Is High-sensitivity CRP an Independent Predictor of Cardiovascular Events? A Systematic Review and Meta-Analysis

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List of abbreviations

AHA	American Heart Association
CI	Confidence interval
CV	Cardiovascular
CVD	Cardiovascular disease
DM	Diabetes Mellitus
ESC	European Society of Cardiology
HDLc	High density lipoprotein cholesterol
HR	Hazard ratio
hsCRP	High-sensitivity C-reactive protein
ln	Natural logarithm
MI	Myocardial infarction
SBP	Systolic blood pressure
SCORE	Systemic Coronary Risk Estimation
SLGI	Systemic low-grade inflammation
SE	Standard error
QUIPS	Quality in Prognostic Studies Tool

Abstract

Background: cardiovascular disease (CVD) causes 1,71 million EU deaths yearly and substantial healthcare costs. While traditional risk factors (e.g systolic blood pressure, lipid profile, smoking status) currently guide CVD risk prediction, high-sensitivity C-reactive protein (hsCRP) has emerged as a potential risk-enhancing factor due to the role of inflammation in the pathophysiology of atherosclerosis. This systematic review and meta-analysis evaluate hsCRP as an independent predictor for the composite outcome of myocardial infarction (MI), stroke, and cardiovascular (CV) death.

Methods: a systematic review was conducted searching MEDLINE, Embase and Cochrane Library up to April 2025. Prospective cohort studies of adults without baseline CVD reporting multivariable-adjusted hazard ratios (HR) for composite CV events (MI, stroke and CV death) were included. The QUIPS tool was used to assess risk of bias. Log-transformed HRs with standard errors derived from 95% confidence intervals (CI) were pooled using random-effects meta-regression (DerSimonian-Laird).

Results: a total of 12,286 unique records were screened of which four prospective cohort studies (n = 23,069; follow-up 6–16 years) met the inclusion criteria. Overall risk of bias was low, with three studies rated as low risk and one as moderate risk of bias. All studies reported multivariable-adjusted HRs comparing higher versus lower hsCRP categories for composite CV events. Random-effects meta-analysis showed that elevated hsCRP was associated with increased risk of CV events (pooled HR 1.23; 95% CI 1.07–1.43), with moderate heterogeneity ($I^2 = 0.64$).

Conclusion: the findings of this systematic review demonstrate that hsCRP is independently associated with CV events after adjustment for traditional risk factors, thereby supporting its potential as an additional risk marker in primary prevention.

Samenvatting

Achtergrond: cardiovasculaire aandoeningen (CVD) veroorzaken jaarlijks 1,71 miljoen sterfgevallen in de EU en leggen een zware last op de gezondheidszorg. Hoewel traditionele risicofactoren (bv. systolische bloeddruk, lipidenprofiel, rokersstatus) op dit moment de CVD-risicoschatting sturen, maakt hoog-sensitieve C-reactieve proteïne (hsCRP) een opmars als potentiële risicoversterkende factor wegens de rol van inflammatie in de pathofysiologie van atherosclerose. Deze systematische review en meta-analyse evalueren hsCRP als onafhankelijke voorspeller van het gecombineerde eindpunt myocardinfarct (MI), beroerte en cardiovasculaire (CV) mortaliteit.

Methode: er werd een systematische review uitgevoerd in MEDLINE, Embase en de Cochrane Library tot en met april 2025. Prospectieve cohortstudies van volwassenen zonder baseline CVD, die multivariaat-gecorrigeerde hazard ratio's (HR) rapporteerden voor een samengesteld CV eindpunt (MI, beroerte en CV mortaliteit), werden geïncludeerd. Het QUIPS-instrument werd gebruikt om het risico op bias te beoordelen. Log-getransformeerde HR's met standaardfouten afgeleid uit 95% betrouwbaarheidsintervallen (CI) werden gepoold met een random-effects meta-regressie (DerSimonian-Laird).

Resultaten: in totaal werden 12,286 unieke rapporten gescreend, waarvan vier prospectieve cohortstudies (n = 23,069; follow-up 6–16 jaar) aan de inclusiecriteria voldeden. Het algemene risico op bias was laag, gezien drie studies beoordeeld werden als laag risico en één als matig risico op bias. Alle studies rapporteerden multivariaat-gecorrigeerde HR's waarin hogere met lagere hsCRP-categorieën voor een samengesteld CV eindpunt werden vergeleken. Een random-effects meta-analyse toonde aan dat verhoogd hsCRP geassocieerd was met een verhoogd risico op CV events (gepoolde HR 1.23; 95% CI 1.07–1.43), met gematigde heterogeniteit ($I^2 = 0.64$).

Conclusie: de resultaten van deze systematische review tonen aan dat hsCRP onafhankelijk geassocieerd is met CV events na correctie voor traditionele risicofactoren en ondersteunen daarmee het potentieel ervan als aanvullende risicomarker in primaire preventie.

Introduction

Cardiovascular diseases (CVD) remain the leading cause of death in the European Union, accounting for 1,71 million deaths in 2021, equivalent to 32.4% of all deaths (1). Beyond their high mortality rate, CVDs place a substantial burden on the healthcare system, as patients often require prolonged hospital stays and frequently undergo surgical procedures such as coronary artery bypass grafting or transluminal angioplasty. This considerably increases the contribution of CVD to global healthcare expenditure (2,3). The underlying mechanisms of CVD have been extensively studied, and atherosclerosis has been identified as a key process in its development. Atherosclerosis is characterized by arterial wall thickening due to plaque formation, which may lead to arterial stenosis or thrombosis and subsequent obstruction of blood flow to vital organs. Increasing evidence links the pathophysiology of atherosclerosis to inflammation and, more specifically, to its transition to systemic low-grade inflammation (SLGI) or chronic inflammation (4).

The main causal and modifiable risk factors for CVD include elevated low-density lipoprotein cholesterol, high blood pressure, cigarette smoking and diabetes mellitus (DM) (5). Although adiposity is independently associated with CVD, it does not enhance risk prediction when information on the established risk factors is already available (6). The 2021 European Society of Cardiology (ESC) guidelines use age, sex, non-high-density-lipoprotein cholesterol (HDLc), smoking status and systolic blood pressure (SBP) in the Systemic Coronary Risk Estimation 2 (SCORE2) algorithm to estimate an individual's 10-year risk of fatal and non-fatal cardiovascular (CV) events and to guide prevention goals such as antihypertensive and lipid-lowering therapy (5). As absolute CV risk increases, so does the absolute benefit of risk factor management, warranting more intensive therapeutic interventions (5). In addition to these traditional risk factors, non-traditional markers are also being investigated for their potential to enhance risk stratification, with increasing attention to the role of inflammation in the pathogenesis of atherosclerosis. In contrast to chronic inflammation, acute inflammation is a beneficial short-term reaction that protects the body against loss of homeostasis following infection or tissue injury (7,8). These inflammation-induced changes are usually reversible and subside once the triggering factor is eliminated. However, if this recovery phase fails, SLGI can arise (8). Due to the role of SLGI in the pathogenesis of atherosclerosis, high-sensitivity C-reactive Protein (hsCRP) has been proposed as a potential additional risk factor in the prediction of incident CVD.

CRP is an acute-phase protein and a highly sensitive marker of systemic inflammation and tissue injury. In healthy young adults, the median CRP concentration is approximately 0.8 mg/L (9). As a well-standardized, reproducible, and readily accessible biomarker, CRP is widely used in both primary care and hospital settings. Owing to these characteristics, it may have potential as a predictive marker in clinical practice. Current guidelines diverge on hsCRP’s clinical use: the 2021 ESC Guidelines consider hsCRP to have limited additional value in CV risk assessment (5). In contrast, the 2019 American Heart

Association (AHA) Guideline for primary prevention of CVD notes hsCRP as a risk-enhancing factor that may be particularly useful in individuals at intermediate risk (10). This systematic review and meta-analysis aim to evaluate the predictive value of hsCRP as a risk factor for incident CV events in patients without previous CVD. Specifically, it investigates whether elevated hsCRP levels are independently associated with an increased risk of myocardial infarction (MI), stroke and CV death after adjustment for traditional risk factors.

Methods

Search strategy

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations. Eligible studies were identified through comprehensive searches of three scientific databases: MEDLINE, Embase, and the Cochrane Library. Studies were included up to April 2025. A tailored search strategy was developed for each database, with full details available in the Appendix. Retrieved studies were imported into Rayyan for screening, and duplicates were removed.

An initial screening of title and abstract followed by a full-text assessment was conducted by a single reviewer to identify studies meeting the eligibility criteria. Prospective cohort studies were eligible if they enrolled adults without established CVD at baseline, measured hsCRP at baseline and reported multivariable-adjusted hazard ratios (HR) with 95% confidence intervals (CI) for hard CV events: MI, stroke and CV death. Only studies published in English, Dutch, French, or Spanish were included. Reference lists of included studies and relevant reviews were hand-searched. The primary outcome used for this meta-analysis was the composite of non-fatal or fatal MI, non-fatal or fatal stroke and CV death as reported by individual studies. Studies reporting only MI, stroke or CV death as outcomes were not included in the meta-analysis to ensure endpoint comparability

From included studies, the following were extracted using a standardized form: author/year, country, population characteristics (N, age, sex), follow-up duration, event incidence, hsCRP categorization, covariates adjusted and multivariable-adjusted HRs with 95% CIs.

Quality assessment

The quality of the studies was assessed with the Quality in Prognostic Studies Tool (QUIPS) as recommended by the Cochrane Prognosis Methods Group. The QUIPS tool evaluates six domains relevant to quality of prognostic studies: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. For each domain, signalling questions were rated and an overall judgement of risk of bias (low, moderate, high) was assigned. All assessments were performed by a single reviewer, using a standardized QUIPS extraction form.

Statistical analysis

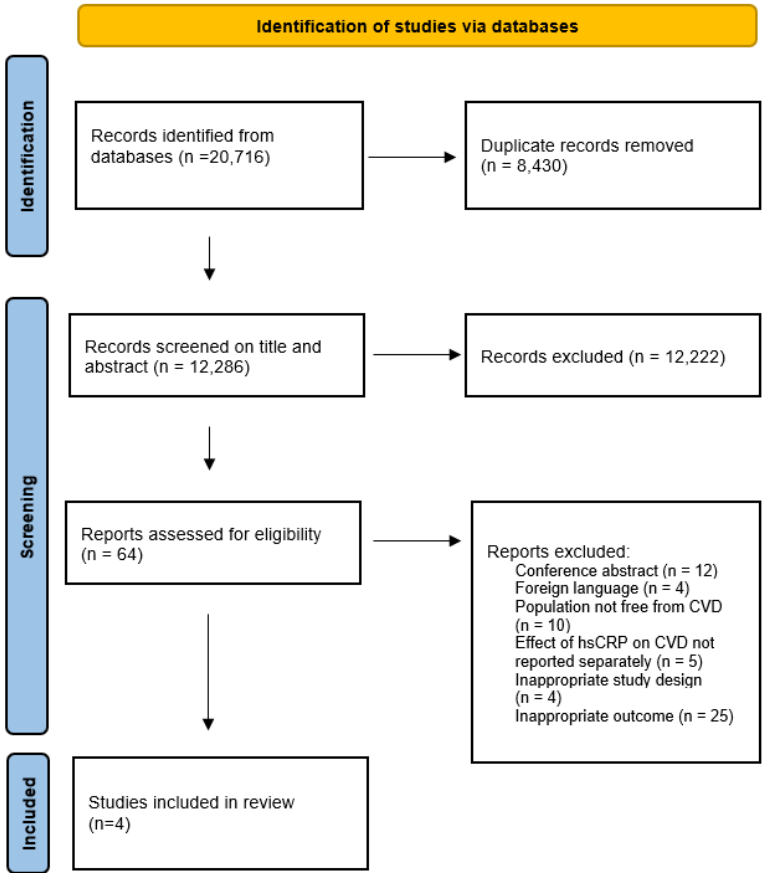
For each study included for the meta-analysis, the multivariable-adjusted HR and its 95% CI for the association between the highest versus the lowest hsCRP categories were extracted. HRs were transformed to the natural logarithm (ln) scale and standard errors (SE) were derived from the reported 95% CI using the formula $SE = \frac{upper\ CI - lower\ CI}{2\ x\ 1.96}$. Weight was then calculated from inverse variance: $\frac{1}{SE^2}$. As heterogeneity between studies was expected, random-effects meta-analysis was performed using an inverse-variance weighting scheme with the DerSimonian-Laird estimator. Pooled lnHR and 95% CI were obtained and then back-transformed to the HR scale for interpretation. Heterogeneity between studies was assessed using the I^2 statistic. A forest plot was generated to visualize individual and pooled estimates, with study weights proportional to inverse variance. All analyses were conducted in SPSS (version 30.0) using the meta-analysis module.

Results

Study selection

Database searches identified 20,716 records, of which 8,430 duplicates were removed. A total of 12,286 unique records were screened based on title and abstract, and 12,222 were excluded at this stage. The full texts of 64 reports were assessed for eligibility; of these, 60 were excluded for the following reasons: conference abstracts (n = 12), foreign language (n = 4), study population not free of CVD (n = 10), effect of hsCRP on CVD not reported separately (n = 5), inappropriate study design (n = 4), and inappropriate outcome (n = 25). Ultimately, four studies met the inclusion criteria and were included in the qualitative synthesis. The selection process is summarized below in Figure 1.

Figure 1. PRISMA 2020 flow diagram of the study selection process



Study characteristics

The four included studies were published between 2011 and 2022. Total sample size was 23,063 with sample sizes ranging from 3,147 to 9,785 participants and with median follow-up durations between 6 and 16 years. HsCRP was analysed as categorical in all studies (e.g. quartiles, clinical cut-offs of ≥2mg/L, ≥3mg/L). All studies adjusted for traditional CV risk factors including age, sex, SBP (or hypertension), smoking, DM, total cholesterol and HDLc. Beer et al. did not adjust for sex as they used a men-only cohort. Cainzos-Achirica et al. stratified analyses by statin use, with the non-statin user cohort included in this meta-analysis. Three studies additionally adjusted for adiposity measures (11–13) (body mass index, waist circumference and waist-to-hip ratio), with some reporting further covariates. Ikezaki et al. did not adjust for adiposity. Key characteristics of the included studies are presented in Table 1.

Table 1. Characteristics of included studies

Author (year)	Country	N	Age (years)	% male	Median FU (years)	Events/N (%)	hsCRP analysis	Covariates
Beer et al. 2011 (12)	Australia	4,382	75.4 (mean)	100	6	15.7	≥3 mg/L	age, SBP, smoking, DM, TC, HDLc, DBP, homocysteine, WHR, self-reported health
Cainzos-Achirica et al. 2018 (11)	USA	5,755	62.0 (median)	47	13.2	10.5	≥2mg/L	age, sex, SBP, smoking, DM, TC, HDLc, race/ethnicity, education, HTN medication, chronic aspirin use, waist circumference
Ikezaki et al. 2019 (14)	USA	3,147	58.0 (mean)	44.5	16	11.2	quartiles	age, sex, HTN, smoking, DM, TC, HDLc, HTN medication, cholesterol medication
Riggs et al. 2022 (13)	USA	9,785	57.0 (median)	46.1	13.4	8.6	quartiles	age, sex, SBP, smoking, DM, TC, HDLc, HTN medication, cholesterol medication, BMI, race/ethnicity.

BMI = body mass index; DBP = diastolic blood pressure; DM = diabetes mellitus; HDLc = HDL cholesterol; HTN = hypertension; SBP = systolic blood pressure; TC = total cholesterol; USA = United States of America; WHR = waist-to-hip ratio

Risk of bias assessment

Overall, the risk of bias was judged to be low to moderate across the included studies with three studies rated as low risk (11–13) and one as moderate risk (14). The latter received high risk rating for the confounding domain due to a lack of adjustment for adiposity, a known CV risk factor that may introduce bias (6). In the same study, moderate risk ratings were also assigned to the study attrition and outcome measurement domains. Specifically, study attrition was rated as moderate due to unclear handling of loss of follow-up, while outcome measurement received a moderate rating because of possible recall bias. A summary of the risk of bias ratings for each study is provided in Table 2 below.

Table 2. Risk of bias ratings summary for included studies

Author, year	Participation	Attirition	Prognostic factor	Outcome	Confounding	Analysis	Overall
Beer et al. 2011 (12)	L	L	L	L	L	L	Low risk
Cainzos-Achirica et al. 2018 (11)	L	L	L	L	L	L	Low risk
Ikezaki et al. 2019 (14)	L	M	L	M	H	L	Moderate risk
Riggs et al. 2022 (13)	L	L	L	L	L	L	Low risk

Ratings: L = low risk of bias; M = Moderate risk of bias; H = high risk of bias. Domains assessed: study participation, study attrition, prognostic factor measurement (hsCRP), outcome measurement, confounding and statistical analysis.

Quantitative synthesis

All four cohort studies reported multivariable-adjusted HRs for the association between higher versus lower hsCRP categories and incident CV events (see Table 3 below). Study-specific HRs ranged from 0.98 to 1.35. Three studies (12–14) showed a positive association between higher hsCRP and risk of hard CVD whereas one study (11) reported a null association.

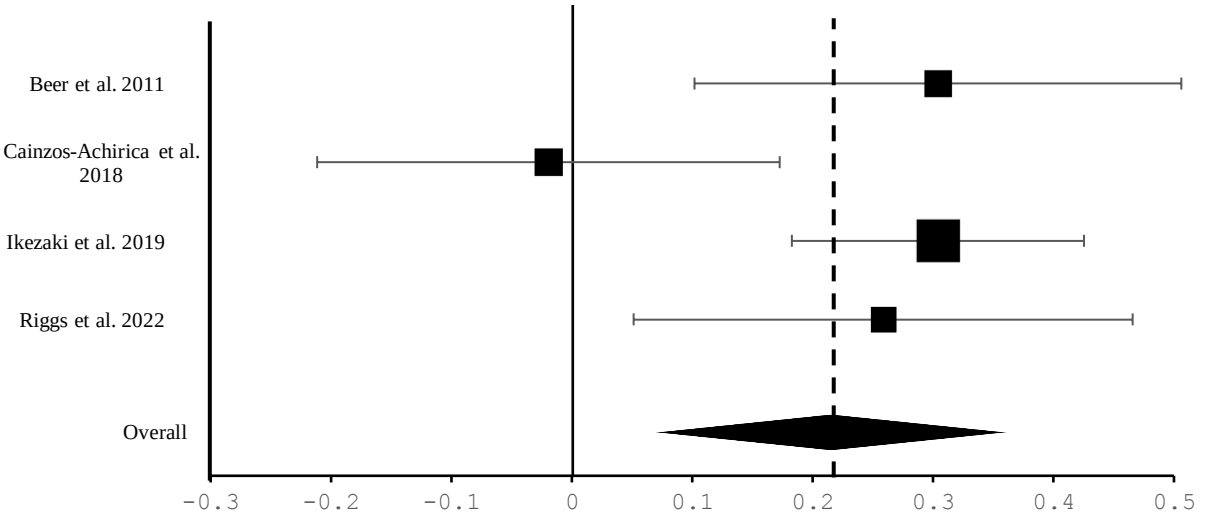
Table 3. Study-specific and Pooled Hazard ratios with ln(HR), Standard Error, Weights and P-value

Author, year	HR (95% CI)	lnHR ± SE (95% CI)	Weight	P-value
Beer et al. 2011 (12)	1.35 (1.11-1.64)	0.30 ± 0.100 (0.10-0.50)	100	<0.01
Cainzos-Achirica et al. 2018 (11)	0.98 (0.81-1.19)	-0.02 ± 0.10 (-0.21-0.17)	104	0.84
Ikezaki et al. 2019 (14)	1.35 (1.15-1.47)	0.30 ± 0.06 (0.18-0.42)	254	<0.01
Riggs et al. 2022 (13)	1.29 (1.05-1.59)	0.26 ± 0.11 (0.05-0.46)	89	0.02
Pooled	1.23 (1.07-1.43)	0.21 ± 0.07 (0.07-0.36)		<0.01

CI = confidence interval; HR = hazard ratio; ln = natural logarithm; SE = standard error

Random-effects meta-analysis of log-transformed HRs demonstrated a statistically significant association between higher hsCRP category and risk of hard CVD (pooled HR 1.23; 95% CI 1.07-1.43; $p < 0.01$). Heterogeneity was moderate ($I^2 = 0.64$), although the estimate is imprecise given the small number of studies. Figure 2 displays the forest plot with study-specific lnHRs, 95% CIs, weights and pooled estimate. Squares represent individual study point estimates (size proportional to inverse-variance weight), horizontal lines show 95% CIs, and the diamond indicates the pooled random-effects estimate. A sensitivity analysis excluding the highest-weighted study (Ikezaki et al.) with a moderate risk of bias, showed result fragility: the effect attenuated to non-significant (HR 1.19; 95% CI 0.79-1.46; $p = 0.08$), suggesting that results depend on this study.

Figure 2. Forest plot of log-transformed hazard ratios for hsCRP association with cardiovascular events.



Forest plot displaying study-specific and pooled log-transformed hazard ratios (HRs; squares proportional to weight) for the association between high-sensitivity C-reactive protein (hsCRP) and cardiovascular events (MI, stroke, CV death). Horizontal lines represent 95% confidence interval. Diamond represents pooled estimate (HR 1.23; 95% CI (1.07-1.43)) from DerSimonian-Laird random-effects meta-regression model. $I^2 = 0.64$.

Discussion

This systematic review and meta-analysis show a statistically significant association between hsCRP and CV events in patients without previous CVD. Data was synthesized from four prospective cohort studies (n = 23,069) examining hsCRP as an independent predictor of incident CV events in primary prevention. Three studies reported a positive association between elevated hsCRP and CV events after multivariable adjustment, while one found no significant association. The latter categorized hsCRP using a 2mg/L cut-off (11), whereas the other studies used a 3mg/L threshold (12) or compared highest versus lowest hsCRP quartiles (13,14). The use of a lower cut-off and a narrower risk contrast could have attenuated the effect estimate and may explain the absence of a statistically significant association in that study. The pooled multivariable-adjusted HR was 1.23 (95% CI 1.07-1.43; $p < 0.01$), indicating a modest but statistically significant association.

The findings of this review are consistent with existing literature supporting hsCRP as an independent predictor of CV events in primary prevention. A recent systematic review and meta-analysis in middle-aged adults without prior CVD reported modest associations between hsCRP and CVD outcomes (HR 1.17; 95% CI 1.06-1.30), including soft endpoints: milder CV events prone to subjectivity of treatment influence like coronary revascularization procedures, peripheral artery disease, etc. (15). Similarly, a recent large prospective study confirmed hsCRP as an independent risk factor for major CV events (HR 1.34 (95% CI 1.29-1.39) for hsCRP >3mg/L vs <1mg/L and HR 1.22 (95% CI 1.19-1.24) for hsCRP ≥2mg/L) and demonstrated enhanced risk stratification when integrated into SCORE2 (16).
The incremental value of hsCRP as an additional risk stratifier in established scores remains debated. The Emerging Risk Factors Collaboration provided seminal evidence supporting hsCRP addition to the Framingham risk score, particularly among individuals at intermediate risk (17). However, a more recent systematic review of the US Preventive Services Task Force reported inconsistent findings and concluded that evidence is insufficient to assess the benefits of hsCRP for CV risk assessment (18). Current guidelines reflect this debate: the ESC guidelines note hsCRP's limited additional value and do not incorporate it into recommendations, whereas the AHA endorses hsCRP ≥2mg/L as a risk-enhancing factor in adults aged 40-75 years with a borderline CV risk when considering initiation of moderate-intensity statin therapy (5,10). This recommendation is primarily grounded in the JUPITER trial (2008), which demonstrated that apparently healthy individuals without hyperlipidaemia but with elevated baseline hsCRP experienced improved CV outcomes with statin therapy compared to placebo (HR 0.53; 95% CI, 0.40-0.69) (19). This suggests that statins may reduce CV risk through anti-inflammatory effects in individuals with elevated hsCRP.

This systematic review benefits from several methodological strengths. First, the comprehensive literature search screened over 12,000 articles for eligibility, maximizing the likelihood of identifying all relevant studies. Second, strict inclusion criteria focused exclusively on hard CVD outcomes (MI, stroke and CV death), facilitating direct comparability across studies. All included studies reported multivariable-adjusted HRs from high-quality prospective cohorts with overall low risk of bias.
Several limitations should also be acknowledged. Grey literature was not systematically searched, potentially introducing publication bias by missing unpublished studies. Furthermore, this review relied on a single reviewer for both study selection and risk of bias assessment, introducing potential subjectivity. Only four studies met the inclusion criteria, exhibiting moderate heterogeneity, likely due to differences in hsCRP exposure definitions and population differences (age, sex distribution, ethnicity). A sensitivity analysis excluding Ikezaki et al. (highest weight) revealed study fragility: the HR attenuated to 1.19 (95% CI 0.79-1.46; $p = 0.08$), no longer statistically significant. This highlights the need for additional high-quality prospective studies to confirm the robustness of the association. Finally, despite multivariable adjustment for traditional risk factors, the observational nature of included studies cannot exclude residual confounding.

This systematic review and meta-analysis suggest hsCRP may serve as a complementary risk marker. In particular among individuals at intermediate CV risk where the decision to initiate lipid-lowering or antihypertensive therapy is uncertain, hsCRP could potentially help guide treatment decisions. Additional prospective studies are needed to establish a more robust evidence base, while adapting uniform hsCRP cut-offs to improve comparability and to develop clear guidelines for clinical use. Ultimately, the findings of this systematic review demonstrate that hsCRP is independently associated with CV events after adjustment for traditional risk factors, thereby supporting its potential as an additional risk marker in primary prevention.

Bibliography

1. Eurostat. Causes of death - deaths by country of residence and occurrence [Internet]. 2024 [cited 2025 May 1]. Available from: https://ec.europa.eu/eurostat/databrowser/view/hlth_cd_aro/default/table?lang=en doi:https://doi.org/10.2908/HLTH_CD_ARO

2. Eurostat. In-patient average length of stay (days) [Internet]. 2024 [cited 2025 May 1]. Available from: https://ec.europa.eu/eurostat/databrowser/view/hlth_co_inpst/default/table?lang=en doi:https://doi.org/10.2908/HLTH_CO_INPST

3. Eurostat. Surgical procedures [Internet]. 2024 [cited 2025 May 1]. Available from: https://ec.europa.eu/eurostat/databrowser/view/hlth_co_proc3/default/table?lang=en doi:https://doi.org/10.2908/HLTH_CO_PROC3

4. Ajoolabady A, Pratico D, Lin L, Mantzoros CS, Bahijri S, Tuomilehto J, et al. Inflammation in atherosclerosis: pathophysiology and mechanisms. Cell death & disease. 2024. p. 817. doi:10.1038/s41419-024-07166-8 PubMed PMID: 39528464.

5. Visseren F, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. European Heart Journal. Oxford University Press; 2021. p. 3227–337. doi:10.1093/eurheartj/ehab484 PubMed PMID: 34458905.

6. Emerging Risk Factors Collaboration T. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies [Internet]. 2011. doi:10.1016/S0140

7. Kotas ME, Medzhitov R. Homeostasis, Inflammation, and Disease Susceptibility. Cell. Cell Press; 2015. p. 816–27. doi:10.1016/j.cell.2015.02.010 PubMed PMID: 25723161.

8. Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, et al. Chronic inflammation in the etiology of disease across the life span. Nat Med. 2019 Dec 1;25(12):1822–32. doi:10.1038/s41591-019-0675-0 PubMed PMID: 31806905.

9. Pepys MB, Hirschfield GM. C-reactive protein: A critical update. Journal of Clinical Investigation. 2003. p. 1805–12. doi:10.1172/JCI200318921 PubMed PMID: 12813013.

10. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. NLM (Medline); 2019. p. e596–646. doi:10.1161/CIR.0000000000000678 PubMed PMID: 30879355.

11. Cainzos-Achirica M, Miedema MD, McEvoy JW, Cushman M, Dardari Z, Greenland P, et al. The prognostic value of high sensitivity C-reactive protein in a multi-ethnic population after >10 years of follow-up: The Multi-Ethnic Study of Atherosclerosis (MESA). Int J Cardiol. 2018 Aug 1;264:158–64. doi:10.1016/j.ijcard.2018.02.027 PubMed PMID: 29776564.

12. Beer C, Alfonso H, Flicker L, Norman PE, Hankey GJ, Almeida OP. Traditional risk factors for incident cardiovascular events have limited importance in later life compared with the health in men study cardiovascular risk score. Stroke. 2011 Apr;42(4):952–9. doi:10.1161/STROKEAHA.110.603480 PubMed PMID: 21311063.

13. Riggs KA, Joshi PH, Khera A, Otvos JD, Greenland P, Ayers CR, et al. GlycA, hsCRP differentially associated with MI, ischemic stroke: In the Dallas Heart Study and Multi-Ethnic Study of Atherosclerosis: GlycA, hsCRP Differentially Associated MI, Stroke. Am J Prev Cardiol. 2022 Dec 1;12. doi:10.1016/j.ajpc.2022.100373

14. Ikezaki H, Fisher VA, Lim E, Ai M, Liu CT, Adrienne Cupples L, et al. Direct versus calculated LDL cholesterol and C-reactive protein in cardiovascular disease risk assessment in the Framingham Offspring Study. Clin Chem. 2019;65(9):1102–14. doi:10.1373/clinchem.2019.304600 PubMed PMID: 31239251.

15. Romero-Cabrera JL, Ankeny J, Fernández-Montero A, Kales SN, Smith DL. A Systematic Review and Meta-Analysis of Advanced Biomarkers for Predicting Incident Cardiovascular Disease among Asymptomatic Middle-Aged Adults. International Journal of Molecular Sciences. MDPI; 2022. doi:10.3390/ijms232113540 PubMed PMID: 36362325.

16. Kurt B, Reugels M, Schneider KM, Spiesshoefer J, Milzi A, Gombert A, et al. C-reactive protein and cardiovascular risk in the general population. Eur Heart J. 2025 Dec 11. doi:10.1093/eurheartj/ehaf937

17. Emerging Risk Factors Collaboration. C-Reactive Protein, Fibrinogen, and Cardiovascular Disease Prediction. New England Journal of Medicine. 2012 Oct 4;367(14):1310–20. doi:10.1056/NEJMoa1107477

18. Lin JS, Evans C V, Johnson E, Redmond N, Coppola EL, Smith N. Nontraditional Risk Factors in Cardiovascular Disease Risk Assessment: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2018 Jul 17;320(3):281–97. doi:10.1001/jama.2018.4242

19. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, et al. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. New England Journal of Medicine. 2008 Nov 20;359(21):2195–207. doi:10.1056/NEJMoa0807646