

High-sensitivity C-reactive protein across the cardiovascular–kidney–metabolic syndrome spectrum: a nationally representative, survey-weighted analysis of US adults

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Cardiovascular–kidney–metabolic (CKM) syndrome, defined by the American Heart Association (AHA) in 2023 and codified in the 2026 AHA/American College of Cardiology (ACC)/American Diabetes Association (ADA)/American Society of Nephrology (ASN) clinical practice guideline, integrates excess and dysfunctional adiposity, metabolic risk factors, chronic kidney disease, and cardiovascular disease into a 0–4 staging framework.^{1,2} Dysfunctional adipose tissue, central to CKM pathophysiology, produces proinflammatory and prooxidative mediators that contribute to systemic inflammation, a state implicated in the metabolic, renal, and cardiovascular manifestations that define higher CKM stages.¹ High-sensitivity C-reactive protein (hsCRP) is the most accessible clinical index of this inflammatory burden and is embedded in cardiovascular prevention guidelines.³ A rapidly expanding National Health and Nutrition Examination Survey (NHANES) literature links systemic inflammation to CKM syndrome but has relied predominantly on composite blood-count indices, such as the systemic immune-inflammation index and leukocyte-to-HDL-cholesterol ratio, rather than a single guideline-endorsed acute-phase biomarker; few studies have mapped hsCRP onto the full 0–4 staging spectrum in a nationally representative, survey-weighted sample.^{4,5} We hypothesized that hsCRP would show a graded association with CKM stage severity that persists after multivariable adjustment.

We analysed the NHANES 2015–2018 fasting subsample, a complex multistage probability sample of US adults. This

window is the only continuous NHANES period in which standardized hsCRP measurement, introduced in 2015–2016, coincides with the detailed prescription-medication data required for CKM staging, given the Coronavirus disease 2019 (COVID-19) interruption of 2019–2020 collection and the absence of medication-name data in the 2021–2023 cycle. Participants with hsCRP > 10 mg/L ($n = 425$) were excluded *a priori* as likely reflecting acute rather than chronic inflammation, consistent with established convention; the analytic sample comprised 4315 adults. Cardiovascular–kidney–metabolic Stages 0–4 were operationalized per the AHA framework using examination and laboratory data, the 2021 race-free Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation, and the Kidney Disease: Improving Global Outcome (KDIGO) albuminuria criteria; our staging reproduced previously published national CKM stage distributions.^{1,2} High-sensitivity C-reactive protein was modelled continuously (per 1 mg/L), dichotomized at the 2-mg/L primary-prevention cut-point,³ and in clinical categories (<1, 1–3, and ≥ 3 mg/L). Because the AHA CKM stages form an ordered but non-equidistant clinical hierarchy for which a fully survey-weighted proportional-odds model did not converge stably, the primary analysis was a survey-weighted multinomial logistic model of the five-level stage variable, from which stage-specific odds ratios (each stage vs. the immediately preceding stage, e.g. Stage 1 vs. Stage 0) were derived; this specification allows the hsCRP association to vary freely across stages and estimates

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each contrast using a fixed, non-overlapping referent. As a sensitivity analysis assessing robustness to model specification, we additionally fit cumulative dichotomizations of the ordinal stage (stage $\geq k$ vs. stage $< k$) in separate survey-weighted binary logistic models; this specification estimates the association of hsCRP with the odds of being at or beyond each severity threshold, using a pooled lower-stage referent that provides larger, more stable comparison groups than the adjacent-stage contrasts. Both specifications incorporated NHANES strata, primary sampling units, and the fasting subsample weight and adjusted for age, sex, race and ethnicity, education, income, heart rate, blood pressure, total cholesterol, fasting glucose, fasting insulin, smoking, and physical activity; missing covariates were handled by multiple imputation by chained equations. To assess potential over-adjustment by cardiometabolic covariates related to CKM staging, we additionally fit minimally adjusted models, including only demographic and socioeconomic covariates, smoking, and physical activity. Analyses used public, de-identified data and were exempt from institutional review.

The weighted sample represented 212 847 593 US adults (mean age 48.0 years; 50.2% women; mean hsCRP 2.40 mg/L). Survey-weighted CKM stage prevalence was 10.4%, 25.8%, 50.6%, 4.2%, and 9.0% for Stages 0–4. The unweighted analytic sample comprised 4315 adults (unweighted $n = 347, 946, 2,247, 256$, and 519 for Stages 0–4). Mean hsCRP rose stepwise across stages (1.09, 2.06, 2.75, 2.80, and 2.79 mg/L; $P < 0.001$ for trend), with the single largest increment between Stage 0 and Stage 1 (+0.97 mg/L; +89%), the stage defined by excess or dysfunctional adiposity, and a plateau thereafter (Figure 1A and B).

In the primary adjacent-stage multinomial models, the hsCRP association was strongest for Stage 1 vs. Stage 0 [hsCRP ≥ 2 vs. < 2 mg/L: odds ratio (OR), 1.76; 95% confidence interval (CI), 1.50–2.06; per 1 mg/L: OR, 1.26; 1.20–1.32]. Subsequent adjacent-stage associations were generally smaller and varied by hsCRP specification: for the binary specification, associations remained significant for Stage 2 vs. Stage 1 (OR, 1.25; 1.04–1.50) and Stage 3 vs. Stage 2 (OR, 1.34; 1.12–1.60), whereas the continuous specification was significant only for Stage 2 vs. Stage 1 (OR, 1.06; 1.05–1.08) and not for Stage 3 vs. Stage 2 (OR, 1.06; 0.98–1.15); both specifications were null for Stage 4 vs. Stage 3 (binary OR, 0.94; 0.79–1.13; per 1 mg/L OR, 1.02; 0.98–1.05) (Figure 1C).

As a sensitivity analysis, cumulative-threshold models reproduced this pattern using an independent parameterization: hsCRP ≥ 2 vs. < 2 mg/L was associated with 2.5-fold higher odds of CKM stage ≥ 1 (OR, 2.54; 1.64–3.95) and 55% higher odds of stage ≥ 2 (OR, 1.55; 1.18–2.04), but was not statistically significant at stage ≥ 3 (OR, 1.37; 0.98–1.92) or ≥ 4 (OR, 1.32; 0.92–1.91). Because the referent group in this specification pools all lower stages and changes composition at each threshold, these estimates are not stage specific; the apparent discordance between the non-significant cumulative estimate at stage ≥ 3 and the significant Stage 2 vs. Stage 3 multinomial contrast (OR, 1.34; 1.12–1.60) reflects this difference in estimand rather than conflicting findings. Each 1-mg/L higher hsCRP yielded cumulative ORs of 1.45 (1.27–1.65), 1.13 (1.06–1.21), 1.07 (1.01–1.13), and 1.06 (1.00–1.14) for stages ≥ 1 through ≥ 4 . In clinical categories (reference < 1 mg/L), hsCRP ≥ 3 mg/L conferred 4.48-, 2.13-, and 1.48-fold higher odds of stage ≥ 1 , ≥ 2 , and ≥ 3 (95% CI, 2.71–7.43; 1.60–2.84; 1.04–2.11), while

the intermediate 1–3-mg/L category was independently significant only at stage ≥ 1 (OR, 2.11; 1.29–3.42). Minimally adjusted models reproduced this pattern in both specifications, with modestly larger point estimates at lower thresholds; at CKM stage ≥ 3 , for example, the minimally adjusted estimate reached significance (OR, 1.43; 95% CI, 1.05–1.94), where the fully adjusted estimate did not (OR, 1.37; 0.98–1.92), and the fully adjusted models are reported as primary throughout as the more conservative specification.

In this nationally representative analysis, hsCRP increased stepwise across the AHA CKM spectrum and was most strongly and independently associated with Stage 1 vs. Stage 0, with generally smaller adjacent-stage associations at higher stages that varied by hsCRP specification. This pattern is biologically coherent: adipose-derived interleukin-6, reflected by hsCRP, has been described as an early inflammatory perturbation in CKM pathophysiology,⁶ whereas at advanced stages, inflammation becomes one of several competing pathologies. Several factors beyond competing pathophysiology may contribute to the attenuated associations at advanced stages. First, the smaller number of participants at Stage 3 (unweighted $n = 256$) yields wider CIs and limited power to detect associations of the magnitude observed at earlier stages, so attenuation towards the null may partly reflect imprecision. Second, medications more commonly used at higher CKM stages, including statins, renin-angiotensin system inhibitors, and glucose-lowering agents, such as metformin and sodium-glucose cotransporter 2 (SGLT2) inhibitors, can lower hsCRP and may mask associations in advanced disease. Third, higher stages encompass clinically heterogeneous phenotypes; Stage 4, for example, aggregates coronary disease, heart failure, stroke, and peripheral artery disease, which may dilute stage-specific inflammatory signals. Residual confounding by unmeasured factors may also differentially affect estimates across stages. The gradient mirrors prospective data from Li *et al.*,⁷ in which the hsCRP–mortality association was steepest in early CKM stages and attenuated in advanced disease and is broadly consistent with a UK Biobank cohort in which CKM Stages 2–4 carried markedly elevated all-cause mortality risk relative to Stage 0,⁸ underscoring that the prognostic weight of inflammatory and overall CKM burden may diverge across the staging continuum.

Our findings extend a rapidly expanding NHANES literature that has examined inflammation in CKM syndrome largely through composite blood-count indices: the systemic immune-inflammation index shows a graded, dose-responsive association with CKM syndrome and its components⁴ and leucocyte-to-HDL-cholesterol ratios rise across CKM Stages 0–4.⁵ Our analysis differs by quantifying a single, standardized acute-phase reactant that reflects hepatic interleukin-6 signalling rather than a cellular index and by modelling the formal AHA stages with stage-resolved contrasts that localize the strongest hsCRP association to the earliest CKM stage rather than to advanced disease.

These findings should be interpreted with the distinction between marker and mediator in mind. High-sensitivity C-reactive protein is predominantly a biomarker rather than a confirmed causal agent; Mendelian randomization has not supported a causal role for circulating C-reactive protein in cardiovascular disease,⁹ and the validated therapeutic targets lie upstream, in the interleukin-1 β /interleukin-6 axis that hsCRP reflects and

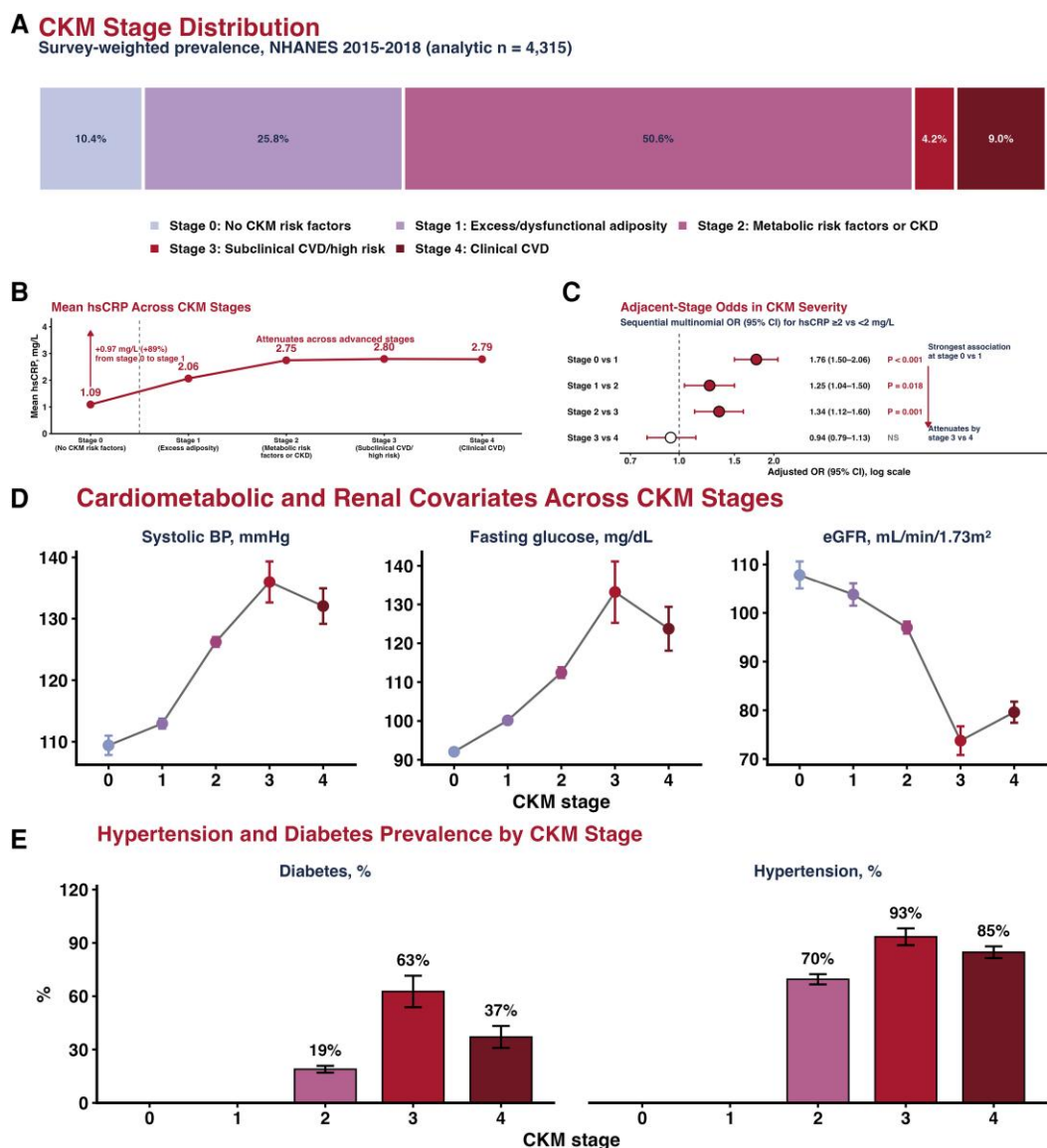


Figure 1 High-sensitivity C-reactive protein across the cardiovascular–kidney–metabolic syndrome continuum in US adults (National Health and Nutrition Examination Survey 2015–2018; unweighted analytic n = 4315). (A) Survey-weighted prevalence of each American Heart Association cardiovascular–kidney–metabolic stage (0–4). (B) Survey-weighted mean high-sensitivity C-reactive protein (mg/L) by cardiovascular–kidney–metabolic stage; the largest increase occurs between Stage 0 and Stage 1 (+0.97 mg/L, +89%), the stage defined by excess or dysfunctional adiposity, with a plateau across Stages 2–4. (C) Primary analysis: fully adjusted adjacent-stage odds ratios (95% confidence interval) from sequential multinomial models for high-sensitivity C-reactive protein ≥ 2 vs. < 2 mg/L, comparing each cardiovascular–kidney–metabolic stage with the immediately preceding stage. The association is strongest for Stage 1 vs. Stage 0 (odds ratio 1.76, 95% confidence interval 1.50–2.06) and generally smaller for subsequent comparisons, which vary by high-sensitivity C-reactive protein specification and are null for Stage 4 vs. Stage 3 (odds ratio 0.94, 0.79–1.13). (D) Survey-weighted mean systolic blood pressure, fasting glucose, and estimated glomerular filtration rate by cardiovascular–kidney–metabolic stage. (E) Survey-weighted prevalence of hypertension and diabetes by cardiovascular–kidney–metabolic stage; both are 0% at Stages 0–1 by definition, as neither condition is among the American Heart Association criteria for those stages. All regression models adjusted for age, sex, race/ethnicity, education, income, heart rate, systolic and diastolic blood pressure, total cholesterol, fasting glucose, fasting insulin, smoking, and physical activity. CI, confidence interval; CKM, cardiovascular–kidney–metabolic; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein; OR, odds ratio.

that anti-inflammatory therapy has been shown to modify in secondary prevention.¹⁰ High-sensitivity C-reactive protein is therefore optimal as an accessible surrogate of a modifiable

inflammatory pathway, supporting its potential evaluation for early CKM risk assessment and as a possible marker of disease severity, rather than as a target itself. Future studies are

warranted to determine which upstream drivers of inflammation hsCRP reflects across the CKM continuum, particularly insulin resistance and dysfunctional adiposity at the earliest stages.

Because the design is cross-sectional, all estimates reflect associations at a single point in time and cannot establish that inflammation precedes, drives, or predicts CKM development or progression. Additional limitations include the single-occasion hsCRP measurement, whereas guideline classification recommends two: the clinical heterogeneity of AHA Stage 2 and possible residual confounding by acute or chronic infection. The adjacent-stage multinomial models also estimate more parameters than the pooled cumulative specification and are correspondingly less precise where stage-specific samples are small (unweighted $n = 347$ and 256 at Stages 0 and 3), so the Stage 3 vs. Stage 2 and Stage 4 vs. Stage 3 contrasts should be interpreted with appropriate caution.

In a nationally representative US adult sample, hsCRP rises stepwise across the AHA CKM spectrum and is most strongly and independently associated with the earliest CKM stage progression. These findings support incorporating inflammation into early, stage-based CKM risk stratification, consistent with the emphasis on early CKM identification in the 2026 AHA/ACC/ADA/ASN guideline, (ii) and provide a population-level rationale for prospective and interventional studies of inflammation-targeted prevention along the CKM continuum.

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Author contributions

Douglas R. Corsi (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Visualization, Writing—original draft [lead], Writing—review & editing [equal]), Mahidere W. Ali (Formal analysis, Methodology, Writing—review & editing [supporting]), and Andrew O. Agbaje (Conceptualization, Formal analysis, Methodology [supporting], Supervision, Writing—review & editing [lead])

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Data availability

This study analysed publicly available third-party data. The NHANES 2015–2016 and 2017–2018 demographic, examination, laboratory, questionnaire, and prescription-medication files that underlie this article are freely available without restriction from the National Center for Health Statistics at <https://wwwn.cdc.gov/nchs/nhanes/>. No new data were generated in the course of this study. The analytic code used to derive CKM stages and fit the reported models is available from the corresponding author on reasonable request.

Ethical approval

Analyses used public, de-identified data and were exempt from institutional review board review.

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