the Population-Concept-Context framework, this scoping review will map evidence on adults with metabolic dysfunction-associated steatotic liver disease (MASLD), MASLD with increased alcohol intake (MetALD), alcohol-associated liver disease, chronic kidney disease, cardiovascular disease, or metabolic risk factors (obesity, prediabetes, type 2 diabetes, hypertension, dyslipidemia), with priority given to veterans receiving VHA care (Population); addressing epidemiology, genetic architecture, risk stratification, pharmacotherapy, lifestyle and surgical therapy, system-level implementation, and

clinical outcomes across the CKLM spectrum (Concept); within the VHA, including Corporate Data Warehouse and Million Veteran Program analyses, VA/DoD clinical practice guidelines, national formulary policy, and VHA quality improvement programs, supplemented by the landmark randomized trials and consensus documents that govern therapy in populations relevant to veterans (Context).

The specific objectives are: (1) to map the epidemiology and clinical characteristics of CKLM syndrome and its components in the veteran population, including the burden of undiagnosed and unstaged steatotic liver disease; (2) to synthesize veteran-specific and pivotal randomized evidence on therapies with benefit across the CKLM axis (incretin-based therapy, SGLT2 inhibitors, nonsteroidal mineralocorticoid receptor antagonists, thyroid hormone receptor-beta agonists, statins, and lifestyle, pharmacologic, and surgical weight management) and on the system-level strategies that determine their reach; and (3) to identify evidence gaps and propose a testable augmentation of

cardiovascular-kidney-metabolic staging that incorporates hepatic fibrosis assessment for prospective validation in veterans.

Background The cardiovascular-kidney-metabolic (CKM) syndrome framework, operationalized by the 2026 AHA/ACC/ADA/ASN guideline, recommends fibrosis screening for metabolic dysfunction-associated steatotic liver disease (MASLD) but omits the liver from its staging criteria. A cardiovascular-kidney-liver-metabolic (CKLM) construct has been proposed. The Veterans Health Administration (VHA), the largest integrated US health system, carries a heavy burden of this disease and holds the infrastructure to act on it. We mapped evidence on CKLM populations, therapies, and outcomes in veterans.

Rationale The 2023 American Heart Association presidential advisory defined cardiovascular-kidney-metabolic (CKM) syndrome as a single systemic disorder, and the 2026 AHA/ACC/ADA/ASN clinical practice guideline now specifies screening, staging, and stage-based treatment for it. The liver is the conspicuous omission. The guideline acknowledges that metabolic dysfunction-associated steatotic liver disease (MASLD) arises from the same ectopic fat deposition, inflammation, and insulin resistance that define CKM pathophysiology, states that fibrosis stage best predicts adverse outcomes in MASLD, and recommends Fibrosis-4 screening, yet hepatic fibrosis appears nowhere in the staging criteria. Groups in hepatology, endocrinology, and nephrology have therefore proposed a cardiovascular-kidney-liver-metabolic (CKLM) syndrome in which the liver is both a target and an amplifier of multiorgan metabolic injury. To date that proposal has been developed in narrative reviews, consensus statements, and general-population cohorts; it has not been examined within a defined population served by a health system that could act on it.

The Veterans Health Administration (VHA) is the natural setting for that examination. It is the largest integrated health system in the United States, and the veterans it serves are older, predominantly male, and disproportionately affected by obesity, type 2 diabetes, hypertension, alcohol use, chronic kidney disease, and steatotic liver disease. The VHA pairs that burden with assets no other American delivery system holds together: a single national electronic health record and Corporate Data Warehouse, the Million Veteran Program genomic biorepository, a national formulary, the VA/DoD clinical practice guideline program, and mature population health and clinical decision

support tools. Veteran cohorts have generated much of the defining real-world evidence for incretin-based therapy, SGLT2 inhibitors, statins, and bariatric surgery, including hepatic outcomes. At the same time, pharmacotherapy with benefit across all four CKLM domains now exists, but primary care and specialty pathways remain organized by organ and do not reliably identify the veterans who stand to gain.

This evidence is dispersed across hepatology, nephrology, cardiology, endocrinology, genetics, and health services research, and no prior review has brought it together under a CKLM framework for veterans or for any single health system. A scoping review is the appropriate design because the question is one of mapping: establishing what evidence exists on the veteran CKLM population, which therapies and delivery strategies have been evaluated in that population, where the evidence is concentrated, and where it is absent. The review is intended to inform VHA clinical pathways, formulary and guideline decisions, and the design of a prospective validation study of hepatic augmentation of CKM staging in veterans.

METHODS

Strategy of data synthesis Consistent with scoping review methodology, no meta-analysis or pooled estimate will be produced and no formal critical appraisal of individual sources will be performed. Data will be recorded on a standardized charting form capturing first author, year, journal, study design, setting, population, sample size, intervention or exposure, comparator, outcomes, the CKLM domain or domains addressed (cardiovascular, kidney, liver, metabolic), and the principal finding. Interventions will be classified a priori as pharmacologic, lifestyle or surgical, or system-level implementation strategies, the last encompassing clinical decision support, population health dashboards, academic detailing, telehealth, and formulary policy. Quantitative findings will be extracted verbatim from published abstracts or results sections; for sources cited in the narrative synthesis, values will be rechecked against the publisher record, and for guideline and guidance documents against the full text. Sources whose abstract is absent or whose veteran setting cannot be confirmed from the abstract will be flagged for full-text confirmation.

The characteristics of the included sources will be summarized descriptively by design, publication period, sample size, CKLM domains addressed, number of domains per source, and intervention class, and reported in a summary table and a

PRISMA-ScR flow diagram. Findings will then be synthesized narratively within five prespecified thematic domains: (1) the epidemiology and clinical characteristics of the veteran CKLM population, including diagnostic and staging gaps; (2) genetic architecture derived from the Million Veteran Program; (3) therapies across the CKLM axis, organized by agent class and pairing pivotal randomized evidence with veteran-specific real-world evidence on effectiveness, uptake, persistence, and equity; (4) system-level implementation and care delivery within the VHA; and (5) evidence gaps, enumerated using a population-intervention-outcome structure. Evidence tables will map, for each agent class, the CKLM domains in which benefit has been demonstrated and the status of its implementation in the VHA. The synthesis will conclude with a proposed augmentation of cardiovascular-kidney-metabolic staging that incorporates hepatic fibrosis assessment, presented explicitly as a testable framework for prospective validation rather than as a validated staging system.

Title and abstract screening and charting of database-identified records will be performed with large language model assistance applying the written eligibility criteria and charting form under the direction of the first author, who will review the decision log, adjudicate uncertain records with the coauthors, and serve as guarantor of the data.

Eligibility criteria Eligibility is defined using the Population-Concept-Context framework.

Population: adults (18 years or older) with metabolic dysfunction-associated steatotic liver disease (MASLD), MASLD with increased alcohol intake (MetALD), alcohol-associated liver disease (ALD), chronic kidney disease, cardiovascular disease, or metabolic risk factors (obesity, prediabetes, type 2 diabetes, hypertension, dyslipidemia), with priority given to United States veterans receiving care in the Veterans Health Administration (VHA).

Concept: epidemiology and natural history, genetic architecture, risk stratification and noninvasive fibrosis assessment, pharmacotherapy, lifestyle and surgical therapy, system-level implementation strategies, and clinical outcomes (cardiovascular, kidney, liver, metabolic, and mortality) across the cardiovascular-kidney-liver-metabolic spectrum.

Context: the VHA, including analyses of the Corporate Data Warehouse and the Million Veteran Program, VA/DoD clinical practice guidelines, national formulary policy, and VHA quality

improvement and care delivery programs, supplemented by the landmark randomized trials and consensus or guideline documents that govern therapy for populations relevant to veterans.

Types of sources: observational cohort, cross-sectional, and case-control studies; randomized and nonrandomized trials; quality improvement, qualitative, and mixed-methods evaluations; systematic reviews and pooled analyses; modeling and economic analyses; and clinical practice guidelines, consensus statements, and scientific statements. Sources published from January 2000 through August 2026 are eligible, in any language.

Exclusion criteria: pediatric populations; liver disease without a metabolic component, such as isolated viral or autoimmune hepatitis; records outside the Population-Concept-Context criteria; preclinical and mechanistic studies without clinical outcomes; case reports; meeting abstracts without a full report, protocols, registry entries, news items, and editorials without primary data; narrative reviews that duplicate retained primary sources; duplicate co-publications of the same consensus document in a second journal; methodological guidance superseded by a retained source; and records that cannot be retrieved.

Source of evidence screening and selection All records retrieved from PubMed/MEDLINE, the Cochrane Library (Cochrane Database of Systematic Reviews and CENTRAL), the Web of Science Core Collection, and Ovid MEDLINE, together with records identified through structured citation chasing from prespecified seed documents (guidelines, consensus statements, and landmark veteran cohort publications), grey literature, and direct retrieval, will be compiled into a single bibliographic ledger and deduplicated by PubMed identifier, digital object identifier, and normalized title.

Unique records will be screened on title and abstract against the Population-Concept-Context criteria. Records identified through citation chasing will be screened in a single documented stage that proceeds to full text where eligibility cannot be resolved from the abstract. Cochrane and Web of Science records lacking a corresponding full report will be verified against PubMed to distinguish published articles from meeting abstracts and registry entries; Web of Science records that prove to be meeting abstracts of articles already screened will be treated as duplicates. Records whose abstract is absent or whose veteran setting cannot be confirmed from the abstract will be

retained provisionally and flagged for full-text confirmation.

Screening yields, reasons for exclusion at each stage, and the number of sources retained from each database and from citation chasing will be reported in a PRISMA-ScR flow diagram, and the search strategies, yields, and selection ledger will be reported in full in the supplementary material.

Data management Search results from each database will be exported with the full search string, date, limits, and yield recorded at the time of searching, and all records will be merged into a single bibliographic ledger in which each record carries its source database or identification method, PubMed identifier, digital object identifier, first author, year, journal, and title. Deduplication will be performed in the ledger by PubMed identifier, digital object identifier, and normalized title, and the number of duplicates removed will be recorded for the flow diagram.

Screening decisions will be stored in structured decision logs, one per database batch, with a record-level decision (include or exclude), the assigned exclusion reason code, and a brief justification. Included sources will be assigned a unique study identifier and entered into a master inventory containing the charted fields (bibliographic details, design, setting, population, sample size, intervention class, CKLM domains addressed, principal finding, and a flag for sources requiring full-text confirmation). Abstracts retrieved for database-identified records will be stored with the inventory so that every extracted value can be traced to its source text. Bibliographic details of all cited sources will be verified against PubMed and Crossref records before submission, and a reference verification ledger will record the outcome for each source.

All files (search strategies and yields, bibliographic ledger, decision logs, master inventory, abstracts, charting outputs, and verification ledger) will be maintained by the first author in a version-controlled project folder with date-stamped copies retained at each major stage (initial citation chasing, database searching, screening, charting, and submission). The charting summary for every included source will be published as a supplementary table, the full inventory of included sources not cited in the main text will be published as a supplementary reference list, and the complete decision logs will be available from the corresponding.

Language restriction Yes, only English.

Country(ies) involved United States.

Keywords cardiovascular-kidney-liver-metabolic syndrome; cardiovascular-kidney-metabolic syndrome; metabolic dysfunction-associated steatotic liver disease; liver fibrosis; chronic kidney disease; veterans; Veterans Health Administration; glucagon-like peptide-1.

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