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ORIGINAL RESEARCH

# Exploring the Link Between C-Reactive Protein Change and Stroke Risk: Insights From a Prospective Cohort Study and Genetic Evidence

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**BACKGROUND:** Previous research on how changes in CRP (C-reactive protein) levels predict stroke risk is limited. This study aimed to examine the association between CRP change and the risk of stroke and its subtypes.

**METHODS AND RESULTS:** Based on the UK Biobank data, we investigated the association between CRP change and the risk of stroke and its subtypes with Cox proportional hazards regression analysis. We further performed genetic analyses including genetic correlation, pairwise genome-wide association study, and polygenic risk score. Our study involved 14 754 participants with a median follow-up time of 10.4 years. After categorizing participants by CRP percentage change and making adjustments for potential confounders, it was observed that those with an elevated percentage of CRP change had a higher risk of any stroke (hazard ratio [HR], 1.44 [95% CI, 1.12–1.85]) and ischemic stroke (HR, 1.65 [95% CI, 1.24–2.18]). After categorization by CRP change types and adjustment for confounders, the group that became high level had a higher any-stroke risk (HR, 1.45 [95% CI, 1.04–2.02]), with the group that remained at a high level facing the greatest risk (HR, 1.74 [95% CI, 1.30–2.33]). Similar trends were observed for ischemic stroke. The group that remained at a high level also had a heightened hemorrhagic stroke risk (HR, 1.91 [95% CI, 1.07–3.44]). Genetic analysis showed a significant genetic correlation between CRP and stroke ($r_g$, 0.257; $r_g$–$P$=2.39E-07). Pairwise genome-wide association study analysis identified 5 shared genomic regions between CRP and stroke. Polygenic risk score analysis showed that participants with high stroke polygenic risk score and elevated or remaining high CRP levels have the highest risk of stroke.

**CONCLUSIONS:** Both any stroke and ischemic stroke are related to elevated and remaining high CRP levels, while hemorrhagic stroke is only related to remaining high CRP levels.

**Key Words:** C-reactive protein change ■ genetic analyses ■ stroke



Stroke impacts 1 in 4 individuals in their lifetime, ranking as the second major cause of death and third for disability globally.[1,2] Stroke can be classified as ischemic stroke and hemorrhagic stroke, with ischemic types constituting roughly 80% of cases.[2,3] Stroke can lead to lasting disability and pose

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## CLINICAL PERSPECTIVE

### What Is New?

- In our research, we examined the link between CRP (C-reactive protein) change and the risk of stroke and its subtypes using the UK Biobank cohort data; individuals with elevated CRP demonstrated a heightened risk for any stroke and ischemic stroke, while no significant association was discerned for hemorrhagic stroke.
- In the analysis of CRP change types, the groups that became high level and remained high level manifested the higher risk for any stroke and ischemic stroke; the group that continued to have a high level of CRP also exhibited an augmented risk for hemorrhagic stroke.
- Genetic analysis showed a significant genetic correlation between CRP and stroke; pairwise genome-wide association study analysis identified 5 shared genomic regions between CRP and stroke, and polygenic risk score analysis showed that participants with high stroke polygenic risk score and elevated or remaining high CRP levels have the highest risk of stroke.

### What Are the Clinical Implications?

- Our findings demonstrate that CRP change is associated with different risks of stroke and its subtypes. Monitoring CRP change over time may provide additional information for stroke risk assessment.
- Our genetic analyses suggest shared biological pathways between CRP and stroke risk. These findings may inform future research on risk assessment and prevention strategies.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **PPA** | posterior probability of association |
| **PRS** | polygenic risk score |
| **TDI** | Townsend Deprivation Index |

a significant socioeconomic impact.[4] Identifying markers that predict stroke events is crucial for pinpointing preventive actions.[5]

Prior investigations have substantiated a close association between inflammation and the incidence of stroke.[6–9] CRP (C-reactive protein), recognized as an inflammatory biomarker, has been shown in several studies to have a correlation between its concentration and the risk of ischemic stroke.[10–12] It should be noted that the majority of prior research has focused on 1-time measurements of CRP levels. The limitation of this method lies in its portrayal of merely a momentary glimpse of systemic inflammation. This can potentially lead to inadequate risk profiling. Repeated CRP evaluations can offer richer insights; however, scant studies delve into the significance of CRP variations in forecasting impending ischemic stroke hazards. Furthermore, previous studies have shown that a single measurement of CRP is not related to hemorrhagic stroke,[10] but whether multiple measurements of CRP are associated with hemorrhagic stroke is worth our attention and further investigation.

As large-scale genomic data become increasingly available, genetic factors play an important role in the development of stroke.[13] Past genome-wide association studies (GWAS) have identified hundreds of genetic variants linked to stroke,[14,15] which sets the stage for assessing genetic correlation between different traits. Cross-trait linkage disequilibrium score regression, for example, can assess genetic correlations across traits, providing valuable biological insights.[16] Additionally, the polygenic risk score (PRS) aggregates multiple risk alleles and effectively predicts disease and aids in risk stratification.[17] Analyzing the combined effects between genetic and other factors enhances the precision risk differentiation and investigates potential effect modifiers, advancing the identification and targeted interventions for susceptible populations. Currently, no research has explored the whole-genome genetic correlation between CRP levels and stroke or examined how CRP changes affect stroke risk in genetically susceptible individuals.

In our research, we examined the link between CRP change and the risk of stroke and its subtypes using the UK Biobank cohort data. We pursued 3 inquiries: (1) Does the twice-measured CRP percentage change correlate with risks of various strokes? (2) Do different types of 2-time measured CRP influence these stroke risks? (3) How do genetic analyses reveal potential links between CRP levels or changes in CRP and the risk of stroke?

## METHODS

The data supporting our findings can be obtained through the corresponding author with a reasonable request.

### Study Population

The UK Biobank, one of the preeminent biomedical sample databases worldwide, collected data from participants, aged between 40 and 69 years, across the United Kingdom between 2006 and 2010.[18,19] Participants completed comprehensive health and lifestyle questionnaires during the initial recruitment and submitted blood samples for biomarker assays.

Between 2012 and 2013, the UK Biobank conducted its first repeat assessment visit and undertook repetitive measurements of key biomarkers for some participants. Limiting the sample to self-identified White individuals minimizes racial confounding, given evidence of varied serum biomarker levels, like CRP, among races and ethnicities.[20] Our research focused on 16 549 participants who had complete data from 2 CRP measurements. After excluding those who had a stroke before the first repeat assessment visit, non-White participants, and those with CRP levels exceeding 10 mg/L, the study ultimately incorporated 14 754 participants into the analysis. An overview of the study design can be found in Figure 1. This research was conducted using the UK Biobank Resource under project number 104830. The UK Biobank research received formal endorsement from the Northwest Multicenter Research Ethics Committee, with all participants furnishing informed consent for their involvement.[21] The study complies with the Declaration of Helsinki.

## Exposure

During the initial recruitment, participants' blood specimens were procured. The serum CRP levels (mg/L) were quantified using a high-sensitivity immunoturbidimetric assay on a Beckman Coulter AU5800 analyzer.[22,23] The second evaluations of serum CRP concentrations occurred during the first repeat visit. The median time between the 2 CRP measurements was 4.4 years. As in previous studies,[24,25] participants were excluded from analyses if CRP was >10.0 mg/L, because CRP levels exceeding 10.0 mg/L may indicate additional infection or inflammation. We used 2 grouping methods. First, we categorize CRP group alterations by quantifying the initial CRP level's percentage change, standardizing the initial level at 100%. Based on the second CRP level showing a 50% reduction or increase from the initial level, we classify these percentage changes into 3 categories: the stable group (change ranging from −50% to 50%), the reduced group (decrease >50%), and the elevated group (increase >50%). Second, considering the definition of a high inflammation state as CRP ≥2 mg/L,[26,27] we used 2 mg/L as the classification value to categorize the population into 4 groups on the basis of the types of CRP change observed in 2 assessments: remained low level (both CRP <2 mg/L), became low level (initial CRP ≥2 mg/L and second CRP <2 mg/L), became high level (initial CRP <2 mg/L and second CRP ≥2 mg/L), and remained high level (both CRP ≥2 mg/L).

## Outcomes

The primary end points of this investigation encompassed stroke and its subtypes, including ischemic stroke and hemorrhagic stroke. Within hemorrhagic stroke, we included intracerebral hemorrhage and subarachnoid hemorrhage. Stroke events were determined via the UK Biobank's health-related outcomes, combining algorithmically defined outcomes with previously validated *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes.[28,29] This incorporated participant self-reported medical conditions, medications, and linked data from hospital admissions and death registries. Individuals who experienced a stroke

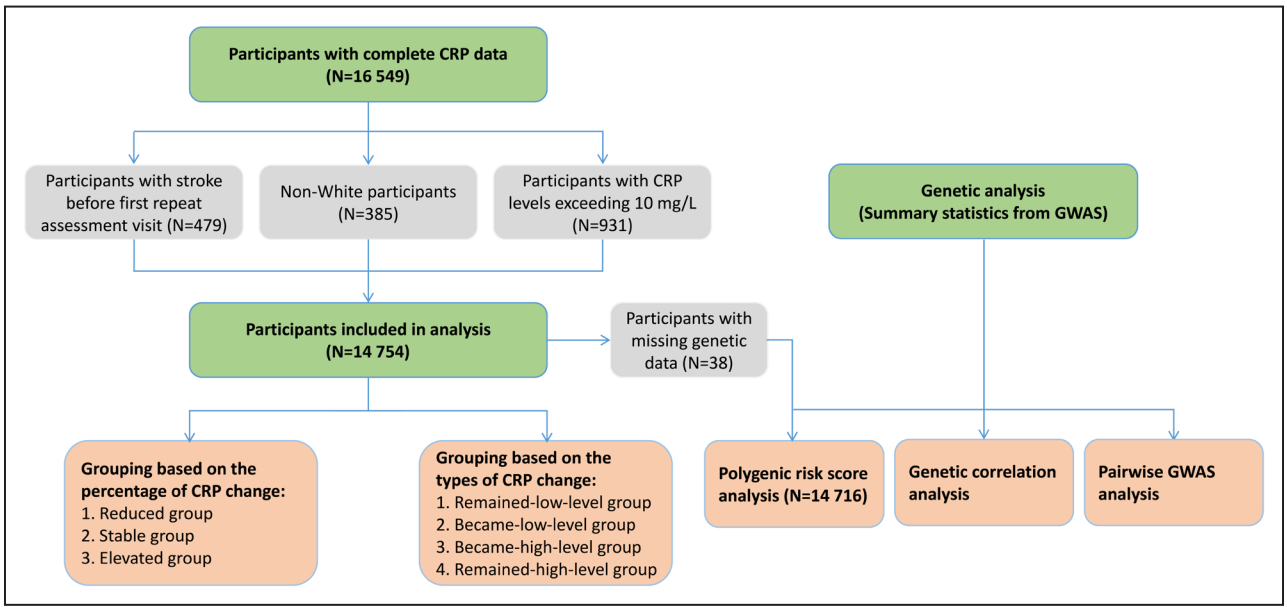


**Figure 1. Flowchart of participant inclusion and exclusion criteria.**
CRP indicates C-reactive protein; and GWAS, genome-wide association study.

before the first repeat assessment visit were excluded, focusing solely on analyzing stroke occurrences after the last CRP evaluation. We computed the follow-up time from the first repeat assessment visit to the time of stroke diagnosis, death, or the last data collection time (July 16, 2023), adopting the earliest event.

## Covariates

The covariates in our study encompass baseline data measured at initial recruitment, including age, sex, body mass index (BMI), Townsend Deprivation Index (TDI), educational level, healthy diet, white blood cell count, smoking status, alcohol consumption, and medical history such as hypertension, hypercholesterolemia, and diabetes. BMI was calculated as weight divided by the square of height (kg/m$^2$). The TDI served as an indicator of socioeconomic status, with elevated scores signifying a greater level of deprivation.[30] Education was classified into those holding a college/university degree and others. The assessment of a healthy diet, based on the consumption of red meat, vegetables, fruits, fish, grains, and urinary sodium concentration, assigns a score of ≥3 as indicative of a healthy diet, as delineated in prior literature.[31–33] Both smoking status and alcohol consumption were classified as never, former, or current. Records of hypertension, hypercholesterolemia, and diabetes were based on self-reported information. Field ID used for all variables analyzed is provided in Table S1.

## Statistical Analysis

Continuous data were presented as means±SDs or medians with interquartile ranges on the basis of distribution, while categorical variable proportions were documented. Through the application of the multiple imputation approach, we performed analyses on a total of 5 multiply imputed data sets before the results were pooled according to Rubin's rule.[34] The percentage of missing values can be found in Table S2.

Using the stable group and remained-low-level group of the CRP as a reference, through the Cox proportional hazards models, we determined the hazard ratios (HRs) and 95% CIs related to the linkage between CRP change and the risk of any stroke, ischemic stroke, and hemorrhagic stroke. Scaled Schoenfeld residuals were used to assess the proportionality of hazards. Variables that had a *P* value >0.05 were considered to meet this assumption. When the assumption was not met, adjustments were made by incorporating time-dependent covariates into the models. We established 2 models using the follow-up period as the time scale. The selection of covariates for the multivariable models was based on prior studies.[12,35] Model 1 was adjusted for age and sex. Model 2 built upon model 1 by additionally adjusting for BMI, TDI, education, healthy diet, smoking status, alcohol consumption, and a history of diseases including hypertension, hypercholesterolemia, and diabetes.

To assess possible effect modification, we conducted analyses stratified by age, sex, BMI, TDI, and education. Likelihood ratio tests were used to determine statistical significance in subgroup heterogeneity. Considering the fewer outcome events of hemorrhagic stroke, we only conducted an analysis of subgroups for any stroke and ischemic stroke.

To validate the robustness of our findings, we performed a series of sensitivity analyses. First, we examined the competing risk of death on the relationship between CRP change and various types of strokes using a competing risk model. Second, participants with incomplete data were excluded, and the analysis was conducted using complete data sets. Third, using covariate indicators measured during the first repeat assessment visit, we incorporated them into the Cox proportional hazards models for the main analyses. Finally, we also made additional adjustments to white blood cell count for the main analysis. Statistical evaluations were conducted using R version 4.2.3 (The R Project). A 2-sided *P* value <0.05 indicated statistical significance.

## Genetic Correlation

Genetic correlation represents the shared genetic basis of 2 traits or diseases, independent of environmental factors. Linkage disequilibrium score regression effectively determines this correlation for complex diseases or traits by assessing trait heritability or trait correlations using $\chi^2$ statistics based on single-nucleotide polymorphisms (SNPs).[16] Using GWAS summary data, we applied linkage disequilibrium score regression to ascertain the genetic correlation between CRP and stroke. We sourced CRP data (N=204 402) from an extensive European GWAS,[36] and stroke data (N=446 696) from another major European GWAS study.[15] The details of data for the GWAS are provided in Table S3. The genetic correlation estimates ($r_g$) indicate the genetic relationship between 2 traits and vary from –1 to 1. A value of –1 indicates a complete negative correlation, while a value of +1 shows a complete positive correlation. The significance of these correlations is indicated by $r_g$–*P*, with values <0.05 deemed statistically significant.

## Pairwise GWAS

We used pairwise GWAS analysis to identify shared genomic regions between CRP and stroke.[37] The genome was partitioned into 1703 independent regions. Using an empirical Bayes approach, we evaluated each region to determine posterior probability of association (PPA) across 4 models: association with CRP only

(PPA1), association with stroke only (PPA2), shared association with both CRP and stroke via an SNP (PPA3), and shared association with both CRP and stroke but via 2 distinct SNPs (PPA4). In this analysis, we selected genomic regions where PPA3 was >0.5, as this threshold has been used in prior studies using the pairwise GWAS analysis.[38,39]

## Polygenic Risk Score Analysis

We used PRSice-2 software for stroke PRS analysis from stroke GWAS effect estimates, to derive the "best-fit" PRS using the established Clumping+Thresholding method.[40] For the stroke GWAS, we filtered out ambiguous SNPs and SNPs with duplicate or minor allele frequency ≤0.01. Previous literature has described detailed information on genome-wide genotyping, imputation, and quality control in the UK Biobank study.[41] After excluding participants with missing genetic data (N=38), PRSice-2 calculated the weighted PRS for stroke in 14 716 participants. We divided the PRS of stroke into low (first tertile), intermediate (second tertile), and high (third tertile) risk categories. Then, participants were categorized into 9 or 12 groups on the basis of different combinations of stroke PRS (low, intermediate, and high) and CRP changes. We selected the stable group or remained-low-level group combined with low stroke PRS as the reference group to examine the association of the other groups with stroke risk.

# RESULTS

## Baseline Characteristics

In total, our study enrolled 14 754 participants with a median follow-up time of 10.4 years. Baseline characteristics were categorized by the percentage or types of CRP change. Table S4 revealed baseline characteristics based on CRP percentage change, with the stable group having more women, the elevated group having a greater prevalence of current smokers, and the reduced group having a high BMI value and a higher proportion of medical history. The Table indicates that the mean age was the youngest in the group that remained low level. The group

**Table. Baseline Characteristics Based on CRP Change Types in the UK Biobank (N=14 754)**

| Characteristics | N (%)* | | | |
|---|---|---|---|---|
| | Remained low level | Became low level | Became high level | Remained high level |
| N | 9026 | 1597 | 1728 | 2403 |
| Age, y, mean±SD | 56.83±7.45 | 57.65±7.23 | 57.72±7.13 | 57.94±6.98 |
| Sex | | | | |
| Female | 4436 (49.1) | 778 (48.7) | 783 (45.3) | 1374 (57.2) |
| Male | 4590 (50.9) | 819 (51.3) | 945 (54.7) | 1029 (42.8) |
| BMI, mean±SD, kg/m$^2$ | 25.60±3.59 | 28.13±4.68 | 26.90±3.83 | 29.76±4.99 |
| TDI, median (IQR) | −2.85 [−4.04 to −1.06] | −2.59 [−3.87 to −0.57] | −2.81 [−4.00 to −0.84] | −2.58 [−3.84 to −0.52] |
| Education | | | | |
| College/University degree | 4277 (47.4) | 660 (41.3) | 719 (41.6) | 833 (34.7) |
| Others | 4749 (52.6) | 937 (58.7) | 1009 (58.4) | 1570 (65.3) |
| Healthy diet | 6298 (69.8) | 1108 (69.4) | 1232 (71.3) | 1706 (71.0) |
| Smoking status | | | | |
| Never | 5608 (62.1) | 855 (53.5) | 977 (56.5) | 1295 (53.9) |
| Previous | 2963 (32.8) | 617 (38.6) | 619 (35.8) | 911 (37.9) |
| Current | 455 (5.0) | 125 (7.8) | 132 (7.6) | 197 (8.2) |
| Alcohol consumption | | | | |
| Never | 218 (2.4) | 41 (2.6) | 32 (1.9) | 77 (3.2) |
| Previous | 206 (2.3) | 42 (2.6) | 38 (2.2) | 66 (2.7) |
| Current | 8602 (95.3) | 1514 (94.8) | 1658 (95.9) | 2260 (94.0) |
| Medical history | | | | |
| Hypertension | 1792 (19.9) | 462 (28.9) | 432 (25.0) | 747 (31.1) |
| Hypercholesterolemia | 1053 (11.7) | 182 (11.4) | 219 (12.7) | 269 (11.2) |
| Diabetes | 273 (3.0) | 77 (4.8) | 72 (4.2) | 121 (5.0) |
| WBC, 10$^9$/L, median (IQR) | 6.33 (1.63) | 6.90 (1.73) | 6.63 (1.52) | 7.23 (1.70) |

BMI indicates body mass index; CRP, C-reactive protein; IQR, interquartile range; TDI, Townsend Deprivation Index; and WBC, white blood cell count.
*Percentages may not sum to 100 because of rounding.

that remained high level had the highest proportion of women, while the group that became high level had the highest proportion of men. The proportion of participants with higher BMI and TDI levels was highest in the group that continued to have a high level of CRP, with the highest proportions found among current smokers, as well as those with hypertension and diabetes. Conversely, this group with a college/university degree exhibited lower proportions. Additionally, the group that continued to have a low level of CRP had the lowest BMI value.

## Association Between CRP Percentage Change and Stroke

After adjusting for age and sex in model 1, the elevated group was associated with a significantly higher risk of both any stroke (HR, 1.44 [95% CI, 1.12–1.84]) and ischemic stroke (HR, 1.62 [95% CI, 1.22–2.14]; Figure 2). After further adjustment for other covariates (model 2), compared with the stable group, an elevated percentage of CRP change had a higher risk of developing any stroke (HR, 1.44 [95% CI, 1.12–1.85]) and ischemic stroke (HR, 1.65 [95% CI, 1.24–2.18]). However, in both model 1 and model 2, the elevated group consistently exhibited no correlation with hemorrhagic stroke.

## Association Between CRP Change Types and Stroke

Further analyses of the association between CRP change and incident stroke were performed after categorizing by the CRP change types (Figure 3). Following the adjustment for potential confounders, the risk of experiencing any stroke, when compared with the group that remained low level, increased for the group that became high level (HR, 1.45 [95% CI, 1.04–2.02]), and the group that remained high level had the highest risk (HR, 1.74 [95% CI, 1.30–2.33]; model 2). This stepwise effect was also evident in ischemic stroke outcomes, where the group that became high level was associated with a heightened risk of ischemic stroke (HR, 1.59 [95% CI, 1.10–2.29]), and the highest risk of ischemic stroke was observed in the group that remained high level (HR, 1.62 [95% CI, 1.15–2.28]; model 2). The group that became low level showed no significant association with the risk of any stroke or ischemic stroke. Significantly, the group that remained high level was associated with an increased risk of hemorrhagic stroke (HR, 1.91 [95% CI, 1.07–3.44]; model 2), while both the group that became high level and the group that became low level showed no association with hemorrhagic stroke.

## Stratified and Sensitivity Analyses

In stratified analyses, the association between CRP change and the incidence of any stroke, as well as ischemic stroke, did not show statistically significant differences when we conducted analyses stratified by age, sex, BMI, TDI, and education (Tables S5 through S8). Moreover, several sensitivity analyses were conducted to support the robustness of our findings. The competing risk analysis yielded results congruent with those obtained via the Cox proportional hazards models (Figures S1 and S2). After excluding participants with incomplete data, the results from the full data set were similar to those obtained from the imputed data analyses (Figures S3 and S4).

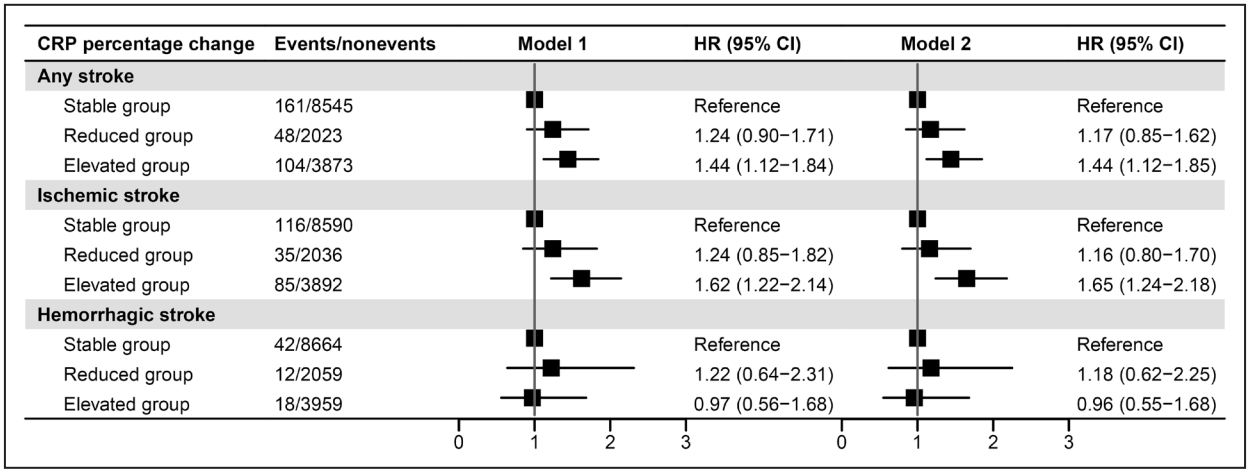


**Figure 2. Association of the CRP percentage change and risk of any stroke, ischemic stroke, and hemorrhagic stroke using Cox proportional hazards models.**

Model 1, adjusted for age and sex. Model 2, adjusted for age, sex, body mass index, Townsend Deprivation Index, education, healthy diet, smoking status, alcohol consumption, and a history of diseases including hypertension, hypercholesterolemia, and diabetes. CRP indicates C-reactive protein; and HR, hazard ratio.

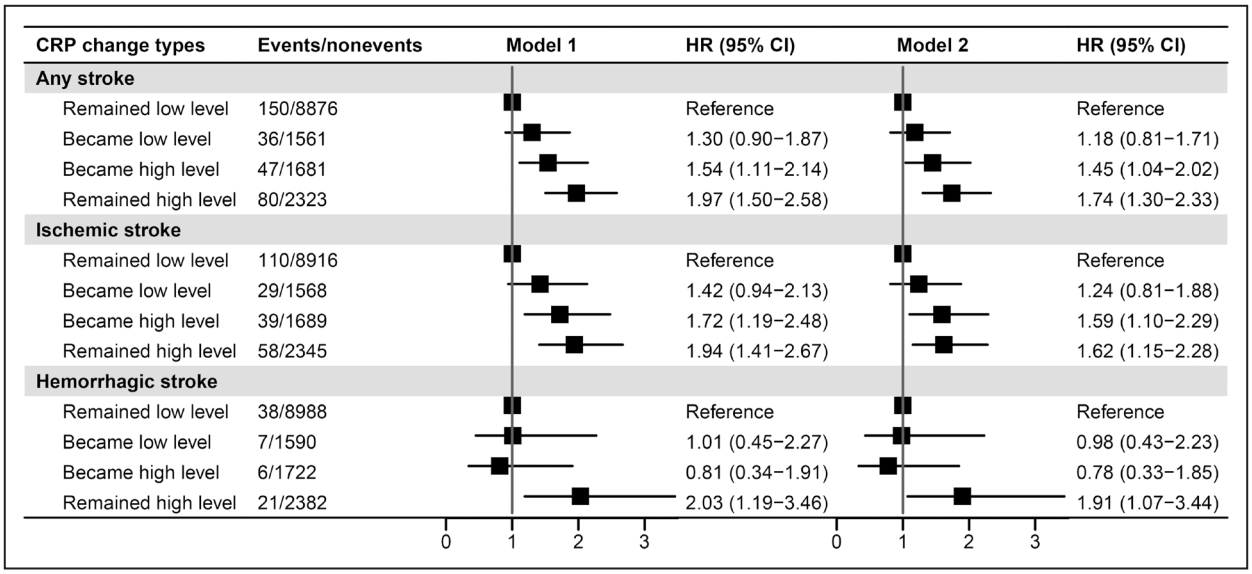


**Figure 3. Association of the CRP change types and risk of any stroke, ischemic stroke, and hemorrhagic stroke using Cox proportional hazards models.**

Model 1, adjusted for age and sex. Model 2, adjusted for age, sex, body mass index, Townsend Deprivation Index, education, healthy diet, smoking status, alcohol consumption, and a history of diseases including hypertension, hypercholesterolemia, and diabetes. CRP indicates C-reactive protein; and HR, hazard ratio.

When using covariate indices measured during the first repeat assessment visit, results did not appreciably change in the primary Cox proportional hazards models (Figures S5 and S6). Furthermore, even with additional adjustments for white blood cell count, the main results remained consistent, as demonstrated in Figures S7 and S8.

## Genetic Analysis

We investigated the genetic linkage between CRP and stroke through linkage disequilibrium score regression analysis of GWAS summaries (Table S9). Our findings showed a significant genetic correlation ($r_g$, 0.257; $r_g$_$P$=2.39E-07) between CRP and stroke risk. Pairwise GWAS analysis identified 5 shared genomic regions between CRP and stroke (Table S10). The shared genomic region with the highest posterior probability is chr12: 89692310–92 065 034. Given the small number of outcome events in stroke subtypes within groups in genetic analysis, we used the Cox proportional hazards models to estimate the association between CRP changes, stroke GRS, and the risk of any stroke. The study found that in the high PRS and elevated group of CRP, the risk of any stroke was highest (HR, 2.04 [95% CI, 1.37–3.06]) as shown in model 2 (Figure S9). In the intermediate stroke PRS group (Figure S10), the group that remained at a high level experienced an increased risk of any stroke (HR, 1.99 [95% CI, 1.23–3.22]; model 2). In the high stroke PRS group, the risk of experiencing any stroke increased for the group that became high level (HR, 1.74 [95% CI, 1.02–2.97]), and the group that remained high level had the highest risk (HR, 1.99 [95% CI, 1.25–3.18]; model 2).

# DISCUSSION

Our study illuminated the intriguing relationship between CRP change and the subsequent risk of incident stroke and its subtypes. First, after categorizing participants by CRP percentage change, individuals with elevated CRP demonstrated a heightened risk for any stroke and ischemic stroke, while no significant association was discerned for hemorrhagic stroke. In the analysis of CRP change types, a stepwise effect was observed. Specifically, the groups that became high level and remained high level manifested the higher risk for any stroke and ischemic stroke. Notably, the group that remained high level of CRP also exhibited an augmented risk for hemorrhagic stroke. Subgroup and sensitivity analyses further confirmed the robustness of our results. It is worth noting that we further analyzed the association between CRP or CRP change and stroke from a genetic perspective. Overall, these findings underscore the potential value of CRP change in assessing stroke risk.

Our research enhances current understanding of the link between CRP change and ischemic stroke risk. In a study on cardiovascular disease, which included both White and Black cohorts, a marked risk increase for ischemic stroke was observed among those with sustained elevated CRP levels (HR 1.65 [95% CI, 1.26–2.15]).[12] Our research, primarily involving

British White individuals, corroborated these findings. Uniquely, we also identified an elevated risk associated with the group whose CRP levels became high, which differs from the findings of the American study (HR, 1.26 [95% CI, 0.88–1.79]).[12] Potential reasons for these differences include the racial composition of our study compared with the American one, which had 16.0% to 30.6% Black participants, suggesting potential racial disparities. Additionally, the US research defined stroke as the inaugural occurrence of adjudicated hospitalization or death due to a definite/probable ischemic event.[12] In contrast, our definition of stroke was more comprehensive, not only hospital admissions (diagnoses and procedures) and death registries but also integrated participants' self-reported medical histories, surgeries, and medications, providing another potential explanation for the difference in our results. Notably, in the analysis of CRP change types, the group that remained high level showed higher HR for the risk of both any stroke and ischemic stroke than the group that became high level, with the trend reflecting a stepwise effect. These findings highlight associations between different patterns of CRP change and stroke risk.

One strength of our study is the use of 2 grouping methods. Of these, the percentage change method emphasizes the magnitude of change. By standardizing the initial CRP level at 100%, we aimed to quantify the subsequent change in a way that would be comparable across all participants, regardless of their absolute CRP values. More importantly, this method enables us to capture even small changes in CRP levels. For example, in cases where the initial CRP level is minimal, even a small increase can represent a change exceeding 50% of the initial value, thus categorizing it into the elevated group. This sensitive approach allows for a more detailed observation of CRP fluctuations, which might be clinically significant but often overlooked with broader categorization methods. In contrast, the type method offers a straightforward classification based on categorizing CRP levels using a high inflammation state (CRP ≥2 mg/L). It allows for a quick identification of significant changes in inflammatory status, such as transitions from low to high inflammation states or vice versa, which is crucial for understanding the progression or amelioration of the inflammatory response in the context of the conditions being studied. The combination of these 2 approaches enhances the depth and breadth of our findings, allowing for a more robust and comprehensive analysis of CRP alterations and their clinical implications.

Some potential mechanisms may explain the link between CRP change and ischemic stroke. First, CRP contributes to endothelial dysfunction by increasing endothelin-1, cell adhesion molecules, interleukin-8 levels, and prompting tissue factor secretion in monocytes/macrophages.[42] What needs to be explained is that the endothelial dysfunction can possibly signify the advancement of atherosclerosis.[42,43] Furthermore, CRP hinders NO production and angiogenesis, which may play a role in chronic ischemia pathogenesis.[44] It is important to note that CRP may have a more direct role in atherosclerosis development. It functions in innate immunity as an opsonin, binds to complement factors C1q and factor H to activate the complement pathway,[45] and interacts with leukocyte receptors Fc-γ receptor 1 and Fc-γ receptor 2.[46] CRP's presence in atherosclerotic plaques, where it colocalizes with the terminal complement complex, and its ability to induce tissue factor expression in monocytes further support its involvement in plaque formation and thrombosis.[47,48]

While our study emphasizes the significance of CRP changes in stroke risk prediction, other biomarkers merit consideration in this context. Fibrinogen, which plays crucial roles in platelet aggregation and thrombogenesis,[49] and interleukin-6, which has been independently associated with stroke risk in primary prevention cohorts, complement CRP in evaluating inflammation-related stroke risk.[50] The mechanisms through which interleukin-6 influences stroke risk include alterations in endothelial function, vascular permeability, and smooth muscle cell behavior.[51,52] By considering these additional biomarkers alongside CRP, we can gain a more nuanced understanding of the inflammatory processes underlying stroke risk, potentially improving risk prediction and opening avenues for targeted interventions. Future research should explore whether the dynamic changes in these complementary biomarkers could enhance stroke risk prediction accuracy.

To the best of our knowledge, our study is the first to investigate the association between CRP changes and hemorrhagic stroke. The association between CRP and the risk of hemorrhagic stroke is not yet fully understood but may be related to CRP being an inflammatory biomarker. Prior studies have noted perivascular inflammation in cerebral amyloid angiopathy, which is also a significant contributor to intracerebral hemorrhage among older adults.[53] In addition, CRP has been linked to compromise blood vessel integrity and is recognized as a marker of vascular vulnerability.[54] These mechanisms include altering NO bioavailability, its role in modulating the expression of adhesion molecules, and modifying macrophage uptake function.[55] These findings provide potential mechanistic explanations for the observed association between CRP changes and hemorrhagic stroke in our study, although the precise relationship requires further investigation. While previous studies have found no correlation between 1-time CRP measurement and hemorrhagic stroke,[10] our research indicates that consistently high CRP levels are associated with hemorrhagic stroke. One-time high CRP measurement may reflect a transient inflammatory

response, susceptible to short-term variations.[56,57] In contrast, multiple-time high CRP measurements might better represent chronic inflammation.[58] This indirectly suggests that persistent chronic inflammation may be a cause of increased risk of hemorrhagic stroke. By establishing a link between consistently high CRP levels and hemorrhagic stroke, it provides a new perspective on predictive and preventive strategies. This research suggests that regular multiple-time monitoring of CRP levels could become an important method in assessing the long-term risk of hemorrhagic stroke.

In our genetic analysis, we identified a significant genetic correlation between CRP and stroke, indicating a strong link between CRP levels and stroke risk. Additionally, by using PRS for risk stratification, we further explored the association between changes in CRP and stroke risk. To our knowledge, this is the first study to assess the combined association of CRP change and genetic susceptibility with stroke risk. Our findings show that participants with high stroke PRS and elevated or remaining high CRP levels have the highest risk of stroke. This suggests that both genetic predispositions and CRP play a critical role in stroke risk, underscoring the importance of integrating genetic and biomarker data to improve risk stratification and preventative strategies in clinical settings.

Our stratified and sensitivity analyses reaffirm the robustness of our core findings. In particular, we further analyzed the association between CRP or CRP change and stroke from a genetic perspective. In short, our study underscores the critical role of dynamic CRP changes in predicting the risk of stroke and its subtypes, making it an important contribution to CRP change-based recommendations for stroke prevention.

Like all studies, ours is not without limitations. First, the blood sample used to assess CRP for the second time was obtained roughly a decade before the outcome event. Despite the stability of CRP over time,[59] such a significant time difference might weaken the correlation between stroke and CRP. Second, while we accounted for many pertinent confounders, we cannot entirely eliminate the chance of residual confounding. Third, due to the lack of large-scale longitudinal GWAS on CRP change, our genetic correlation analysis and pairwise GWAS primarily rely on cross-sectional CRP data, which may limit a comprehensive understanding of the dynamic relationship between CRP change and stroke risk. Fourth, our study solely encompasses European White participants, constraining the broader applicability of our findings. This limitation is particularly important when considering the potential differences in inflammatory profiles and genetic backgrounds across diverse populations. For instance, a study of adults from diverse ethnic backgrounds in Canada showed that CRP levels vary significantly among different ethnic groups, with the highest levels observed in Aboriginals, followed by South Asians, Europeans, and lowest in Chinese.[60] These differences in CRP levels are influenced by variations in abdominal adiposity, body weight, and glucose metabolism.[60] These ethnic differences in CRP levels highlight the need for caution when generalizing our findings to diverse populations. Future studies should include participants from various ethnic backgrounds to validate our results for broader application.

## CONCLUSIONS

In our study on CRP change, we observed that both any stroke and ischemic stroke are related to elevated and remaining high CRP levels, while hemorrhagic stroke is only related to remaining high CRP levels.

## ARTICLE INFORMATION

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### Disclosures

None.

### Supplemental Material

Tables S1–S10
Figures S1–S10

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