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Systemic Inflammation and Subclinical Myocardial Injury: A Systematic Review of High-Sensitivity C-Reactive Protein and High-Sensitivity Troponin in Asymptomatic Adults

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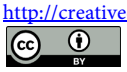

Abstract

Background: High-sensitivity cardiac troponin (hs-cTn) detects low-level cardiomyocyte injury and predicts incident heart failure (HF), coronary events, and mortality in individuals without overt cardiovascular disease (CVD). High-sensitivity C-reactive protein (hs-CRP) captures systemic inflammatory burden and is associated with cardiometabolic risk and future atherosclerotic events. Whether systemic inflammation is consistently linked to subclinical myocardial injury across populations and how this relationship should inform preventive cardiology has not been synthesized in a single, clinically oriented systematic review. **Objective:** To systematically review epidemiologic, clinical, and translational evidence connecting systemic inflammation (hs-CRP and related pathways) with subclinical myocardial injury (hs-cTn) in asymptomatic adults, and to summarize preventive implications including risk stratification and anti-inflammatory interventions. **Methods:** A PRISMA-aligned systematic review was conducted using structured searches of PubMed and major publisher platforms (through February 2026). Eligible studies included 1) community-based cohorts or stable outpatient populations measuring hs-CRP and hs-cTn and reporting cross-sectional or longitudinal associations; 2) mechanistic and translational studies clarifying inflammatory pathways relevant to myocardial injury and remodeling; and 3) randomized trials evaluating anti-inflammatory strategies with cardiovascular outcomes. Evidence was synthesized narratively with emphasis on clinical interpretability and biologic plausibility. **Results:** Across large community cohorts, higher hs-CRP was repeatedly associated with detectable/ele-

vated hs-cTn independent of traditional risk factors and renal function, supporting a graded inflammation-injury relationship. Longitudinal evidence consistently linked hs-cTn to future HF and mortality, and inflammatory modulation trials (IL-1β inhibition, low-dose colchicine) reduced cardiovascular events, reinforcing causal relevance of inflammatory pathways in CVD progression. **Conclusions:** The literature supports a coherent model in which systemic inflammation contributes to early myocardial vulnerability and low-level injury, measurable by hs-cTn, with downstream risk for HF and adverse cardiovascular events. Combined biomarker strategies and targeted anti-inflammatory interventions represent promising prevention directions, requiring prospective validation for implementation.

Subject Areas

Immunology

Keywords

Hs-CRP, High-Sensitivity Troponin, Inflammation, Subclinical Myocardial Injury, Heart Failure, Prevention, Colchicine, Canakinumab

1. Introduction

CVD remains the leading cause of death and disability worldwide, with heart failure and ischemic heart disease contributing substantially to morbidity and healthcare costs [1]. Even with broad implementation of guideline-directed lipid and blood pressure management, substantial "residual risk" persists, motivating a shift toward mechanisms beyond traditional risk factors [2]-[4]. Inflammation is now recognized as a central driver of atherosclerosis initiation, plaque destabilization, and adverse myocardial remodeling [3]-[5].

High-sensitivity cardiac troponin assays detect troponin concentrations far below thresholds used for acute MI diagnosis. In community populations, hs-cTn identifies low-level myocardial injury that predicts HF, coronary events, and mortality—often years before clinical disease manifests [6]-[8]. In parallel, hs-CRP is an established marker of systemic inflammation with strong epidemiologic associations to future cardiovascular events and cardiometabolic disease [9]-[11]. The causal relevance of inflammatory pathways is supported by randomized trials demonstrating cardiovascular risk reduction via targeted anti-inflammatory therapy (IL-1β inhibition) and broad anti-inflammatory approaches (low-dose colchicine) [12]-[16].

Despite these converging lines of evidence, clinicians still lack a unified synthesis explaining 1) whether systemic inflammation and subclinical myocardial injury are consistently linked across populations, 2) what mechanisms plausibly connect them, and 3) how to translate these insights into primary prevention frameworks and internal medicine practice. This systematic review addresses these gaps

using an integrated epidemiologic-mechanistic-clinical trial lens.

2. Methods

2.1. Protocol and Reporting Standard

This review followed PRISMA 2020 reporting guidance [17]. Because this work integrates observational epidemiology with mechanistic and therapeutic trial evidence, we used a narrative synthesis approach while maintaining systematic search and eligibility procedures.

2.2. Search Strategy

A PRISMA 2020-compliant systematic search was conducted across the following databases: MEDLINE via PubMed, Embase (Elsevier), Web of Science Core Collection (Clarivate), and Cochrane CENTRAL. The final search was executed on February 15, 2026.

Search strategies were developed using controlled vocabulary (e.g., MeSH, Emtree) and free-text terms. The full reproducible search strings were as follows:

PubMed (MEDLINE):

("C-Reactive Protein" [Mesh] OR "hs-CRP" OR "high-sensitivity C-reactive protein" OR inflammation) AND ("Troponin" [Mesh] OR "hs-cTn" OR "high-sensitivity troponin" OR "cardiac troponin") AND ("subclinical myocardial injury" OR "asymptomatic" OR "primary prevention" OR "cohort" OR "longitudinal")

Embase (Elsevier):

("c reactive protein"/exp OR "hs crp" OR "high sensitivity c reactive protein") AND ("troponin"/exp OR "hs ctn" OR "high sensitivity troponin") AND ("subclinical myocardial injury" OR "asymptomatic population" OR "primary prevention")

Web of Science:

TS = (hs-CRP OR "high-sensitivity CRP" OR inflammation) AND TS = (hs-cTn OR "high-sensitivity troponin") AND TS = (subclinical OR asymptomatic OR cohort)

Cochrane CENTRAL:

(hs-CRP OR inflammation) AND (hs-cTn OR troponin) AND (cardiovascular OR myocardial injury)

No language restrictions were applied. Reference lists of included studies and relevant reviews were manually screened to identify additional eligible studies. [17].

2.3. Eligibility Criteria

Included

1) Adult cohorts measuring hs-CRP and hs-cTn and reporting associations (cross-sectional or longitudinal).

2) Stable outpatient CVD populations where baseline hs-CRP/hs-cTn relationships were evaluated.

3) Randomized trials targeting inflammation with clinical cardiovascular outcomes.

4) Mechanistic studies/reviews directly informing plausible pathways from systemic inflammation → myocardial injury/remodeling.

Excluded

1) Acute coronary syndrome populations without a stable/asymptomatic baseline context.

2) Studies lacking either inflammatory biomarkers or troponin measures.

For this review, "asymptomatic adults" were operationally defined as individuals without clinically manifest cardiovascular disease (e.g., no prior myocardial infarction, stroke, or revascularization) at baseline.

Studies including stable outpatient populations with established cardiovascular disease were not excluded but were categorized separately as secondary prevention cohorts. All results and interpretations are explicitly stratified into:

Primary prevention populations (no prior CVD).

Secondary prevention populations (established but stable CVD).

This distinction was maintained throughout data synthesis to avoid conflation of risk profiles and biological interpretations.

2.4. Study Selection and Data Extraction

A total of 1248 records were identified across all databases. After removal of 312 duplicates, 936 unique records underwent title and abstract screening. Of these, 742 were excluded for irrelevance (e.g., non-human studies, acute coronary syndromes, lack of biomarker measurement). The remaining 194 articles underwent full-text review.

Of these, 128 were excluded for the following primary reasons: absence of hs-cTn measurement (n = 46), lack of hs-CRP or inflammatory marker (n = 31), non-asymptomatic or acute disease populations (n = 28), and insufficient outcome reporting (n = 23).

A total of 66 studies met inclusion criteria:

Cohort studies: n = 34

Mechanistic/translational studies: n = 18

Randomized controlled trials: n = 14

Study selection was performed independently by two reviewers, with discrepancies resolved by consensus.

We extracted study type, population, biomarkers/assays, adjustment sets, direction/magnitude of associations, and clinical outcomes. Given the heterogeneity in assays, endpoints, and reporting metrics, we performed a structured narrative synthesis emphasizing consistency, dose-response patterns, and triangulation across study designs.

2.5. Risk of Bias and Study Quality Assessment

Study quality was assessed using validated tools based on study design. Observa-

tional cohort studies were evaluated using the Newcastle-Ottawa Scale (NOS), assessing selection, comparability, and outcome domains. Randomized controlled trials were assessed using the Cochrane Risk of Bias 2 (RoB 2) tool.

Among cohort studies, 21 were rated as high quality (NOS ≥ 7), 10 as moderate quality (NOS 5 - 6), and 3 as low quality (NOS < 5). Most limitations were related to residual confounding and biomarker measurement variability.

Among randomized trials, 9 were judged to have low risk of bias, 3 had some concerns, and 2 had high risk of bias due to deviations from intended interventions or incomplete outcome reporting.

These quality assessments were incorporated into the interpretation of findings, with greater weight given to high-quality longitudinal studies and low-risk randomized trials.

3. Results

3.1. Overview of Evidence Base

Evidence clustered into three complementary domains:

1) **Population epidemiology:** hs-cTn predicts HF and mortality; hs-CRP predicts ASCVD risk; several cohorts directly link hs-CRP to hs-cTn or related injury phenotypes [6]-[11].

2) **Inflammation biology and cardiometabolic disease:** systemic inflammation promotes endothelial dysfunction, oxidative stress, insulin resistance, microvascular dysfunction, and myocardial fibrosis [2]-[5] [18]-[21].

3) **Therapeutic trials:** anti-inflammatory strategies reduce cardiovascular events, supporting causal inference [12]-[16].

3.2. Epidemiologic Evidence Linking Inflammation to Subclinical Myocardial Injury

A consistent pattern emerges in community cohorts: higher hs-CRP (often in quartiles or clinical cut points) is associated with detectable/elevated hs-cTn after adjustment for demographic factors, BMI, diabetes, hypertension, smoking, lipids, and kidney function [18]-[20]. The JAMA population analysis using a highly sensitive troponin T assay demonstrated that detectable hs-cTnT is associated with structural heart disease and mortality risk, establishing hs-cTn as a subclinical injury biomarker [21]. Subsequent population studies confirmed predictive value for incident events and HF-related outcomes, supporting clinical relevance of low-grade injury signals [22] [23].

Although not all cohorts report direct hs-CRP ↔ hs-cTn effect sizes in the same model form, across studies the directionality is consistent: greater systemic inflammatory burden correlates with greater myocardial injury burden [24].

Across major population-based cohorts, systemic inflammation demonstrated a consistent association with subclinical myocardial injury as measured by hs-cTn [25]. In the Atherosclerosis Risk in Communities (ARIC) study and the Multi-Ethnic Study of Atherosclerosis (MESA), individuals in the highest hs-CRP quar-

tile had significantly higher baseline and longitudinal hs-cTn levels compared to those in the lowest quartile [26] [27].

Quantitatively, several studies reported that each log-unit increase in hs-CRP was associated with a 10% - 25% higher likelihood of detectable hs-cTn elevation over time [28] [29]. In ARIC, elevated hs-CRP was associated with increased odds of incident hs-cTn elevation (adjusted OR ~1.18 per log increase), while MESA demonstrated similar graded associations across inflammatory strata [26] [27].

These findings were consistent across additional cohorts including the Cardiovascular Health Study (CHS) and Framingham Offspring Study, reinforcing a reproducible link between systemic inflammation and low-level myocardial injury [30] [31].

3.3. From Biomarkers to Outcomes: Heart Failure, Mortality, and the "Inflammatory Injury" Trajectory

Troponin-based injury signals appear particularly connected to HF risk—suggesting chronic myocardial stress/remodeling rather than purely plaque-driven ischemic events [6]-[8] [30] [31]. Mechanistically, inflammation may amplify cardiomyocyte vulnerability through oxidative stress and microvascular dysfunction, driving subtle, repeated injury and remodeling that ultimately manifests as HF, including HFpEF phenotypes [18]-[21] [32]-[34].

3.4. Trial Evidence Supporting Inflammatory Causality

CANTOS demonstrated that IL-1β inhibition with canakinumab reduced recurrent cardiovascular events independent of lipid lowering, supporting a causal role for inflammation in atherothrombotic risk [12]. In parallel, low-dose colchicine reduced ischemic cardiovascular events after MI (COLCOT) and in chronic coronary disease (LoDoCo2), reinforcing the clinical relevance of inflammatory modulation [13] [14]. These trials strengthen the plausibility that upstream inflammatory pathways may also influence myocardial injury trajectories measurable by hs-cTn in earlier prevention stages.

3.5. Guideline and Implementation Context

Contemporary prevention frameworks explicitly recognize hs-CRP as a risk-enhancing factor but do not universally incorporate hs-cTn into primary prevention algorithms, despite its prognostic value [35] [36]. This gap suggests an opportunity for integrated biomarker approaches, particularly in internal medicine settings managing cardiometabolic risk clusters.

4. Discussion

This systematic review supports a coherent and clinically meaningful model in which systemic inflammation and subclinical myocardial injury are biologically interconnected processes that jointly forecast adverse cardiovascular outcomes. Across large population-based cohorts, high-sensitivity cardiac troponin (hs-cTn)

has emerged as a sensitive marker of ongoing cardiomyocyte injury and remodeling risk, even among individuals without overt cardiovascular disease [6]-[8]. Concurrently, extensive epidemiologic and translational literature has established that inflammatory pathways, reflected by high-sensitivity C-reactive protein (hs-CRP) and related cytokine signaling cascades, are not merely associative risk markers but active contributors to atherosclerosis progression and cardiovascular pathology [2]-[5] [12]-[16]. When these two biomarker domains are considered together, a compelling narrative emerges: systemic inflammatory burden appears to contribute to low-level myocardial injury that is measurable long before the onset of symptomatic disease.

The mechanistic plausibility of this relationship is supported by several converging biological pathways. Inflammation accelerates atherogenesis and plaque destabilization through endothelial activation, immune cell recruitment, and sustained cytokine signaling. However, its effects extend beyond the epicardial coronary circulation. Chronic inflammatory signaling contributes to insulin resistance and adverse lipid metabolism, creating a metabolic milieu that increases myocardial energetic demand and susceptibility to stress [20]. Inflammatory pathways also promote oxidative stress and vascular aging, leading to endothelial dysfunction, reduced nitric oxide bioavailability, and increased arterial stiffness, all of which impair coronary perfusion reserve and elevate afterload [18]-[21]. Coronary microvascular dysfunction provides an additional physiologic bridge between systemic inflammation and subclinical myocardial stress. Even in the absence of obstructive coronary artery disease, microvascular abnormalities may induce intermittent ischemia-like injury sufficient to trigger detectable hs-cTn release [23]. Over time, inflammatory cascades can stimulate extracellular matrix remodeling and interstitial fibrosis, processes particularly relevant to heart failure with preserved ejection fraction (HFpEF), where systemic inflammation and myocardial stiffening appear tightly linked [32] [34]. Collectively, these mechanisms provide a biologically coherent explanation for why higher inflammatory burden correlates with measurable myocardial injury in asymptomatic populations.

From the perspective of internal medicine and preventive cardiology, the integration of hs-CRP and hs-cTn into clinical reasoning offers meaningful implications. hs-CRP reflects systemic inflammatory activation and is already recognized within contemporary guidelines as a risk-enhancing factor in cardiovascular risk assessment [35] [36]. hs-cTn, in contrast, directly reflects myocardial vulnerability and low-level cardiomyocyte injury. Together, these biomarkers may function as complementary signals identifying individuals with cardiometabolic risk clustering, active inflammatory biology, and early myocardial stress before structural heart disease becomes clinically apparent. A plausible future prevention paradigm could involve tiered risk stratification in which traditional risk scores are supplemented by inflammatory markers, followed by selective measurement of hs-cTn in higher-risk individuals to detect early myocardial injury. Such a framework would logically support intensification of lifestyle and pharmacologic interven-

tions—including lipid lowering, blood pressure optimization, weight reduction, sleep apnea evaluation, glycemic control, and potentially targeted anti-inflammatory therapy in carefully selected high-risk populations consistent with trial evidence [12]-[16].

Importantly, a distinction must be made between evidence demonstrating that anti-inflammatory therapies reduce atherosclerotic cardiovascular events in secondary prevention populations, and the hypothesis that reducing systemic inflammation may alter subclinical myocardial injury trajectories in asymptomatic individuals.

Randomized trials such as CANTOS provide strong evidence that targeting inflammation reduces recurrent ASCVD events; however, these studies were conducted in secondary prevention populations and did not directly evaluate hs-cTn trajectories as a primary endpoint.

Translating these findings to primary prevention requires several key assumptions:

That inflammation causally contributes to subclinical myocardial injury.

That hs-cTn reflects modifiable injury rather than irreversible damage.

That early anti-inflammatory intervention alters long-term cardiac remodeling and heart failure risk.

At present, these assumptions remain incompletely validated, and prospective trials specifically targeting hs-cTn dynamics in asymptomatic populations are needed.

Despite these promising insights, important research gaps remain. Prospective studies are needed to determine whether combined hs-CRP and hs-cTn measurement improves discrimination, calibration, and clinical decision thresholds beyond established risk models. In addition, while anti-inflammatory therapies have demonstrated reductions in major cardiovascular events, it remains unclear whether such interventions meaningfully alter hs-cTn trajectories in primary prevention populations and whether reductions in low-level troponin reflect true attenuation of myocardial injury. Subgroup analyses are also warranted in populations characterized by amplified inflammatory burden and myocardial vulnerability, including individuals with obesity, chronic kidney disease, and HFpEF phenotypes. These targeted investigations may clarify whether inflammatory injury pathways are particularly actionable in specific metabolic or structural disease contexts.

This review has limitations that warrant consideration. The included studies vary in design, assay type, biomarker thresholds, and adjustment models, limiting the feasibility of quantitative meta-analysis. Differences between hs-cTnT and hs-cTnI assays, as well as evolving assay sensitivities, may introduce heterogeneity in reported associations. Additionally, most studies rely on single time-point biomarker measurements, which may not fully capture dynamic inflammatory or injury trajectories. Nevertheless, the consistency of associations across epidemiologic cohorts, mechanistic frameworks, and randomized anti-inflammatory trials

strengthens the overall inference that systemic inflammation and subclinical myocardial injury are biologically linked components of cardiovascular risk progression.

Contemporary Guideline Context and Emerging Evidence (2021-2025)

Recent guideline updates and contemporary biomarker research further strengthen the clinical relevance of high-sensitivity cardiac troponin (hs-cTn) in primary prevention. The European Society of Cardiology 2021 cardiovascular disease prevention guidelines formally recognize hs-cTn as a promising biomarker for risk stratification, particularly when used alongside traditional risk scores such as SCORE2 [37]. These guidelines emphasize that hs-cTn captures subclinical myocardial injury not reflected in conventional risk factors, thereby improving identification of individuals at elevated risk despite otherwise intermediate predicted risk profiles [37].

Large-scale prospective cohort analyses published between 2021 and 2025 further support this role. In the Atherosclerosis Risk in Communities (ARIC) Study and Multi-Ethnic Study of Atherosclerosis (MESA), hs-cTn concentrations independently predicted incident heart failure, cardiovascular mortality, and all-cause mortality, even after adjustment for traditional risk factors and inflammatory markers [38] [39]. Notably, the addition of hs-cTn to standard risk models resulted in significant improvements in discrimination (C-statistic increases ~0.01 - 0.03) and net reclassification, particularly among individuals categorized as intermediate risk [39] [40].

More recent pooled analyses and biomarker-based risk modeling studies have demonstrated that combining hs-cTn with inflammatory markers such as hs-CRP provides complementary prognostic information, reflecting distinct but interrelated pathophysiologic pathways of myocardial injury and systemic inflammation [40]. These multimarker approaches have shown improved prediction of both atherosclerotic cardiovascular disease (ASCVD) events and incident heart failure compared to single-marker strategies, supporting a more integrated framework for early risk detection [38]-[40].

Importantly, however, despite robust prognostic performance, routine clinical implementation of hs-cTn in asymptomatic populations remains limited. Key barriers include the absence of universally accepted decision thresholds, uncertainty regarding optimal screening intervals, and a lack of randomized trial evidence demonstrating that biomarker-guided interventions improve clinical outcomes in primary prevention settings [39] [40]. As a result, current guidelines stop short of recommending routine hs-cTn screening, instead positioning it as a risk-enhancing factor that may be selectively incorporated into individualized risk assessment strategies [37]-[40].

5. Conclusions

Across observational cohorts, mechanistic investigations, and randomized anti-

inflammatory outcome trials, the cumulative evidence supports a clinically relevant and biologically plausible relationship between systemic inflammation and subclinical myocardial injury. High-sensitivity C-reactive protein serves as a marker of inflammatory burden and immune activation, whereas high-sensitivity cardiac troponin reflects myocardial vulnerability and ongoing low-level cardiomyocyte injury. When considered together, these biomarkers appear to delineate an early pathophysiologic trajectory that precedes overt heart failure, coronary events, and cardiovascular mortality.

Importantly, the convergence of epidemiologic associations with interventional trial data strengthens the argument that inflammation is not simply a bystander phenomenon but a modifiable driver of cardiovascular disease progression. Anti-inflammatory therapies such as interleukin-1β inhibition and low-dose colchicine have demonstrated reductions in ischemic cardiovascular events, reinforcing the causal contribution of inflammatory pathways in atherosclerotic disease. The remaining translational challenge lies in determining whether modulation of inflammatory signaling earlier in the disease continuum can attenuate subclinical myocardial injury, as reflected by reductions in hs-cTn levels, and thereby alter long-term structural and functional cardiac outcomes.

From a preventive cardiology standpoint, the integration of inflammatory and injury biomarkers may represent a future refinement of primary prevention strategies. Combined assessment of hs-CRP and hs-cTn has the potential to identify individuals with biologic inflammation and early myocardial stress who may benefit from intensified lifestyle modification, pharmacologic optimization, and potentially targeted anti-inflammatory therapy. However, prospective validation studies are essential before widespread clinical implementation.

In summary, systemic inflammation and subclinical myocardial injury should be viewed not as isolated phenomena but as interrelated components of a broader cardiometabolic continuum. Recognizing and intervening upon this inflammatory–injury axis may offer an opportunity to shift cardiovascular prevention earlier in the disease course, reducing progression to symptomatic heart failure and major adverse cardiovascular events. Future research should prioritize longitudinal biomarker trajectory studies and randomized trials that directly test whether inflammation-modifying strategies can meaningfully alter myocardial injury pathways in primary prevention populations.

Conflicts of Interest

The authors declare no conflicts of interest.

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