C-reactive protein and stroke risk in blacks and whites: The REasons for Geographic And Racial Differences in Stroke cohort

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Background C-reactive protein (CRP) is an inflammatory biomarker used in vascular risk prediction, though with less data in people of color. Blacks have higher stroke incidence and also higher CRP than whites. We studied the association of CRP with ischemic stroke risk in blacks and whites.

Methods REGARDS, an observational cohort study, recruited and followed 30,239 black and white Americans 45 years and older for ischemic stroke. We calculated hazard ratios and 95% CIs of ischemic stroke by CRP category (<1, 1-3, 3-10, and ≥10 mg/L) adjusted for age, sex and stroke risk factors.

Results There were 292 incident ischemic strokes among blacks and 439 in whites over 6.9 years of follow-up. In whites, the risk was elevated for CRP in the range from 3 to 10 mg/L and even higher for CRP >10 mg/L, whereas in blacks, an association was only seen for CRP >10 mg/L. Considered as a continuous variable, the risk factor–adjusted hazard ratios per SD higher lnCRP were 1.18 (95% CI 1.09-1.28) overall, 1.14 (95% CI 1.00-1.29) in blacks, and 1.22 (95% CI 1.10-1.35) in whites. Spline regression analysis visually confirmed the race difference in the association.

Conclusions CRP may not be equally useful in stroke risk assessment in blacks and whites. Confirmation, similar study for coronary heart disease, and identification of reasons for these racial differences require further study. (Am Heart J 2019;217:94-100.)

Stroke is the fifth leading cause of death in the United States,[1] with a disproportionate burden in blacks compared to whites; at ages 45 to 65 years, death from stroke is 3 times higher for blacks, a difference that diminishes at older ages.[2] This racial disparity in stroke has existed for decades and is increasing, with temporal declines in stroke mortality marginally higher in whites than blacks.[3] Only recently, studies elucidated that about one half of this disparity is attributable to traditional stroke risk factors,[4] suggesting that novel risk factors including biomarkers could play a role.[5-8]

C-reactive protein (CRP) is an extensively studied inflammation biomarker associated with risk of cardiovascular events and stroke. CRP measurement is advocated by a multisociety guideline to risk classify patients for primary prevention interventions such as statin use.[9,10] Although CRP measurement is recommended, blacks have substantially higher CRP levels than whites independent of other factors,[11] and there is minimal literature on the association of CRP with cardiovascular disease and stroke in blacks.[12]

We addressed gaps in the literature by studying whether the association of CRP with stroke risk differed in blacks compared to whites. Specifically, given that CRP is higher in blacks than whites, a single threshold value for risk prediction (currently ≥2 or> 3 mg/L) may not accurately reflect risk in both racial groups, and we hypothesized that a higher value might be more appropriate among blacks.

Methods

Study participants and data collection

The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study is a longitudinal observational study addressing why blacks have higher stroke mortality than whites in the United States. A population sample of 30,239 participants was recruited by mail and telephone between 2003 and 2007 as previously described.[13] We included 42% black and 58% white participants ≥45 years of age with

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oversampling of participants residing in the Southeastern stroke belt (56%; a region with higher stroke mortality than the rest of the country); 44% of the cohort resided in the remaining 40 contiguous states.

Participant characteristics were obtained via a computer-assisted telephone interview followed by in-home examination. The interview obtained demographic information, medical information, and verbal informed consent. The in-home examiner measured blood pressure, performed an electrocardiogram (ECG), collected blood and urine samples, and obtained written informed consent. Blood was processed and shipped to a central laboratory,[14] and CRP was measured using a high-sensitivity immunonephelometric method. Characterization of CRP correlates in REGARDS by race has been published.[11] Study methods were approved by institutional review boards at all participating institutions.

The following participants were excluded from analysis: those with data anomalies (n = 56), prebaseline stroke or transient ischemic attack (n = 1930), missing CRP (n = 1773), and no follow-up (n = 407). After exclusions, the analysis data set included 26,069 participants.

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Definitions of baseline variables

Race was determined by self-report as black or white. *Hypertension* was defined as blood pressure >140/90 mm Hg or use of antihypertensive medications. Heart disease was defined by ECG evidence of myocardial infarction; self-report of a physician diagnosis of myocardial infarction1; or self-reported coronary artery bypass, angioplasty or stent. Prebaseline stroke was determined by self-report of a physician diagnosis. *Diabetes* was defined as fasting glucose >126 mg/dL or self-reported use of diabetic medications. Atrial fibrillation was ascertained by ECG or self-report of a physician diagnosis. Left ventricular hypertrophy was defined by ECG.

CRP was categorized as <1 mg/L, 1-3 mg/L, ≥3-10 mg/L, and ≥10 mg/L.[15] The cutoff of ≥10 mg/L was used to determine if marked elevation in CRP previously reported in relation to coronary disease risk (but also suggested by guidelines to indicate inflammation due to other causes than vascular risk) reflected a degree of inflammation important in stroke risk.[16]

Stroke ascertainment

Participants and/or proxies were contacted every 6 months by telephone to identify potential strokes, and medical records were obtained in the case of positive responses. Two expert physicians independently reviewed medical records to validate stroke. Stroke verification and etiologic subtyping were based on methods developed by previous stroke studies.[2,13] The end point in this analysis was fatal and nonfatal ischemic stroke through October 31, 2014.

Statistical analysis

Participant characteristics were tabulated. Associations of baseline CRP with stroke risk in the entire population and in blacks and whites were analyzed. With our focus on etiologic relationships between CRP and ischemic stroke, cumulative incidence functions were used to display the time to incident ischemic stroke, accounting for the competing risks of hemorrhagic/unknown type stroke and death.[17] Cause-specific Cox proportional hazard models were used to calculate hazard ratios (HRs) and 95% CIs of ischemic stroke by CRP, accounting for the competing risks above and censoring at hemorrhagic stroke, death, or loss to follow-up.[17,18] Models were adjusted for baseline age, race, and sex and then further adjusted for baseline Framingham stroke risk factors: hypertension status, systolic blood pressure, history of heart disease, diabetes, current smoking, left ventricular hypertrophy, and atrial fibrillation. A third model additionally adjusted for household income and education. Interaction terms for race*CRP as a continuous variable (log-transformed CRP) were evaluated to determine the statistical difference in the association of CRP with stroke by race. Proportional hazard assumptions for the cause-specific Cox models were assessed with formal statistical tests.[19] In addition to standard clinical cut points, the relationship between continuous CRP and ischemic stroke risk was modeled using penalized splines separately by race. Statistical analyses were performed with SAS 9.4 and R 3.5.1.[20,21]

Results

Participant characteristics and stroke incidence

Baseline characteristics by race are shown in Supplemental Table I and by CRP categories stratified by race in Table I. Although blacks had a more unfavorable risk profile than whites, correlations of risk factors with CRP were similar by race. With average follow-up of 6.9 years, 730 (2.8%) participants had an incident ischemic stroke, for an incidence rate of 4.0 per 1,000 person years (95% CI 3.8-4.4). Three participants with cerebral hemorrhage prior to their ischemic stroke were censored and not included as having ischemic stroke. There were 292 ischemic strokes among blacks and 438 in whites, for respective incidence rates of 3.9 per 1,000 person-years (95% CI 3.5-4.3) and 4.2 per 1,000 (95% CI 3.8-4.7). The mean ± SD follow-up was 6.7 ± 2.8 years among blacks and 7.1 ± 2.5 years among whites. Death rates were 19.4 per 1,000 person-years among blacks (95% CI 18.4-20.5) and 16.9 per 1,000 among whites (95% CI 16.1-17.6). The hemorrhagic stroke rate was 0.5 per 1,000 for whites (95% CI 0.4-0.6) and 0.5 per 1,000 for blacks (95% CI 0.4-0.7). Supplemental Table II shows that participants with

Table I. Baseline characteristics by CRP category and race

Characteristic mean or frequency (%)		CRP categories			
		<1 mg/L	1-3 mg/L	3-10 mg/L	≥10 mg/L
Age, y (mean)	Black	64.2 ± 9.8	64.2 ± 9.3	63.5 ± 8.9	63.1 ± 8.8
	White	64.8 ± 9.7	65.6 ± 9.3	65.1 ± 9.3	65.2 ± 9.4
Sex (male)	Black	50	43	31	24
	White	58	51	41	42
Hypertension	Black	61	69	73	78
	White	40	50	56	58
Diabetes	Black	24	27	30	36
	White	12	13	17	23
Current smoker	Black	15	15	19	20
	White	9	11	16	21
Left ventricular hypertrophy	Black	11	14	16	15
	White	5	6	8	7
Atrial fibrillation	Black	6	7	8	9
	White	8	9	10	13
History of cardiovascular disease	Black	12	14	14	18
	White	17	19	19	23
High school graduate education or less	Black	42	45	48	51
	White	25	31	35	41
Income <$20,000	Black	21	23	28	34
	White	8	10	13	18

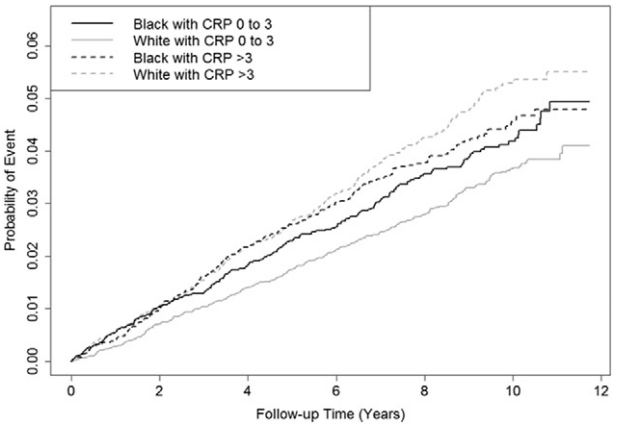
incident ischemic stroke were more likely to be older males with traditional stroke risk factors and were more likely to have CRP ≥3 mg/L.

Figure 1 shows the cumulative ischemic stroke incidence stratified by race and CRP, accounting for the competing risks of hemorrhagic stroke and death. Among whites with elevated CRP, the rate was higher throughout follow-up compared to whites with normal CRP ($P < .0001$). In blacks, the difference in ischemic stroke incidence by CRP was also apparent, but the magnitude of difference was smaller than in whites and was not statistically significant ($P = .39$). There was no evidence to contradict the proportionality assumptions of the models used.

Association of CRP with stroke incidence

Associations of CRP categories with ischemic stroke risk overall and by race are shown in Table II. Compared to CRP <1 mg/L, in all models, the ischemic stroke risk increased monotonically by increasing CRP category among whites. The risk was elevated for CRP 3-10 mg/L and even higher for CRP >10 mg/L (fully adjusted HR 2.07 [95% CI 1.46-2.95]). In contrast, for all models, in blacks, ischemic stroke risk was only increased for CRP >10 mg/L. Although the HRs of stroke by CRP categories in blacks compared to whites were different, the interaction term for lnCRP*race suggested that these differences were not

Figure 1



Cumulative incidence of ischemic stroke stratified by race and CRP.

statistically significant (P race*lnCRP > .10 in all models). In the sequential models in blacks and whites separately, adjustment for stroke risk factors modestly attenuated the association of CRP with ischemic stroke, and there was minimal confounding by socioeconomic factors. Considered as a continuous variable, the risk factor–adjusted HRs per SD higher lnCRP were 1.18 (95% CI 1.09-1.28) overall, 1.14 (95% CI 1.00-1.29) in blacks, and 1.22 (95% CI 1.10-1.35) in whites. In all models, added adjustment for baseline use of statins, regular aspirin, or warfarin did not materially alter the HRs (data not shown).

Results of race-stratified spline regression analysis examining the continuous relation of CRP to ischemic stroke are shown in Figure 2. Interpretation was similar to the analyses above, namely, that the association of CRP with ischemic stroke risk was more apparent among whites than blacks.

The Supplementary Figure shows race-stratified risk factor–adjusted HRs of ischemic stroke by CRP as a binary variable with increasing threshold values. Using the commonly used clinical threshold of CRP ≥3 mg/L, whites were 40% more likely to have an ischemic stroke than whites with lower CRP, whereas blacks had no increased risk at this level. Among blacks, a CRP threshold of ≥9 mg/L would have to be used to show a similar increase in ischemic stroke risk as whites with CRP ≥3 mg/L.

Discussion

In this large contemporary cohort of black and white Americans, elevated CRP was associated with increased risk of fatal or nonfatal ischemic stroke, but the association was weaker in blacks than whites. Although the race difference in associations of CRP with ischemic stroke risk was not statistically significant based on multiplicative interaction terms, CRP ≥3 mg/L was not associated with ischemic stroke risk in blacks (even

Table II. Cause-specific HR of ischemic stroke by CRP categories for races combined and separately

Adjustment variables	Group	HRs of ischemic stroke by CRP Categories				*P* for trend	Interaction *P* values for race*lnCRP/ race*categorical CRP
		<1 mg/L	1-3 mg/L	3-10 mg/L	≥10 mg/L		
		n cases/N noncases (%)					
	All	156/6893 (2.3%)	240/8710 (2.8%)	233/7991 (2.9%)	101/2475 (4.1%)		
	Black	51/2131 (2.4%)	94/3207 (2.9%)	99/3651 (2.7%)	52/1396 (3.7%)		
	White	105/4762 (2.2%)	146/5503 (2.7%)	134/4340 (3.1%)	49/1079 (4.5%)		
Demographic*	All	1.0 (ref)	1.23 (1.01-1.51)	1.44 (1.17-1.78)	2.32 (1.79-3.00)	<.0001	
	Black	1.0	1.23 (0.87-1.74)	1.21 (0.85-1.71)	1.99 (1.34-2.95)	.007	.48/.45
	White	1.0	1.22 (0.95-1.58)	1.61 (1.24-2.08)	2.57 (1.82-3.63)	<.0001	
+ Risk factors†	All	1.0	1.19 (0.96-1.46)	1.26 (1.02-1.57)	1.91 (1.46-2.50)	<.0001	
	Black	1.0	1.25 (0.87-1.79)	1.10 (0.77-1.59)	1.65 (1.08-2.51)	.07	.40/.32
	White	1.0	1.15 (0.88-1.49)	1.38 (1.06-1.79)	2.15 (1. 51-3.06)	<.0001	
+ Socioeconomic status‡	All	1.0	1.16 (0.94-1.43)	1.23 (0.99-1.52)	1.84 (1.40-2.41)	.0001	
	Black	1.0	1.22 (0.85-1.75)	1.08 (0.75-1.56)	1.59 (1.04-2.42)	.09	.48/.39
	White	1.0	1.12 (0.87-1.46)	1.33 (1.02-1.73)	2.07 (1.46-2.95)	.0003	

* Adjusted for age, sex, and race.
† Additionally adjusted for hypertension status, systolic blood pressure, history of heart disease, diabetes, current smoking status, left ventricular hypertrophy, and atrial fibrillation.
‡ Additionally adjusted for income and education.

before adjustment for risk factors), whereas it was associated with a 40% increased risk of ischemic stroke in whites after multivariable adjustment. Consideration of CRP as a continuous variable yielded similar conclusions.

To the best of our knowledge, the association of CRP and ischemic stroke risk has not yet been established in a black population this large. Current CRP threshold values used in clinical practice to predict cardiovascular diseases were derived almost exclusively from white populations.[22] A large meta-analysis by the Emerging Risk Factors Collaboration showed a positive relationship between increasing CRP and ischemic stroke risk[23]; however, race-specific analysis was not presented, and the 15 included studies enrolled mostly white participants such that the findings do not necessarily apply to other race/ethnic groups, who have a different CRP distribution. Given our findings and results of trials of inflammation lowering for vascular risk reduction, it will be important in that work and future work to evaluate effects separately in blacks and whites.[24,25]

We anticipated studying whether CRP mediated the excess ischemic stroke risk in blacks compared to whites in REGARDS, but because the association of CRP differed in blacks versus whites, this analysis was not conducted given the likely violation of traditional mediation method assumptions.[19]

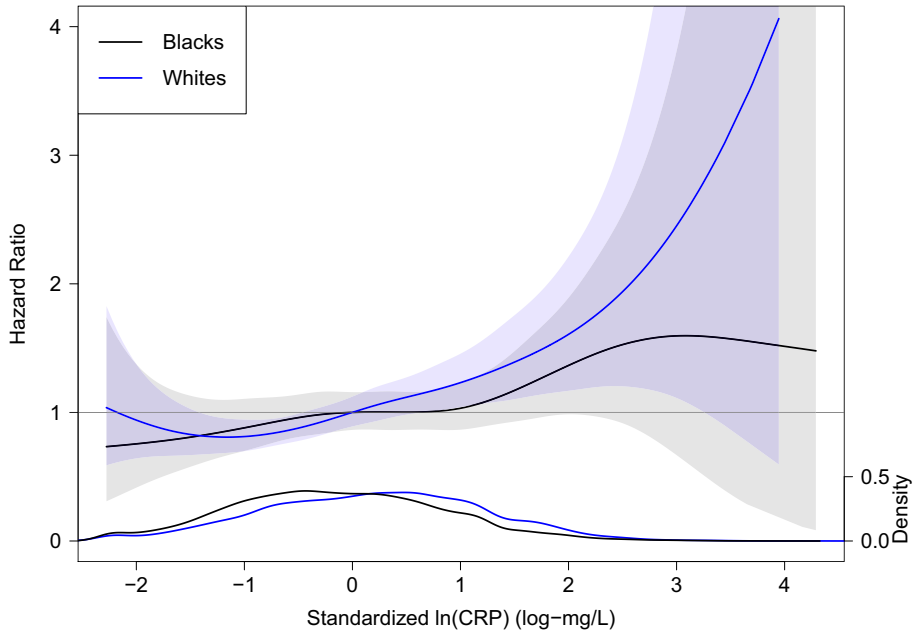
Mechanisms for the differential association of CRP with ischemic stroke risk should be considered. Although we adjusted for socioeconomic status using education and income, early-life adversity is predictive of elevated CRP in blacks.[26] Single-nucleotide polymorphisms associated with CRP may also be responsible for variation in CRP and its different association with ischemic stroke in blacks compared to whites.[27-29]

The current findings have clinical relevance for 2 key reasons. First, findings extend prior research on racial differences in CRP to a clinical context. Blacks with CRP ≥3 mg/L versus <1 mg/L did not have a similarly increased ischemic stroke as whites with these CRP levels. Second, CRP ≥10 mg/L was associated with incident ischemic stroke in blacks and whites; the 6.9-year stroke rate was substantial at 4.1% in those with CRP ≥10 mg/L compared to 2.3% in those with CRP <1. Current guidelines suggest that clinicians should consider causes of overt inflammation or illness when CRP is ≥10 mg/L; however, our findings along with others for coronary heart disease[16,30] suggest that values in this range have important significance and should not be ignored or should trigger other clinical workup. We caution clinicians that our findings are only relevant to ischemic stroke. It is well accepted that statin initiation may be considered to reduce cardiovascular risk in those with CRP >2 mg/L.[31] We advise against using a different cut point of CRP for blacks until further research is available including evaluation of CRP and risk of coronary heart disease in blacks.

Study strengths and limitations

Strengths of this study include the prospective design and large geographically dispersed cohort of blacks and whites

Figure 2



Spline regression analysis illustrating the HR of ischemic stroke based on baseline standardized lnCRP relative to standardized lnCRP 0 mg/L (the mean lnCRP). Shaded area represents the 95% CI. The plot at the bottom of the figure is a density plot of the distribution of standardized lnCRP by race. The black line and shading denote blacks, and the purple line and shading denote whites.

with representation of men and women. Strokes were carefully adjudicated, and cohort retention was high. We studied a uniform phenotype by treating hemorrhagic and unknown type strokes as competing risks.

Study limitations require consideration. Although there were a large number of incident ischemic strokes, interaction testing on the multiplicative scale for race*CRP was underpowered; however, we observed a racial difference that was clear. We assigned race based on participant self-identification and did not address genetic determinants of CRP, genetic admixture, or the full social construct connected to racial identification. Several types of bias could have influenced results. Stroke ascertainment relied on participant contact by phone, and incident cases may have been missed. Misclassification of stroke type as ischemic would have introduced bias, but this is unlikely because cases were carefully adjudicated using well-established methods and expert adjudicators who were not aware of CRP levels. Ascertainment bias could have been present because follow-up time was marginally shorter in blacks; however, this is most likely due to higher occurrence of events or increased withdrawal from the study, factors that would not likely impact the association of CRP with stroke. A single measurement of CRP was used which may have resulted in misclassification and an inability to capture variation that may occur with time. Other inflammation markers were not considered. Lack of inclusion of other racial groups means that our findings are not applicable to these groups. For example, the general population of most Asian races have CRP <1 mg/L[32]; in the Women's Health Study, the average CRP by race/ethnicity in women was 1.1 mg/L in Asians, 2.0 mg/L in whites, 2.1 mg/L in Hispanics, and 3.0 mg/L in blacks.[33] Among Chinese adults, CRP >3 mg/L (HR 1.33) was associated with increased risk of ischemic stroke,[34] supporting this threshold for stroke risk prediction in the Chinese population. Finally, we could not adjust for use of inflammation-lowering medications after baseline because we did not have this information; however, adjustment for baseline aspirin and statin use had no impact on the findings, so this is likely not a drawback.

Conclusions and implications

We present a detailed examination of the association of CRP with ischemic stroke in a large biracial population sample of Americans. Use of a cutoff value of 3.0 mg/L for CRP may not be appropriate for stroke risk prediction in blacks. We are not aware of similar data as presented here for a differential relationship of CRP to coronary heart disease risk in blacks compared to whites. Further research is needed to determine the optimal threshold for CRP and ischemic stroke and cardiovascular risk prediction in blacks and to determine more broadly the

role of inflammation in explaining racial disparities in health. They also point out a need to assess race-specific findings in clinical trials of inflammation lowering to reduce cardiovascular risk.

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Disclosure

The authors declare that there is no conflict of interest. All authors contributed in more than one of study design, analysis, interpretation of the data, and preparation and final approval of the final manuscript.

Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.08.003.

References

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. Circulation 2015;131:e29-322.
2. Howard VJ, Kleindorfer DO, Judd SE, et al. Disparities in stroke incidence contributing to disparities in stroke mortality. Ann Neurol 2011;69:619-27.
3. Vaughan AS, Quick H, Pathak EB, et al. Disparities in temporal and geographic patterns of declining heart disease mortality by race and sex in the United States, 1973-2010. J Am Heart Assoc 2015;4.
4. Howard G, Cushman M, Kissela BM, et al. Traditional risk factors as the underlying cause of racial disparities in stroke: lessons from the half-full (empty?) glass. Stroke 2011;42:3369-75.
5. Arora P, Kalra R, Callas PW. Lp(a) [Lipoprotein(a)] and risk of ischemic stroke in the REGARDS study. Arterioscler Thromb Vasc Biol 2019;39:810-8.
6. Akinkuolie AO, Buring JE, Ridker PM, et al. A novel protein glycan biomarker and future cardiovascular disease events. J Am Heart Assoc 2014;3, e001221.
7. Chauhan G, Debette S. Genetic risk factors for ischemic and hemorrhagic stroke. Current Cardiol Reports 2016;18:124.
8. Cacciapuoti F. Hyper-homocysteinemia: a novel risk factor or a powerful marker for cardiovascular diseases? Pathogenetic and therapeutical uncertainties. J Thromb Thrombolysis 2011;32:82-8.
9. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. Circulation 2019;139, e10-82-1143.
10. Stone NJ, Robinson JG, Lichtenstein AH, et al. ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014 2013;63:2889-934.
11. Cushman M, McClure LA, Howard VJ, et al. Implications of increased C-reactive protein for cardiovascular risk stratification in black and white men and women in the US. Clin Chem 2009;55:1627-36.
12. Khera A, McGuire DK, Murphy SA, et al. Race and gender differences in C-reactive protein levels. J Am Coll Cardiol 2005;46:464-9.
13. Howard VJ, Cushman M, Pulley L, et al. The REasons for Geographic And Racial Differences in Stroke Study: objectives and design. Neuroepidemiology 2005;25:135-43.
14. Gillett SR, Boyle RH, Zakai NA, et al. Validating laboratory results in a national observational cohort study without field centers: the Reasons for Geographic and Racial Differences in Stroke cohort. Clin Biochem 2014;47:243-6.
15. Ridker PM, Buring JE, Cook NR, et al. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. Circulation 2003;107:391-7.
16. Vanderschueren S, Deeren D, Knockaert DC, et al. Extremely elevated C-reactive protein. Eur J Intern Med 2006;17:430-3.
17. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. Circulation 2016;133:601-9.
18. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. Stat Med 2017;36:4391-400.
19. Lin DY, Wei L, Ying Z. Model checking techniques based on cumulative residuals. Biometrics 2002;58:1-12.
20. Therneau T. *A package for survival analysis in S., version 2.38*. 2015.
21. Therneau. *Modeling Survivial Data: Extending the Cox Model.* New York: Springfield. 2000.
22. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107:499-511.
23. Kaptoge S, Di Angelantonio E, Lowe G, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 2010;375:132-40.
24. Ridker PM, Libby P, MacFadyen JG, et al. Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the

Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS). Eur Heart J 2018;39:3499-507.
25. Ridker PM, Everett BM, Pradhan A, et al. Low-dose methotrexate for the prevention of atherosclerotic events. New Engl J Med 2019;380:752-62.
26. Slopen N, Lewis TT, Gruenewald TL, et al. Early life adversity and inflammation in African Americans and whites in the midlife in the United States survey. Psychosomatic Med 2010;72:694-701.
27. Kocarnik JM, Pendergrass SA, Carty CL, et al. Multiancestral analysis of inflammation-related genetic variants and C-reactive protein in the population architecture using genomics and epidemiology study. Circulation Cardiovasc Genet 2014;7:178-88.
28. Li HY, Wang J, Meng F, et al. An intrinsically disordered motif mediates diverse actions of monomeric C-reactive protein. J Biol Chem 2016;291:8795-804.
29. Reiner AP, Beleza S, Franceschini N, et al. Genome-wide association and population genetic analysis of C-reactive protein in African American and Hispanic American women. Am J Human Genet 2012;91:502-12.
30. Cushman M, Arnold AM, Psaty BM, et al. C-reactive protein and the 10-year incidence of coronary heart disease in older men and women: the Cardiovascular Health Study. Circulation 2005;112:25-31.
31. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. New Engl J Med 2008;359:2195-207.
32. Saito I, Maruyama K, Eguchi E. C-reactive protein and cardiovascular disease in East asians: a systematic review. Clin Med Insights Cardiol 2014;8:35-42.
33. Albert MA, Glynn RJ, Buring J, et al. C-reactive protein levels among women of various ethnic groups living in the United States (from the Women's Health Study). Am J Cardiol 2004;93:1238-42.
34. Liu Y, Wang J, Zhang L, et al. Relationship between C-reactive protein and stroke: a large prospective community based study. PloS one 2014;9, e107017.