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The Role of High Sensitivity C- Reactive Protein Level in Predicting Stroke and Other Cardiovascular Events: A Meta-Analysis Review

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Abstract

Background*: Stroke stands as a prominent cause of morbidity and mortality on a global scale. Inflammation assumes a pivotal role in the advancement of stroke, with high-sensitivity C-reactive protein (hs-CRP) showing promise as a potential biomarker for assessing the risk of stroke.* ***Aim****: This meta-analysis seeks to evaluate the predictive capacity of hs-CRP in relation to stroke by comparing hs-CRP levels in stroke patients with those in non-stroke subjects (apparently healthy individuals) and patients with other cardiovascular events versus controls.* ***Method****: A comprehensive search across PubMed, Web of Science, EMBASE, and the Cochrane Library identified studies published from January 2010 to June 2024. Inclusion criteria focused on case-control or cohort studies reporting quantitative hs-CRP levels in stroke and cardiovascular events alongside control groups. Studies were rigorously screened and selected based on predefined criteria (randomised control trials). Data from 13 selected studies were extracted and analysed using RevMan 5.4.1 review manager.* ***Findings****: The meta-analysis included data from 13 studies with a total sample size of 1,486 subjects. The primary comparator analysis showed significantly higher hs-CRP levels in stroke patients than in non-stroke controls (Standardised Mean difference: 0.85 mg/L, 95% CI: 0.4,1.29; p= 0.0002). The secondary comparator analysis demonstrated elevated hs-CRP levels in patients who experienced other cardiovascular events compared to the control group (Standardised Mean Difference: 2.20 mg/L; 96% CI: 1.22, 3.18; p < 0.00001). These findings indicate that increased hs-CRP levels are associated with a heightened risk of stroke and other cardiovascular events. This underscores the potential of hs-CRP as a valuable biomarker in stroke and cardiovascular disease risk assessment.* ***Conclusion:*** *hs-CRP measurement can enhance stroke prediction models, facilitating early intervention and improving outcomes. Further research should focus on standardising hs-CRP measurement protocols and exploring their integration into clinical practice.*

Keywords: *high-sensitivity C-reactive protein, hs-CRP, stroke, cardiovascular event, biomarker, inflammation, meta-analysis*

INTRODUCTION

Cardiovascular Event: An Overview

Cardiovascular events represent a spectrum of serious medical conditions involving the heart and blood vessels, which significantly contribute to global morbidity and mortality (Flora and Nayak, 2019). The aforementioned events encompass peripheral artery disease, myocardial infarction (heart attack), heart failure, and stroke. Each of these conditions holds the potential to precipitate severe health implications or even mortality (Golbidi *et al*., 2015). The pathogenesis of cardiovascular events typically involves the progressive accumulation of risk factors such as atherosclerosis, hypertension, and hyperlipidemia (Golbidi *et al*., 2015). Atherosclerosis, characterised by the buildup of plaques within arterial walls, is a key contributor, leading to the narrowing or blockage of arteries and thereby restricting blood flow to vital organs (Xu *et al*., 2016). Hypertension, or high blood pressure, exerts chronic stress on the cardiovascular system, damaging blood vessels and the heart over time (Frąk *et al.,* 2022). Hyperlipidemia, which involves elevated levels of lipids in the blood, further exacerbates atherosclerosis by promoting plaque formation (Frąk *et al.,* 2022). Together, these conditions compromise the delivery of oxygen and nutrients to critical organs, such as the heart and brain, setting the stage for catastrophic events like heart attacks and strokes (Golbidi *et al.,* 2015).

Epidemiology of Cardiovascular Events

Cardiovascular disease (CVD) stands as the predominant cause of mortality on a global scale, accounting for an estimated 17.9 million fatalities annually, representing approximately 32% of the total global deaths (World Health Organization, 2021). It is noted that an estimated 85% of these deaths are attributed to incidents of heart attack and stroke. The uneven distribution of cardiovascular events is evident globally, with higher mortality rates prevalent in low- and middle-income countries as opposed to high-income countries (Xu *et al*., 2016). The disparity in cardiovascular mortality rates can be ascribed to a nexus of factors, encompassing differential access to healthcare, the prevalence of risk factors, and the efficacy of public health interventions (Ting *et al*., 2016). Notably, in high-income nations, enhancements in medical care, early identification, and risk factor management have engendered a discernible reduction in cardiovascular mortality over recent decades (Frąk *et al*., 2022). Noteworthy is the fact that age-adjusted mortality rates for cardiovascular disease in the United States have exhibited a reduction of more than 60% since the 1960s (WHO, 2021). The prevalence of cardiovascular events persists at a high level, primarily attributed to the advancing age of the population and the escalating prevalence of obesity and diabetes (Frąk *et al*., 2022). In contrast, numerous low- and middle-income countries are undergoing a transition in disease patterns from infectious diseases to non-communicable diseases like cardiovascular disease (CVD), leading to a notable upsurge in cardiovascular mortality (WHO, 2021).

The prevalence of cardiovascular events varies with gender and age. Men typically face an elevated risk of developing cardiovascular diseases at an earlier stage in life compared to women, who demonstrate a notable surge in risk after menopause (Mozaffarian *et al*., 2016). The Framingham Heart Study, renowned for its status as one of the lengthiest ongoing epidemiological studies on cardiovascular disease, has furnished substantial evidence indicating that the cumulative risk of experiencing cardiovascular events escalates with advancing age, particularly beyond the age of 50 (Pearson-Stuttard *et al*., 2016).

Stroke: An Overview

A stroke is a medical event characterised by the interruption or reduction of blood supply to a specific area of the brain, resulting in inadequate oxygen and nutrient delivery to the affected brain tissue (Donkor, 2018). Consequently, the affected brain cells undergo a process of degeneration, leading to the manifestation of neurological impairments that can either be transient or enduring in nature. Strokes are generally classified into two primary types: ischemic and haemorrhagic (O'Donnell *et al*., 2016). Ischemic stroke, the most prevalent type, accounts for approximately 87% of all instances. It occurs when a blood vessel supplying blood to the brain is obstructed, usually due to a blood clot (thrombosis) or the narrowing of arteries (atherosclerosis) (Kuriakose and Xiao 2020). Ischemic strokes are categorised as thrombotic strokes; where a clot forms within the brain's blood vessels, and embolic strokes; where a clot originates elsewhere in the body and travels to the brain (WSO, 2022). Conversely, Haemorrhagic Stroke occurs when a blood vessel in the brain ruptures, leading to bleeding within or around the brain. Although less prevalent, haemorrhagic strokes are often more severe (Kuriakose and Xiao, 2020). They are further classified as intracerebral haemorrhage, involving bleeding within the brain tissue, and subarachnoid haemorrhage, involving bleeding in the space between the brain and the surrounding membrane (Donkor, 2018).

Epidemiology of Stroke

According to the World Stroke Organization (2022), stroke stands as the second leading cause of death globally, attributing to approximately 11% of total deaths. This underscores the significant impact of stroke as a prevalent contributor to mortality and disability on a global scale. The incidence of stroke displays pronounced regional disparities attributable to variations in the prevalence of risk factors, healthcare infrastructures, and socioeconomic circumstances (Saini and Guada, 2021). Within high-income nations, advancements in medical care and public health initiatives have yielded a reduction in stroke mortality rates (WSO, 2022). Nonetheless, the prevalence of stroke remains elevated due to ageing demographics and the escalating prevalence of risk factors such as obesity and diabetes (Béjot *et al*., 2016). Conversely, low- and middle-income countries (LMICs) confront an escalating burden of stroke (Béjot *et al*., 2016). Limited access to healthcare, delayed diagnosis, and inadequate management of risk factors contribute to higher stroke mortality and disability in these regions (Béjot *et al*. 2016). The epidemiology of stroke varies widely between regions. For instance, in Asia, particularly in China and India, the incidence and mortality rates of stroke are increasing due to rapid urbanisation, lifestyle changes, and the high prevalence of hypertension and diabetes (WSO, 2022). In Europe and North America, stroke rates are relatively stable but remain a significant health concern. In Africa, the stroke burden is high, compounded by infectious diseases, poorly controlled hypertension, and inadequate healthcare infrastructure (Saini and Guada 2021).

In essence, stroke is a leading cause of morbidity and mortality worldwide, with significant implications for public health and healthcare systems (Donkor, 2018). The pathogenesis of stroke involves various factors, including thrombosis, embolism, and haemorrhage (Polyakova and Mikhaylov, 2020). However, the role of inflammation in stroke development and progression has been increasingly recognised in recent years.

Risk Factors Associated with Stroke

Numerous factors contribute to an elevated risk of stroke, which can be broadly classified as non-modifiable and modifiable risk factors (Boehme and Esenwa, 2017). Non-modifiable risk factors encompass age, gender, and genetic predisposition. Age is a significant determinant, with the risk of stroke increasing markedly after the age of 55 (Béjot *et al*., 2016). Gender also plays a role, as men generally have a higher risk of stroke than women (O'donnell *et al.* 2016). Genetics is another crucial factor, as a family history of stroke significantly elevates an individual's risk. These non-modifiable factors are intrinsic to an individual's biological makeup and cannot be altered through lifestyle or medical interventions (O'donnell *et al.* 2016). On the other hand, modifiable risk factors are those that can be managed or mitigated through lifestyle changes and medical treatment (Zhou *et al*., 2024). Hypertension, or high blood pressure, stands out as the most significant modifiable risk factor for stroke. It damages blood vessels and can precipitate both ischemic and haemorrhagic strokes (Zhou *et al*., 2024). Diabetes is another critical factor, as it accelerates atherosclerosis and often coexists with hypertension, thereby increasing the risk of stroke (Lee *et al.* 2013). Smoking is a major modifiable risk factor due to its detrimental effects on blood vessels, including raising blood pressure and reducing oxygen levels in the blood (Boehme and Esenwa 2017).

Dyslipidaemia, characterised by anomalous lipid levels in the bloodstream, is a contributing factor in the pathogenesis of atherosclerosis, thus heightening the susceptibility to stroke (Boehme and Esenwa, 2017). Obesity, particularly abdominal obesity, presents a heightened risk of stroke due to its propensity to prompt other health conditions such as hypertension, diabetes, and dyslipidaemia (Gan *et al*., 2021). Physical inactivity further exacerbates these conditions by fostering obesity and increasing the propensity for hypertension and diabetes (Boehme and Esenwa, 2017). Lastly, dietary patterns play a pivotal role, as diets high in saturated fats, trans fats, and cholesterol escalate blood lipid levels and instigate atherosclerosis, consequently augmenting the risk of stroke (Gan *et al*., 2021).

The risk factors for stroke can be categorised into non-modifiable and modifiable factors. Non-modifiable risk factors, including age, gender, and genetics, establish a baseline risk for stroke. In contrast, modifiable risk factors, such as hypertension, diabetes, smoking, dyslipidaemia, obesity, physical inactivity, and poor diet, significantly impact an individual's risk of experiencing a stroke (WSO, 2022). By addressing these modifiable factors through lifestyle changes and medical interventions, the overall risk of stroke can be effectively reduced (Boehme and Esenwa 2017).

The Role of C-Reactive Protein (CRP)

C-reactive protein (CRP) recognized for its importance in medical science, is a key biomarker of inflammation, infection, and tissue damage (Sproston and Ashworth, 2018). As part of the innate immune system, CRP levels rise significantly during inflammatory processes, providing a rapid response to infection and injury (Sproston and Ashworth, 2018). This elevation is a systemic indication of inflammation and is associated with a wide range of pathological conditions, including cardiovascular diseases, arthritis, and infections (Zhou *et al*., 2024).

Historically, CRP has served as a general marker of inflammation, making it invaluable in clinical diagnostics and prognostics (Ansar and Ghosh, 2013). Its role in identifying the presence and intensity of inflammatory responses allows healthcare professionals to monitor disease progression and the effectiveness of treatments (Ansar and Ghosh, 2013). Elevated CRP levels are not specific to any single disease but reflect a broad spectrum of inflammatory conditions, aiding in the

detection and management of various health issues (Sproston and Ashworth, 2018). High-sensitivity C-reactive protein (hs-CRP) is a more sensitive assay that can detect lower levels of CRP in the blood, providing greater precision in assessing chronic inflammation. This enhanced sensitivity makes hs-CRP a valuable tool in evaluating the risk of cardiovascular diseases (Ridker, 2016). Elevated hs-CRP levels have been linked to an increased risk of cardiovascular events, such as myocardial infarction and stroke. Research indicates that even modest elevations in hs-CRP can predict future cardiovascular events, making it a critical component of cardiovascular risk assessment (Ridker, 2016).

The role of C-reactive protein (CRP) in cardiovascular diseases holds particular significance. Chronic low-grade inflammation, as evidenced by elevated high-sensitivity CRP (hs-CRP) levels, contributes to the initiation and advancement of atherosclerosis—a condition characterised by the accumulation of plaque within arterial walls (Zhou *et al*., 2024). This arterial plaque build-up can result in arterial narrowing and hardening, thereby escalating the susceptibility to myocardial infarction and cerebrovascular accidents (Ansar and Ghosh, 2013). Through the measurement of hs-CRP levels, healthcare practitioners can proficiently identify individuals at heightened risk and subsequently institute pre-emptive interventions. such as lifestyle modifications and pharmacological interventions (Zhou *et a*l., 2024). In addition to cardiovascular diseases, CRP is also implicated in other inflammatory conditions. For example, in rheumatoid arthritis, elevated CRP levels correlate with disease activity and can guide treatment decisions (Banait *et al*., 2022). Similarly, in infections, CRP levels can help distinguish between bacterial and viral causes, aiding in the selection of appropriate therapies. In essence, CRP is a vital biomarker in medical science, providing valuable insights into the body's inflammatory response (Banait *et al*., 2022). Its role in detecting and monitoring inflammation is critical in managing a wide range of diseases, particularly cardiovascular conditions. The advent of hs-CRP assays has further enhanced the ability to assess chronic inflammation and predict cardiovascular risk, underscoring the importance of CRP in clinical practice (Ansar and Ghosh, 2013).

The Role of High-Sensitivity C-Reactive Protein (hs-CRP)

High-sensitivity C-reactive protein (hs-CRP) represents a refined assay designed to quantify minimal levels of C-reactive protein (CRP) present in the bloodstream (Ridker, 2016). This protein is an integral component of the innate immune system and holds a pivotal role in the body's defensive response to infection and injury, as outlined by Ridker (2016). Notably, hs-CRP serve as a valuable tool in identifying chronic low-grade inflammation, a factor implicated in various chronic illnesses, including cardiovascular diseases and stroke (Ridker, 2016). The production of CRP is primarily regulated by cytokines, especially interleukin-6 (IL-6), which is released by macrophages and adipocytes during inflammatory responses (Ansar and Ghosh, 2013). When tissue injury or infection occurs, IL-6 stimulates the liver to produce CRP, which then increases rapidly in the bloodstream (Pepys and Hirschfield, 2003). CRP specifically targets phosphocholine residues present on the surfaces of necrotic or apoptotic cells, as well as certain bacterial strains. This interaction triggers the activation of the complement system while also facilitating the process of phagocytosis by macrophages. Consequently, CRP plays a pivotal role in the effective clearance of both cellular debris and pathogenic microorganisms (Black *et al*., 2004). According to Banait *et a*l. (2022), hs-CRP has recently emerged as a more precise measure of C-reactive protein levels, particularly at lower concentrations. Hence, hs-CRP testing can measure concentration levels of CRP as low as 0.3 mg/L. This increased sensitivity allows for detecting chronic low-grade

inflammation (Banait *et al*., 2022). Chronic low-grade inflammation is a critical factor in the pathogenesis of many cardiovascular diseases, including atherosclerosis, where persistent inflammation contributes to plaque formation and instability within the arterial walls (Banait *et a*l., 2022). Hs-CRP is now extensively used in cardiovascular risk assessment, providing insights into the inflammatory processes contributing to atherosclerosis and subsequent cardiovascular events. Elevated hs-CRP levels are linked to an increased risk of heart attacks and strokes, highlighting its importance in predicting cardiovascular outcomes (Banait *et al*., 2022; Sproston and Ashworth, 2018). Studies have revealed that individuals with elevated hs-CRP levels are at a significantly heightened risk of cardiovascular events compared to those with lower levels, even following adjustment for traditional risk factors including cholesterol levels, blood pressure, and smoking (Zhou et al., 2024). (Zhou *et a*l., 2024). This makes hs-CRP a valuable tool in identifying individuals at high risk for cardiovascular events, thereby facilitating early intervention and prevention strategies (Zhou *et al*., 2024). Su *et al*. (2020) and Banait *et al*. (2022) studies suggest that inflammatory markers, including CRP, play a critical role in stroke development and progression. In particular, hs-CRP has gained attention as a potential predictor of stroke risk due to its ability to reflect low-grade systemic inflammation (Zhou *et a*l., 2024).

Elevated hs-CRP levels indicate chronic inflammation, which is a known contributor to atherosclerosis—a major underlying cause of ischemic stroke (Rahali *et al.* 2024). Chronic inflammation can lead to plaque instability and rupture, resulting in the formation of blood clots that can obstruct cerebral arteries. The predictive value of hs-CRP in stroke risk assessment is supported by evidence showing a strong correlation between elevated hs-CRP levels and increased stroke incidence. This relationship holds true even after adjusting for other traditional risk factors, suggesting that hs-CRP provides additional prognostic information (Polyakova and Mikhaylov, 2020). Consequently, hs-CRP measurement could enhance stroke prediction models, allowing for more accurate identification of high-risk individuals and facilitating early intervention strategies to reduce stroke incidence and improve outcomes (Rahali *et al.* 2024). Moreover, Su *et al*. (2020) demonstrated a correlation between elevated levels of hs-CRP and an increased susceptibility to both ischemic and haemorrhagic strokes. Ischemic strokes, stemming from the occlusion of blood vessels supplying the brain, represent the most prevalent stroke subtype and exhibit a robust association with atherosclerosis and inflammatory pathways (Luan and Yao, 2018). Haemorrhagic strokes, caused by the rupture of blood vessels in the brain, are less common but also associated with inflammation. The predictive capability of hs-CRP in assessing stroke risk stems from its ability to capture underlying inflammatory activity, which is known to play a pivotal role in the pathogenesis of vascular events (Su *et al.* 2020).

Research Questions and Motivation for the Study

Numerous epidemiological studies and clinical trials have explored the relationship between hs-CRP levels and stroke risk, yielding valuable insights into the predictive value of this biomarker. However, the findings have been varied, necessitating a comprehensive analysis to consolidate the evidence. A meta-analysis of the role of hs-CRP in predicting stroke is essential to provide a clearer understanding of its predictive utility and potential application in clinical practice, as per Gagnier *et al* (2012). This meta-analysis aims to synthesise existing studies to evaluate the strength of the association between hs-CRP levels and stroke/cardiovascular event risk and explore potential mechanisms underlying this relationship by analysing the pooled data from the various studies. This research also seeks to determine the consistency of hs-CRP as a predictor of

stroke/cardiovascular events, identify potential confounders and moderators, and assess the clinical relevance of incorporating hs-CRP measurement into stroke/cardiovascular event risk assessment protocols. Understanding the role of hs-CRP in predicting stroke can enhance early detection and prevention strategies, ultimately reducing the burden of stroke on individuals and healthcare systems (Luan and Yao, 2018). This research will have two comparators; the primary comparator will compare hs-CRP levels in non-stroke subjects (controls) with stroke subjects who are confirmed cases. The secondary comparator will compare hs-CRP levels in patients with other cardiovascular events against the control groups (apparently healthy individuals) using RevMan review manager 5.4.1 to synthesise and combine the strengths of existing studies on the relationship between hs-CRP with stroke/cardiovascular event risk. The findings will also contribute to a clearer understanding of hs-CRP's predictive value, potentially informing clinical practice and guiding future research in stroke prevention. In summary, this study answers the following questions. First, what is the role of high-sensitivity C-reactive protein in predicting stroke and other cardiovascular events? Second, what are the potential confounders and moderators of the relationship between C-reactive protein and stroke and other cardiovascular events? third, what is the clinical relevance of incorporating hs-CRP measurement into stroke/cardiovascular event risk assessment protocols? By providing answers to these questions, this study has significance for policy, practise and research.

Hypothesis Statements

Null Hypothesis; H_o: There is no significant difference in hs-CRP levels between patients with stroke and other cardiovascular events vs control subjects (apparently healthy individuals).

Alternative Hypothesis; H_1: There is a significant difference in hs-CRP levels between patients with stroke and other cardiovascular events vs control subject

METHODS

Data Acquisition and Criteria

This meta-analysis involved a comprehensive search across multiple databases to identify studies examining the role of hs-CRP in predicting stroke risk among confirmed cases of stroke patients and apparently healthy individuals (age ≥ 18 years). The databases searched included PubMed, Web of Science, EMBASE (Elsevier), and the Cochrane Library for studies measuring hs-CRP in Stroke cases and healthy individuals with or without other cardiovascular diseases. The search period covered studies published from January 2010 to June 2024. Boolean search terms used were (Serum OR plasma OR blood) and (hs-CRP OR "high-sensitivity C-reactive protein") AND (stroke OR cerebrovascular accident) AND (cardiovascular events) NOT reviews.

Studies were independently screened for inclusion based on predefined criteria. Inclusion criteria required studies to quantitatively measure hs-CRP levels in relation to stroke and other cardiovascular events, specifically differentiating between known cases and healthy subjects within the same age ranges. Full-text availability was confirmed for all selected articles. Inclusion and exclusion criteria were rigorously applied to ensure the selection of relevant studies, as summarised in the accompanying Figure 1.

Study Selection

Inclusion criteria:

1. Studies conducted on human subjects only, published between January 2010 and June 2024.
2. Case-control or cohort study designs reporting quantitative measurement of hs-CRP levels.

3. Studies comparing hs-CRP levels in known cases and healthy subjects in relation to stroke incidence.
4. Articles providing sufficient data to extract and analyse effect sizes and confidence intervals.
5. Articles with known duration of studies carried out retrospectively or prospectively.
6. Articles clearly stating the age brackets of subjects as ≥18 years

Exclusion criteria:

1. Studies lacking control groups or clear differentiation between known cases and healthy subjects (control).
2. Articles focusing on animal studies.
3. Articles that did not provide quantitative measurement of hs-CRP and baseline hs-CRP measurements.
4. Review articles, letters, editorials, conference papers, or other non-original research articles.
5. Studies with insufficient data presentation and those not reporting relevant outcomes.
6. Studies which reported findings of subjects who were not ≥18 years

Articles that met the inclusion criteria underwent further review to assess methodological quality and data completeness. The final selection of studies aimed to ensure a robust dataset for meta-analysis, providing comprehensive insights into the predictive role of hs-CRP in stroke risk. This rigorous approach was implemented to augment the reliability and validity of the meta-analysis findings.

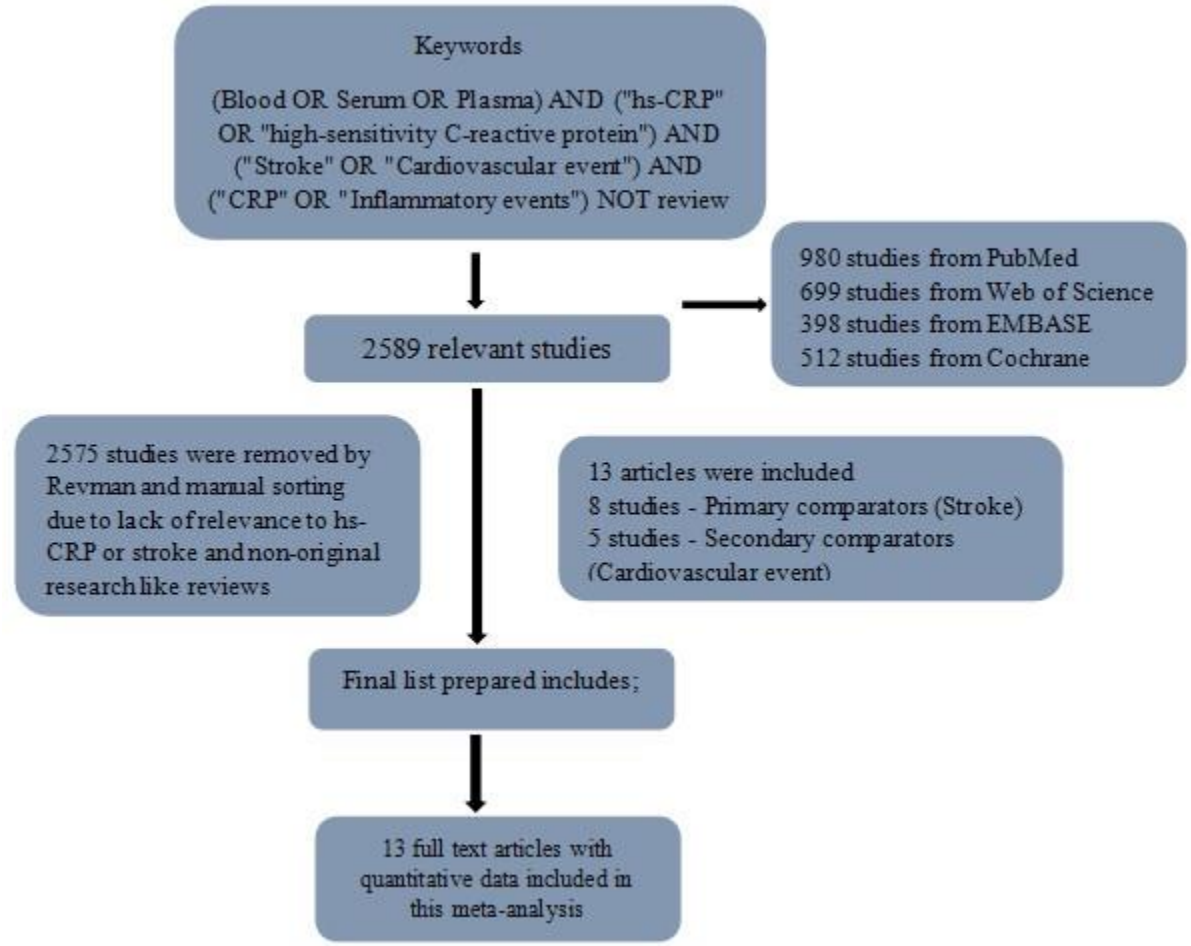

Figure 1. illustrates the PRISMA Flow diagram depicting the study selection process for the meta-analysis. All the studies included in the analysis were randomised controlled trials.

Data Extraction and Assessment

The screening process for this meta-analysis followed the PRISMA guidelines, ensuring a rigorous and transparent selection of studies examining the role of hs-CRP in predicting stroke risk among normotensive and hypertensive subjects.

Initially, a comprehensive search of databases yielded a total of 2589 articles. Following the removal of 2575 articles because they did not meet the inclusion criteria, such as lacking relevance to hs-CRP or stroke, focusing on animal studies, or being non-original research like reviews and editorials. This stringent screening process resulted in the inclusion of 13 articles that met all inclusion criteria. These selected studies provided quantitative measurements of hs-CRP levels and clearly differentiated between Primary comparator – Stroke, Secondary Comparator - Other Cardiovascular Events and control groups in relation to Hs-CRP levels.

Key data extracted included the sample size, mean and standard deviation (SD) of hs-CRP levels, alongside adjusted values for stroke risk. Variables such as the year and country of study, study design, mean age, sample type, assay method used and references were meticulously assessed for each study.

Table 1. *Quantitative details and characteristics of the included publications.*

No	Study	Primary comparator - Stroke: Sample Size, Mean ± SD	Secondary Comparator - Other Cardiovascular Events: Sample Size, Mean ± SD	Control: Sample Size, Mean ± SD	Detection Method	Reference
1	Lin *et al* 2019	56, 2.71± 1.39	-------	161, 1.26 ± 0.91	Immunoturbidimetric assay	Lin *et al* 2019
2	Koosha *et al* 2020	502, 3.51 ± 1.87	-------	538, 3.29 ± 1.6	Immunoturbidimetric assay	Koosha *et al* 2020
3	Ozkan et al 2013	40, 12.5±7.3	-------	22, 10.8±7.7	Enzyme-Linked Immunosorbent Assay	Ozkan et al 2013
4	Menon, 2018	52, 14.2±6.1	------	50, 5.0±1.2	Enzyme-Linked Immunosorbent Assay	Menon, 2018
5	Oprescu *et al* 2021	-------	28, 3.55±0.4	14, 2.2±0.4	Enzyme-Linked Immunosorbent Assay	Oprescu *et al* 2021
6	Golledge *et al* 2023	-------	102, 4.0 ± 2.05	369, 2.0 ± 2.0	Chemiluminescent immunoassay	Golledge *et al* 2023
7	Qin *et al* 2016	-------	47, 5.0±1.18	49, 3.22±0.71	Immunoturbidimetric assay	Qin *et al* 2016
8	Kara et al 2014	102, 7.1±6.0	--------	98, 1.0±1.0	Enzyme-Linked Immunosorbent Assay	Kara et al 2014
9	Maki-Alhindi *et al* 2019	---------	68, 8.2±7.1	50, 0.6±0.4	High-sensitivity immunoturbidometric assay	Maki-Alhindi *et al* 2019
10	Al-Sa'adi *et al* 2015	---------	39, 4.30±0.77	25, 0.77±0.27	Enzyme-Linked Immunosorbent Assay	Al-Sa'adi *et al* 2015
11	Liu *et al* 2018	155, 0.49 ± 0.33	---------	155, 0.28 ± 0.11	Enzyme-Linked Immunosorbent Assay	Liu *et al* 2018
12	Bienek *et al* 2012	69, 27.7±56.21	---------	26, 10.0±6.02	Enzyme-Linked Immunosorbent Assay	Bienek *et al* 2012

13	Prugger *et al* 2013	95, 2.9± 2.35	---------	190, 2.1±1.45	Enzyme-Linked Immunosorbent Assay	Prugger *et al* 2013

Data Analysis

The Review Manager (RevMan) version 5.4.1 from Cochrane (www.cochrane.org) was used to conduct the statistical analyses for this meta-analysis. Using inverse variance for continuous data, the primary and secondary comparisons assessed the mean differences and standard deviations of hs-CRP levels between study groups. The Chi-square test was used to evaluate the degree of heterogeneity among the studies, and a sensitivity analysis was carried out to identify the sources of heterogeneity. To take into consideration the heterogeneity ($P < 0.1$, $I^2 > 50\%$), a random-effects model was employed. For continuous variables, the standardised mean difference (SMD) and 95% confidence intervals (CI) were computed to assess the efficacy of the statistical data. P-values of less than 0.05 were deemed statistically significant for the results. The studies were categorised into two groups for separate meta-analyses within the RevMan Software for a holistic interpretation of result:

Primary Comparison: hs-CRP levels in stroke patients versus control subjects.

Secondary Comparison: hs-CRP levels in patients with cardiovascular events versus control subjects.

The meta-analysis encompassed a total of 13 studies, each providing quantitative data on hs-CRP levels. **Table 1** summarises the study characteristics and quantitative data, including sample size, mean ± SD of hs-CRP levels, and detection methods used.

Overall, **8 studies** contributed to the primary comparison, and **5 studies** contributed to the secondary comparison. The SMD and 95% CI were calculated for each comparison to analyse the overall effect. The results were summarised in forest plots, illustrating the mean differences and the extent of heterogeneity across the studies. The findings provided a comprehensive assessment of hs-CRP as a predictive marker for stroke and other cardiovascular events, highlighting its potential utility in clinical practice.

The detailed statistical analysis ensured robust and reliable results, contributing valuable insights into the role of hs-CRP in stroke/cardiovascular risk assessment.

RESULTS

The meta-analysis has been carried out and the overall pooled/estimated effects of the individual studies including their confidence intervals have been achieved. The meta-analysis enabled the evaluation and synthesis of existing literature on the role of hs-CRP levels in predicting stroke and other cardiovascular events using the RevMan 5.4.1 review manager to pool the included studies to obtain an overall effect size which was a more reliable estimate than the individual studies.

Literature Search Results

The comprehensive literature search conducted for this meta-analysis covered studies, focusing on the role of hs-CRP in predicting stroke and other cardiovascular events with the flow diagram of the literature searches and selection criteria in **Figure 1**. The search identified a total of 1,874 studies. After applying stringent inclusion criteria, **13** studies were ultimately selected for the meta-analysis. Out of these, **8** studies addressed the primary comparator (hs-CRP levels in stroke patients versus control subjects), while **5** studies focused on the secondary comparator (hs-CRP levels in patients with cardiovascular events versus control subjects).

The sample sizes of the included studies varied significantly, ranging from 40 to 502 subjects for the primary comparator and 28 to 377 subjects for the secondary comparator. This variability in sample sizes and the inclusion of diverse populations from different geographic locations enhance the robustness and generalisability of the findings.

The quantitative details and characteristics of the included publications, such as sample sizes, mean ± SD of hs-CRP levels, and detection techniques, are compiled in **Table 1.** The studies employed various detection techniques, such as immunoturbidimetric assay, enzyme-linked immunosorbent assay (ELISA), and chemiluminescent immunoassay, reflecting the diverse methodologies used to measure hs-CRP levels. Studies by Menon (2018), Bienek *et al*. (2012), Prugger *et al*. (2013), Ozkan *et al*. (2013), Liu *et al*. (2018), Koosha *et al*. (2020), Lin *et al*. (2019), and Kara *et al*. (2014) evaluated hs-CRP levels in stroke patients against control participants as the primary comparator. Studies by Oprescu *et al*. (2021), Golledge *et al*. (2023), Qin *et al*. (2016), Maki-Alhindi *et al*. (2019), and Al-Sa'adi *et al*. (2015) examined hs-CRP levels in population with cardiovascular diseases compared to control subjects as the secondary comparator.

The diverse methodologies and wide range of sample sizes in these studies provide a comprehensive overview of hs-CRP's role as a predictive marker for stroke and other cardiovascular events, contributing valuable insights to the existing literature.

Studies on hs-CRP in Stroke Patients with Control

To investigate the levels of hs-CRP in stroke patients compared to control subjects, a meta-analysis was conducted involving eight studies. These studies varied significantly in their sample sizes, ranging from 26 to 502 participants. The pooled results obtained from the forest plot as seen in **Figure 2** revealed a statistically significant elevation in hs-CRP levels among stroke patients. The standardised mean difference (SMD) was found to be 0.85 (95% CI: 0.40, 1.29; P = 0.0002), indicating a moderate effect size. This suggests that stroke patients have moderately higher hs-CRP levels compared to control subjects. The SMD was used for the overall effect size measurement because the included study authors measured the same biomarker (hs-CRP) using slightly different methods and scales.

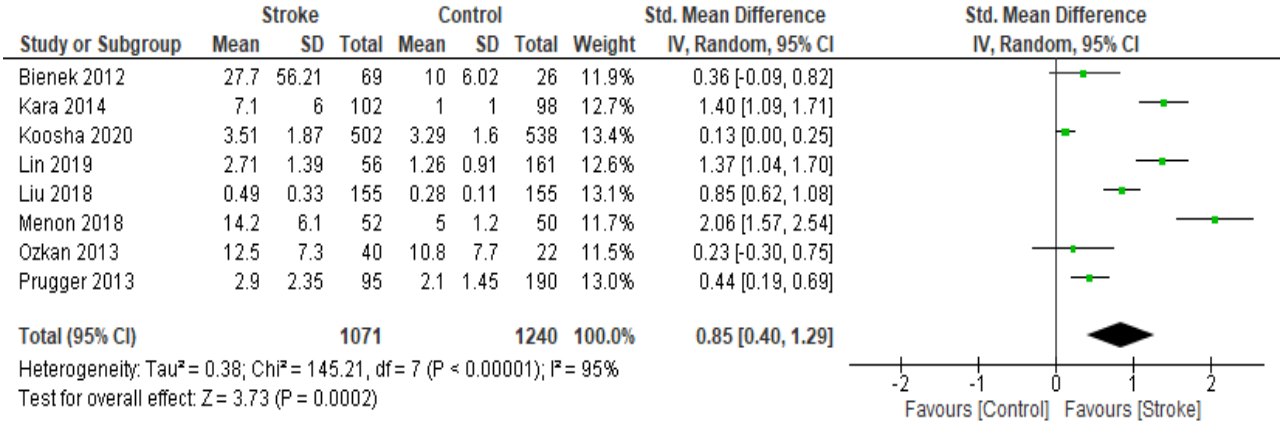

***Figure 2**: Forest Plot for the Primary Comparator showing first author names, year of publication, raw data extracted from individual studies, individual study weight with their confidence intervals, and the graphical representation of the raw data including the pooled overall effect size calculated in standardised mean difference.*

Moreover, the heterogeneity statistics across these studies was significant, ($p<0.00001$) and an I^2 value of 95% (I^2 value is > 50%). This high degree of heterogeneity suggests considerable variability in the effect sizes among the included studies i.e. the studies differ from each other with minimal overlapping. Several factors could contribute to this heterogeneity, including differences in study populations, methodologies, and the timing of hs-CRP measurement relative to stroke

events. For example, variations in the demographic characteristics of the study populations (such as age, gender, and underlying health conditions) could influence hs-CRP levels. Additionally, methodological differences, such as the assays used to measure hs-CRP and the protocols for sample collection and processing, might also contribute to the observed variability.

The timing of hs-CRP measurement is another crucial factor. The levels of hs-CRP can fluctuate significantly in response to acute inflammatory events, including stroke. Studies that measured hs-CRP levels at different time points post-stroke might report varying levels of elevation, contributing to the observed heterogeneity. The relevance of this heterogeneity lies in its implications for the interpretation of the meta-analysis results. High heterogeneity indicates that the pooled effect size may not accurately represent the effect size in all individual studies. Overall, levels of hs-CRP in stroke patients and the control group showed significant differences ($p<0.05$).

Studies on hs-CRP in Patients with Cardiovascular Events Compared to Control Subjects

For the secondary comparator, five studies [Oprescu *et al*. (2021), Golledge *et al*. (2023), Qin *et al*. (2016), Maki-Alhindi *et al*. (2019) and Al-Sa'adi *et al*. (2015)] were included to assess hs-CRP levels in patients with cardiovascular events versus control subjects. The sample sizes in these studies ranged from 25 to 369 participants.

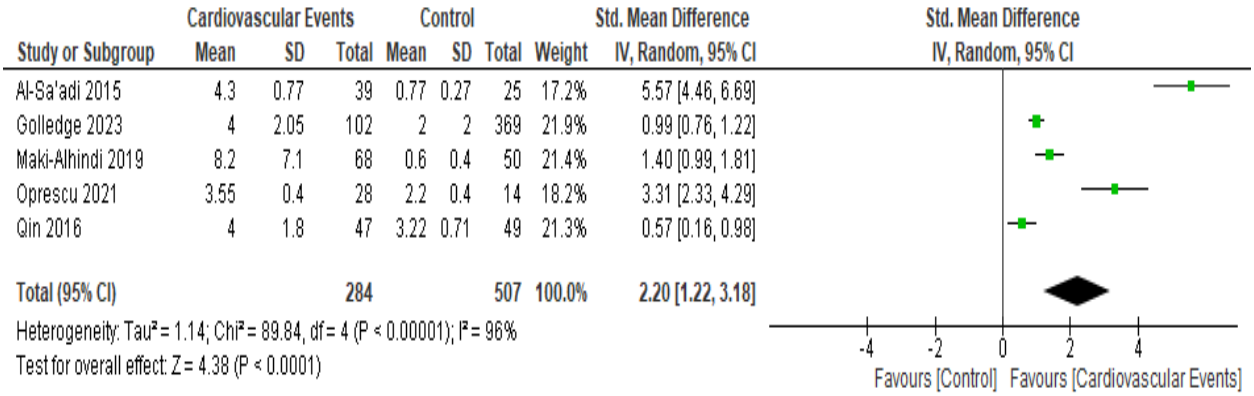

Figure 3: *Forest Plot for the Secondary Comparator showing first author names, year of publication, raw data extracted from individual studies, individual study weight with their confidence intervals, and the graphical representation of the raw data including the pooled overall effect size calculated in standardised mean difference.*

The pooled results demonstrated a significantly higher hs-CRP level in patients with cardiovascular events. The SMD was found to be 2.20 (96% CI: 1.22, 3.18; $P < 0.00001$), indicating a substantial effect size. This suggests that hs-CRP levels are, on average, more than two standard deviations higher in patients with cardiovascular events compared to control subjects. The heterogeneity across these studies was substantial ($P<0.00001$), with I^2 value of 96% (I^2 value is >50%), indicating considerable variability in effect sizes. This high degree of heterogeneity suggests that there are significant differences in the outcomes of the studies included in the meta-analysis. This heterogeneity could stem from variations in patient characteristics, such as age, gender, and comorbidities, which influence hs-CRP levels. Additionally, differences in the types of cardiovascular events (e.g., myocardial infarction, unstable angina) and the methodologies used to measure hs-CRP might contribute to the variability.

Overall, despite the substantial heterogeneity, the meta-analysis reveals a consistent and significant elevation in hs-CRP levels among patients with cardiovascular events compared to control subjects. This result shows that hs-CRP is significantly higher in patients with cardiovascular events, indicating that elevated hs-CRP levels are associated with these conditions ($p<0.05$). The SMD of 2.20 mg/L suggests a large effect size, a tangible measure of the increase. The SMD quantifies the difference in hs-CRP levels between the two groups in terms of standard deviations, showing a large effect size. This indicates that hs-CRP levels are more than two standard deviations higher in cardiovascular patients compared to controls.

The SMD is better in this research because it accounts for variations across studies with different measurement scales. Since hs-CRP levels can be reported in varying units or ranges, SMD allows comparison by standardizing effect sizes, making it easier to combine results across studies. This ensures that differences in study designs, populations, and measurement methods do not skew the overall findings. SMD offers a more versatile approach for meta-analyses involving diverse datasets, enhancing the robustness and generalizability of the research conclusions (Moher *et al*, 2010).

Funnel Plot Interpretation of the Two Comparators

Figures 4 and **5** represent the funnel plot for the primary and secondary comparator which can be used to ascertain the quality of the studies and to make comments on publication bias in the meta-analyses. The study effect sizes were plotted against the standard errors. From the plots, studies with larger sample sizes or effect sizes float at the top while smaller studies with less weight sink to the bottom.

In both cases, the funnel plots show a symmetrically distributed plot even in the presence of bias with an I^2 statistics value of 95% (for the primary comparator) and 96% (for the secondary comparator) respectively. Ideally in the absence of bias, the studies would also show a symmetrically distributed plot of the pooled effect size with a statistics I^2 value of < 50% (less heterogeneity). Smaller studies with null or negative results are less likely to be published. Alternatively, an asymmetry could be due to small-study effects, where smaller studies might show larger effect sizes due to various biases or random variations. The symmetry here could likewise result from small-study effects. Smaller studies of five studies in cardiovascular research might show inflated effect sizes due to more precise measurements or greater variability. This phenomenon skews the distribution, causing an even funnel plot.

Overall, the symmetry observed in the funnel plots highlights the importance of interpreting the meta-analysis results with caution. Publication bias can lead to an overestimation of the true effect size, as the pooled results may be disproportionately influenced by studies with significant findings. Similarly, small-study effects can distort the overall picture, making it appear that there is a stronger association between hs-CRP levels and stroke or cardiovascular events than exists.

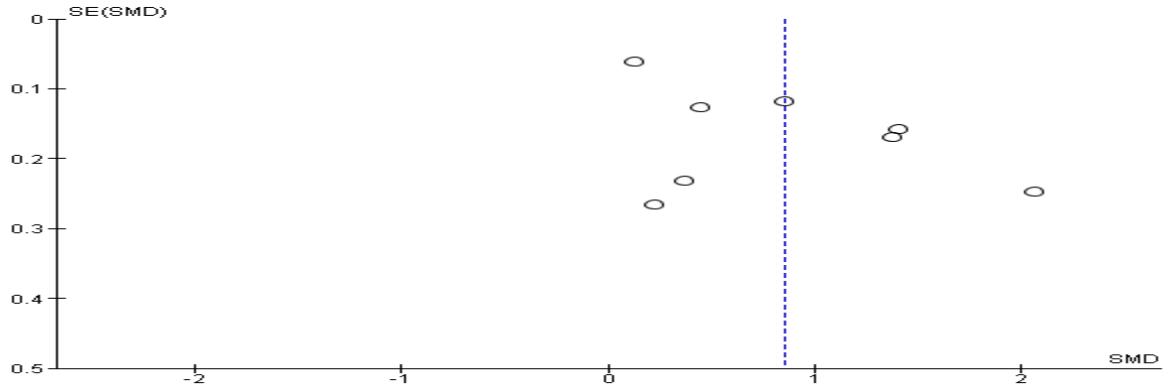

Figure 4: *Funnel plot for Primary Comparator showing the Standard Error (vertical axis), SMD (horizontal axis), the individual included studies (dots) and line of null effect (running across the studies).*

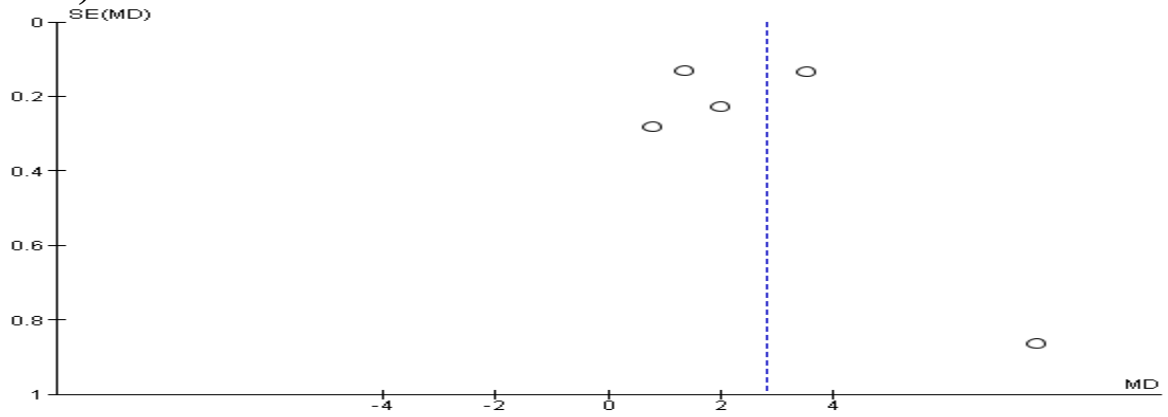

Figure 5: *Funnel plot for Secondary Comparator showing the Standard Error (vertical axis), SMD (horizontal axis), the individual included studies (dots) and the line of null effect (running across the studies).*

Impact of Removing Studies on the Symmetry Line

Removing studies on the line of null effect on the forest plot can provide insight into their influence on the overall meta-analysis results. Through this research, there were only two studies that lie on the line of null effect (Koosha 2020 and Liu 2018) in the primary comparator forest plot (**Figure 6**).

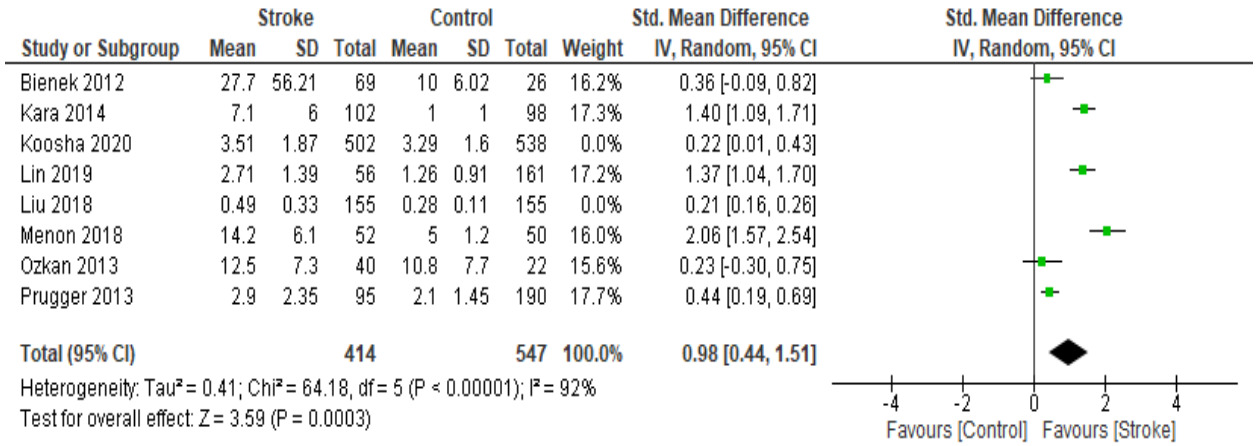

Figure 6: *Forest plot of primary comparator after removal of the two studies lying on the line of null effect*

Excluding these two studies reduces this study's heterogeneity slightly and potentially alters the pooled effect size. However, despite the removal of these two studies, the overall effect size remains the same after exclusion, indicating that this result is stable.

DISCUSSION

Comparison of hs-CRP Levels in Stroke Patients vs. Non-Stroke Controls

This meta-analysis comprehensively evaluates the role of hs-CRP in stroke prediction by comparing hs-CRP levels between stroke patients and controls. The analysis incorporates data from eight studies, revealing a statistically significant elevation in hs-CRP levels among stroke patients compared to controls, with a standardised mean difference (SMD) of 0.85 (95% CI: 0.40, 1.29; P = 0.0002) and a mean difference (MD) of 2.41 (95% CI: 1.57, 3.26; P < 0.00001). This substantial increase underscores the potential of hs-CRP as a biomarker for stroke. The findings consistently demonstrate that elevated hs-CRP levels are associated with an increased risk of stroke, supporting the hypothesis that hs-CRP can be a valuable biomarker for stroke prediction.

The elevation of hs-CRP levels in stroke patients from our findings aligns with the hypothesis that hs-CRP is significantly relevant in predicting stroke and other cardiovascular events. Maki-Alhindi *et al*. (2019), Menon and Krishnan (2018), and Wang *et al*. (2021) studies agree with these findings, highlighting the relevance of hs-CRP in stroke prediction. The inflammatory aspect of stroke risk was highlighted by Maki-Alhindi et al.'s (2019) demonstration that raised hs-CRP levels were highly correlated with an increased incidence of stroke. Wang and colleagues (2021) discovered that those exhibiting elevated levels of hs-CRP had a notably increased risk of stroke, hence validating the usefulness of hs-CRP as a predictor. Maki-Alhindi et al. (2019) have reported that Hs-CRP is a sensitive measure of systemic inflammation that is generated by the liver in response to inflammatory stimuli. Increased risk of stroke and other cardiovascular events has been linked to elevated hs-CRP levels (Kumar et al., 2018). Furthermore, the inflammatory mechanisms underpinning the aetiology of stroke might be responsible for the correlation between increased hs-CRP and stroke (Menon and Krishnan 2018). Chronic inflammation contributes to endothelial dysfunction, atherosclerosis, and plaque instability, which are crucial in stroke development (O'donnell *et al.* 2016). According to O'donnell et al. (2016), elevated hs-CRP levels are indicative of persistent inflammation that can make these problems worse and raise the risk of stroke. Before

delving into the specifics of hs-CRP, Wang et al. (2015) and Ozkan et al. (2013) contend that it's critical to distinguish between non-modifiable and modifiable risk factors for stroke. Non-modifiable factors, such as age, gender, and genetics, set a baseline risk for stroke but cannot be changed. Conversely, modifiable variables can be controlled by dietary modifications and medication, including hypertension, diabetes, obesity, smoking, dyslipidaemia, physical inactivity, and poor nutrition (Liu et al. 2014). Furthermore, chronic inflammation, indicated by elevated hs-CRP levels, is a significant factor in the pathogenesis of stroke, as it impacts key aspects of vascular health including endothelial function, atherosclerosis, and plaque stability (Kara *et al.* 2014).

Elevated hs-CRP levels are linked to compromised endothelial function, which lowers nitric oxide availability and increases oxidative stress, according to Kuriakose and Xiao (2020). Atherosclerosis develops as a result of this malfunction, which produces a pro-inflammatory and pro-thrombotic milieu in blood vessels (AL-Sa'adi *et al*. 2015). Chronic inflammation, as indicated by elevated hs-CRP, further exacerbates endothelial dysfunction by triggering pathways that damage endothelial cells (Bienek *et al*., 2012). Such damage compromises the endothelium's regulatory functions, increasing the risk of plaque formation and thrombosis (AL-Sa'adi *et al.* 2015). Elevated hs-CRP levels are therefore indicative of ongoing endothelial injury, a precursor to severe vascular damage and stroke (Bienek *et al*., 2012). Furthermore, there is a strong correlation between increased hs-CRP levels and the onset and advancement of atherosclerosis (Béjot *et al*., 2016). By a variety of methods, hs-CRP promotes atherosclerosis. First off, according to Andersson *et al*. (2009), it encourages the recruitment of inflammatory cells to the artery wall, which facilitates the development of atherosclerotic plaques. hs-CRP promotes monocyte and lymphocyte infiltration into the subendothelial region by upregulating the expression of adhesion molecules on endothelial cells (Boehme and Esenwa, 2017). Secondly, hs-CRP is associated with increased plaque instability, which heightens the risk of acute cardiovascular events like stroke. Inflammation within plaques degrades the fibrous cap, making it more prone to rupture (AL-Sa'adi *et al*. 2015). This rupture can release pro-coagulant material into the bloodstream, triggering thrombus formation and potentially causing ischemic stroke (Golledge *et al*., 2023). Finally, high hs-CRP levels correlate with plaque progression, accelerating plaque growth and increasing the likelihood of rupture, thereby raising stroke risk (Huang *et al*., 2012).

The importance of hs-CRP in stroke pathology has been reinforced by studies by Gan et al. (2021), Lee *et al*. (2013), and Lin *et al.* (2019) that show a link between high hs-CRP levels and the presence of atherosclerotic plaques, an indication of stroke. Higher levels of hs-CRP have been linked to greater cardiovascular risk and more widespread atherosclerotic disease, according to studies by Lee *et al*. (2013) and Lin *et al*. (2019). The importance of hs-CRP as a measure of systemic inflammation was underlined by Gan *et al*. (2021), who noted that it affects vascular health by increasing atherosclerosis, endothelial dysfunction, and plaque instability. Understanding these biological links provides valuable insights into hs-CRP's potential as a predictive biomarker for stroke risk (Liu *et al*., 2019).

On the other hand, there is some variation in the research on the strength of the correlation between hs-CRP and stroke risk. Variations in research populations, methodological techniques, and the classifications of stroke types employed in the studies might all be contributing factors to this diversity. For example, some studies may include a heterogeneous population with varying stroke subtypes, which can influence the observed association. Additionally, factors such as age, gender,

and comorbid conditions can affect hs-CRP levels and stroke risk, adding another layer of complexity to the analysis (Menon and Krishnan 2018). Overall, the findings suggest that while hs-CRP is a valuable biomarker for stroke prediction, its interpretation should be contextualised within a broader clinical framework. Future research should focus on standardising hs-CRP measurement protocols and examining its role in different stroke subtypes to refine its predictive utility. Further studies could also explore the interplay between hs-CRP and other inflammatory markers or risk factors to provide a more comprehensive assessment of stroke risk.

Comparison of hs-CRP Levels in Patients with Cardiovascular Events vs. Controls

The comparison of hs-CRP levels in patients with cardiovascular events versus control subjects is crucial for understanding whether elevated hs-CRP levels are specifically associated with stroke or if they reflect a general cardiovascular risk. With wide-ranging effects on cardiovascular health, hs-CRP has become a prominent indicator of systemic inflammation (Maki-Alhindi et al., 2019; Oprescu et al., 2021). Several investigations have demonstrated that increased levels of hs-CRP are linked to a variety of cardiovascular disorders, such as myocardial infarction (MI) and heart failure (HF), in addition to stroke (Qin et al., 2016; Roudbary et al. 2011). Because of this broad correlation, it is crucial to determine if hs-CRP is a universal indicator of cardiovascular risk or if it just has a predictive function in specific cases as stroke.

There is ample evidence to support the association between increased hs-CRP levels and cardiovascular events. Maki-Alhindi et al. (2019) and Oprescu et al. (2021), for example, showed that elevated levels of hs-CRP are linked to a higher risk of MI, indicating that hs-CRP is a reflection of systemic inflammation that plays a role in the development of coronary artery disease (CAD). The idea that systemic inflammation is a key factor in the development of acute coronary events is strengthened by the findings of these investigations, which show that increased hs-CRP is an independent predictor of MI risk. Oprescu et al. (2021) noted that MI is primarily caused by the rupture of atherosclerotic plaques in the coronary arteries, leading to thrombosis and subsequent myocardial damage. hs-CRP is involved in the inflammatory processes that drive plaque formation and instability, leading to increased atherosclerotic plaque burden and vulnerability—crucial factors in MI pathogenesis (Qiu et al., 2016). This evidence highlights hs-CRP's relevance in a broader spectrum of cardiovascular events (Huang et al., 2012). Beyond MI, increased hs-CRP levels have also been connected to heart failure, a disorder marked by the heart's incapacity to adequately pump blood (Golledge et al., 2023). Golledge et al. (2023) provided evidence linking hs-CRP to heart failure severity and prognosis. Elevated hs-CRP levels correlate with poor outcomes in heart failure patients, indicating that systemic inflammation contributes to disease progression. Wang et al. (2021) further emphasized that heart failure involves complex pathophysiological mechanisms, including chronic inflammation, which plays a role in myocardial remodeling and deterioration. Heart failure patients with elevated hs-CRP levels indicate higher inflammatory activity and are predictive of worse outcomes. The systemic character of inflammation and its wider influence on cardiovascular health are highlighted by the existence of higher hs-CRP levels in heart failure (Wang et al., 2021).

Elevated hs-CRP levels have been linked to a number of cardiovascular diseases, indicating that hs-CRP is not exclusive to stroke but rather a sign of overall cardiovascular risk. Oprescu et al. (2021) state that hs-CRP is a sensitive measure of systemic inflammation, which is frequently the underlying cause of cardiovascular disorders such as MI, heart failure, and stroke. This broad applicability of hs-CRP as a cardiovascular risk marker is supported by findings from the JUPITER

trial (Kuriakose & Xiao, 2020), which demonstrated that statin therapy significantly reduced hs-CRP levels and the risk of cardiovascular events in individuals with elevated hs-CRP but without established cardiovascular disease. This trial highlights the utility of hs-CRP in identifying high-risk individuals across various cardiovascular conditions and guiding preventive strategies.

In comparing hs-CRP levels among patients with stroke versus those with other cardiovascular events, it becomes evident that while elevated hs-CRP is a common feature across different cardiovascular conditions, its predictive value for stroke may be particularly pronounced. Studies indicate that stroke patients often exhibit higher hs-CRP levels compared to those with other cardiovascular conditions (Oprescu *et al*., 2021). This distinction could be attributed to specific inflammatory pathways involved in stroke, such as those affecting plaque instability and thrombus formation (Boehme and Esenwa, 2017). The particular role of hs-CRP in stroke may lie in its involvement in the destabilization of atherosclerotic plaques, which leads to ischemic events.

This meta-analysis supports the hypothesis that there is a significant difference in hs-CRP levels between patients with cardiovascular events and control subjects, particularly highlighting elevated hs-CRP levels in stroke patients. The pooled results indicate that both the standardized mean difference (SMD) and mean difference (MD) analyses show a significant increase in hs-CRP levels in stroke patients, reinforcing the association between elevated hs-CRP levels and stroke. Additionally, the high heterogeneity observed in our results underscores the variability in effect sizes across different studies, which could be linked to differences in study populations, methodologies, and timing of hs-CRP measurements.

Overall, this research provides strong evidence that elevated hs-CRP levels are a key marker for predicting cardiovascular events, particularly stroke. The findings suggest that while hs-CRP reflects general cardiovascular risk, its association with stroke is uniquely significant, making it a valuable biomarker for stroke risk assessment. Understanding the mechanisms by which hs-CRP contributes to stroke pathology offers valuable insights into the potential for targeted preventive strategies and interventions.

CONCLUSION AND RECOMMENDATION

In summary, the overall pooled/estimated effects of the individual studies including their confidence intervals have successfully been achieved as shown in the forest plots represented in **Fig. 2** and **Fig. 3** respectively. This meta-analysis confirms that elevated hs-CRP levels are associated with an increased risk of stroke and cardiovascular events, supporting its role as a predictive biomarker. The comparison of hs-CRP levels in stroke patients versus non-stroke controls highlights its potential for stroke risk assessment, and the comparison with other cardiovascular events highlights the need for a clear interpretation of hs-CRP levels. The findings revealed that hs-CRP levels are consistently elevated in individuals who experience stroke /cardiovascular events compared to apparently healthy individuals. Conclusively, the meta-analysis supports the alternative hypothesis H_1 that 'there is a significant difference between the hs-CRP level of stroke/cardiovascular events vs control patients. The findings from this meta-analysis underscore the potential of hs-CRP as a predictive biomarker for stroke/cardiovascular events. Elevated hs-CRP levels could serve as a warning sign, prompting more aggressive management of stroke risk factors, especially in hypertensive individuals.

The findings of this meta-analysis have significant implications for healthcare policy, clinical practice, and future research. For health care policy, the result of this study unravels the importance of including hs-CRP measurements in local, national and international guidelines for

cardiovascular risk assessment. The is a need for advocacy by policymakers for the adoption of hs-CRP screening in populations at risk, potentially leading to more effective allocation of resources toward prevention and early detection strategies, thereby leading to medical and health care costs associated with stroke and other cardiovascular diseases. For practice, the confirmation that elevated hs-CRP levels are associated with an increased risk of stroke and cardiovascular events in this study suggests that hs-CRP could be integrated into routine risk assessment protocols for individuals with strokes and other cardiovascular diseases, as well as being put forth as a preventive measure for those with a family history of the disease. Furthermore, healthcare providers could use hs-CRP as an additional tool to identify individuals at higher risk, enabling earlier interventions and personalized treatment plans to prevent stroke and cardiovascular events. Finally, in research, the findings of the study highlight the need for further enquiry into the mechanisms that link hs-CRP to stroke and cardiovascular events. Future studies should focus on identifying specific pathways through which hs-CRP influences these outcomes, as well as exploring potential confounding factors. Additionally, research should aim to refine hs-CRP measurement techniques and develop standardized thresholds for clinical use, enhancing its predictive accuracy and utility.

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