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Common variants in the CRP gene in relation to longevity and cause-specific mortality in older adults: the Cardiovascular Health Study

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Abstract

Common polymorphisms in the CRP gene are associated with plasma CRP levels in population-based studies, but associations with age-related events are uncertain. A previous study of CRP haplotypes in older adults was broadened to include longevity and cause-specific mortality (all-cause, non-cardiovascular (nonCV), and cardiovascular (CV)). Common haplotypes were inferred from four tagSNPs in 4512 whites and five tagSNPs in 812 blacks from the Cardiovascular Health Study, a longitudinal cohort of adults over age 65. Exploratory analyses addressed early versus late mortality.

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CRP haplotypes were not associated with all-cause mortality or longevity overall in either population, but associations with all-cause mortality differed during early and late periods. In blacks, the haplotype tagged by 3872A (rs1205) was associated with increased risk of nonCV mortality, relative to other haplotypes (adjusted hazard ratio for each additional copy: 1.42, 95% CI: 1.07, 1.87). Relative to other haplotypes, this haplotype was associated with decreased risk of early but not decreased risk of late CV mortality in blacks; among whites, a haplotype tagged by 2667C (rs1800947) gave similar but nonsignificant findings. If confirmed, CRP genetic variants may be weakly associated with CV and nonCV mortality in older adults, particularly in self-identified blacks.

Human longevity has in part a genetic basis, and inflammation genes are possible candidates¹ Circulating plasma levels of C-reactive protein, an acute phase reactant, are associated with diseases occurring in older age, both cardiovascular and noncardiovascular in origin². That persons with higher plasma CRP levels are at greater risk of cardiovascular as well as noncardiovascular mortality^{3, 4} suggests that CRP may be a candidate gene associated with human longevity.

Circulating plasma CRP is partially regulated at the genetic level. Twin and family studies observe substantial heritability (20–40 percent) for CRP levels^{5, 6}. Common and functional polymorphisms in the CRP gene have consistently been associated with inter-individual differences in plasma CRP levels^{7, 8}. Recently, Lange, et al. reported that, among persons at risk for a first MI or stroke, several common variants in the CRP gene were associated with increased relative risk of cardiovascular events in the Cardiovascular Health Study (CHS), a longitudinal cohort study of adults over the age of 65⁹. These associations were stronger for fatal than non-fatal coronary events. Whether these same CRP genetic variants are related more generally to other aging-related outcomes in older adults remains unknown.

The primary aim of this study was to assess whether CRP genotype is associated with number of years lived, number of healthy years lived, and all-cause (including both cardiovascular and non-cardiovascular) mortality during follow-up in the entire CHS cohort of older adults. The relationship between CRP levels and mortality in CHS has recently been clarified as more strongly predictive of early (within the first three years of baseline) rather than late (> 3 years) death¹⁰. Therefore, a secondary exploratory analysis investigated whether associations between CRP variants and mortality differed according to early or late time of death.

Methods

Study population

CHS study design and participant recruitment are described in detail elsewhere¹¹. Briefly, 5201 individuals from random samples of Medicare eligibility lists in four U.S. communities were recruited in 1989–1990. In 1992–1993, a supplemental cohort of 687 self-identified African-Americans was recruited. The institutional review committees of all participating institutions approved this study and subjects gave informed consent. Since the current analysis focuses on all-cause mortality, we included all CHS participants without regard to a history of prior cardiovascular disease (MI and stroke).

Follow-up and baseline data collection

At the baseline exam, extensive demographic, physical and laboratory measurements were collected¹¹. Race was defined as the category chosen by a participant that best described his/her race: white, black, American Indian/Alaskan native, Asian/Pacific Islander, or other. Medication¹² and self-reported hypertension data were collected at each clinic visit. CRP levels were measured on baseline EDTA-stored blood samples using a high-sensitivity assay (coefficient of variation = 8.9 percent)¹³.

The cohort was followed with semi-annual contacts, alternating between telephone calls and clinic examinations. Data on fatal events were obtained from next-of-kin interviews, physician questionnaires, medical records, death certificates, Medicare utilization data, and the National Death Index. Cause of death for all fatal events was adjudicated by committee using previously published definitions¹⁴. Mortality was classified into cardiovascular causes (deaths attributed to atherosclerotic, cerebrovascular, or other cardiovascular causes), and noncardiovascular causes (all other deaths). Mortality follow-up was complete through June, 2002 (median follow-up time for original cohort, 12.2 years; for second cohort, 9.1 years). Classification of noncardiovascular causes of death into five subcategories (dementia, cancer, respiratory, infection, and other) was available for deaths occurring through June, 2001¹⁵.

Longevity measures were derived from information on mortality and self-reported health status (excellent/very good/good/fair/poor) collected at each follow-up visit; missing data were imputed by linear interpolation¹⁶. Years of life at year 10 (YOL10) refers to the number of years an individual was alive (out of 10 years of follow-up). Years of healthy life (YHL10) refers to the number of years an individual self-reported good or better health at his/her annual visit. Fair or poor health and death were counted as zero.

SNP selection and genotyping

TagSNPs, a set of maximally informative common SNPs, were chosen based on a previous analysis of CRP haplotypes and CRP levels⁷. The tagSNPs are referenced in dbSNP with the following accession numbers: 790 (rs3093058), 1919 (rs1417938), 2667 (rs1800947), 3872 (rs1205), and 5237 (rs2808630). A previous study observed that the 790 minor allele was prevalent primarily in blacks⁷, so SNP 790 was genotyped only in self-identified blacks. TagSNPs were genotyped as previously described⁹. Genotype data were missing for an average of 0.05 percent of participants (per-SNP range, 0 – 0.11 percent).

For self-identified blacks, percentage of African ancestry was estimated by genotyping 24 biallelic ancestry-informative markers (AIMs)¹⁷. Additional adjustment for a genetic similarity variable, also derived from these AIMs, did not materially alter the results and are not shown.

Statistical analysis

For the present study, participants were excluded if they did not self-identify as black or white (n = 39), did not consent to use of their genetic information for the study of cardiovascular or noncardiovascular disease (n = 285), or did not have available CRP levels or DNA (n = 240). Following exclusions, information on 5324 participants (4512 whites and 812 blacks) was available for analysis.

Statistical analysis was conducted using Stata (Intercooled STATA, Stata Corporation). Missing data on covariates were present for fewer than 2 percent of individuals (with the exception of income, 6 percent) and were imputed using multivariate imputation sampling¹⁸. A participant was classified as diabetic according to American Diabetes Association (ADA) criteria¹⁹. Self-reported annual income levels were categorized into three groups: <\$8000, \$8000–35,000 and >\$35,000. Education was classified as none to grade 9; high school or general equivalency diploma; or college, vocational, graduate, or professional training. Categorical variables for three levels of occupation were created from a participant's response to a card that indicated lifetime occupation: 1) professional / technical / managerial / administrative / sales / clerical; 2) craftsman / machine operator / laborer and farming / forestry work; and 3) housewife / other / or refusal to answer.

Probability weights for haplotypes were inferred from unphased genotype data using PHASE 2.0²⁰. The haplotype associated with the lowest CRP levels in each population⁹ was arbitrarily chosen as the reference. Effective sample sizes for each haplotype were calculated by summing the individual haplotype probabilities, and rounding to the nearest whole number. Very little uncertainty in haplotype inference was observed. Among the 5324 participants, the most probable haplotype was inferred with greater than 90 percent probability for 5312 (99.8 percent) individuals.

Average difference in YHL10 or YOL10 per additional copy of each common haplotype (≥ 5 percent frequency) was estimated by weighted linear regression, and hazard ratios (HR) for common haplotypes in relation to mortality were similarly estimated by weighted Cox regression, assuming a log-additive model for additional haplotype copies. Robust standard errors accounted for haplotype uncertainty. Two-sided p-values ≤ 0.05 were declared statistically significant. Global tests of all of the haplotype coefficients in the model were assessed with Wald tests. For cardiovascular mortality analyses, participants with non-cardiovascular-related death were censored at time of death, and vice versa. Two extended Cox models were used to assess interactions of haplotype effects with early or late time period in the study (<3 versus ≥ 3 years) and with median age at baseline (≤ 72 versus >72 years old). Events occurring within 3 years of baseline were defined as early based on year-by-year analyses of CRP levels and mortality, which showed a clear cutpoint at 3 years (N. Jenny, unpublished results).

Analyses were initially stratified by gender and race. Risk estimates did not differ significantly by gender, so both groups were combined and subsequent models adjusted for gender. All risk estimates for longevity and mortality are adjusted for age, recruitment community, diabetes, cancer, CHD, treated hypertension (self-reported hypertension in addition to use of an antihypertensive medication), current smoking, income, education, occupation and, in blacks, percent African ancestry. Additional adjustment for log(plasma CRP), history of MI or stroke, or APOE genotype did not materially alter the results.

Results

Participant characteristics

Participant characteristics at the time of study enrollment are described for 4512 whites and 812 blacks in Table 1. Blacks and whites differed according to presence of several traditional cardiovascular risk factors, annual income, education, plasma CRP levels, and YHL10. Frequencies of the five CRP tagSNPs, the haplotypes tagged by these SNPs, and their associations with plasma CRP level are similar to those previously published in this⁹ and younger⁷ populations (data not shown). All SNPs were in Hardy-Weinberg equilibrium. Minor allele frequencies differed significantly in whites compared to blacks ($p < 0.0005$ for all SNPs). The SNPs resolved five unique haplotypes in whites and blacks (Table 2).

CRP haplotypes in relation to longevity

Quartiles of plasma CRP were significantly associated with differences in YOL10 and YHL10 in whites (global p-values < 0.0001 ; Supplemental Table 1). Relative to the first quartile, the third and fourth quartiles were associated with significantly fewer years of life and healthy life. Results in blacks were attenuated but followed a similar trend. In general, CRP haplotypes were not globally associated with YOL10 or YHL10 in either whites or blacks (Table 2; YOL10: global p-value = 0.42, whites; global p = 0.48, blacks; YHL10: global p = 0.20, whites; global p = 0.31, blacks). The average difference for either measure did not exceed 0.5 years for any haplotype, and all confidence intervals overlapped one, except for HapC in blacks (average difference in YHL10 for each additional copy, relative to HapB: 0.48, 95 percent CI

0.02, 0.94). The proportion of YHL10 or YOL10 explained by CRP haplotypes was very small (<1 percent for all models).

CRP haplotypes in relation to mortality

Consistent with the longevity results, CRP haplotypes were not globally associated with all-cause mortality in either whites or blacks (Table 3; global $p = 0.57$ and 0.21 , respectively). Relative to the reference haplotype, each additional copy of HapD was associated with a decreased relative risk of all-cause mortality in blacks (HR: 0.76, 95 percent CI 0.58, 0.99).

Several subgroup analyses were conducted. For noncardiovascular causes, the overall association between CRP haplotypes and mortality was not statistically significant in whites (Table 3; global $p = 0.92$). In blacks, an overall association between CRP haplotypes and noncardiovascular mortality was observed (Table 3; global $p = 0.02$). When HapB was modeled individually compared to all other haplotypes combined, each additional copy of HapB was associated with a 1.4-fold increased risk of noncardiovascular mortality in blacks (HR: 1.42, 95 percent CI: 1.07, 1.87). For cardiovascular mortality, there was an overall absence of association with CRP haplotypes (global $p = 0.21$ in whites, global $p = 0.80$ in blacks; please see Supplemental Table II).

Time scale of mortality

In both whites and blacks, CRP haplotypes were associated with differences in early versus late all-cause mortality (Table 4; p -value for time interaction = 0.031 in whites, $p = 0.011$ in blacks). For each race group, the baseline haplotype tended to be associated with a reduced risk of early all-cause deaths, relative to all other haplotypes. In whites, each additional copy of HapA was associated with an early HR of 0.62 (0.40, 0.97) and a late HR of 1.06 (0.92, 1.21). In blacks, each additional copy of HapB was associated with an early HR of 0.71 (0.44, 1.14) and late HR of 1.37 (1.08, 1.74).

There was little evidence that the overall association of CRP haplotypes with cardiovascular mortality in whites differed according to whether cardiovascular deaths occurred early or late (global p -value for interaction = 0.31; also see Supplemental Table III). Relative to all other haplotypes combined, each additional copy of HapA was associated with a tendency toward reduced risk of early cardiovascular mortality (early HR: 0.56, 95 percent CI 0.29, 1.08; late HR: 1.00, 95 percent CI 0.81, 1.25). In blacks, all CRP haplotypes were associated with more than a 2-fold greater risk of early cardiovascular mortality relative to HapB, and the association of the CRP haplotypes with early cardiovascular mortality differed significantly according to timing of the cardiovascular death (global p -value for interaction = 0.0013). When compared to all other haplotypes combined, each additional copy of HapB was associated with a lower relative risk of early cardiovascular mortality (HR: 0.29, 95 percent CI: 0.11, 0.78) but not a decreased risk of late cardiovascular mortality (HR: 1.29, 95 percent CI: 0.88, 1.87; interaction p -value = 0.0056). The overall association between CRP haplotypes and noncardiovascular mortality did not differ according to timing of noncardiovascular mortality in whites or blacks (global p -values for interaction = 0.08 and 0.83, respectively; see Supplemental Table IV).

We further analyzed the interaction of CRP haplotypes with time on cardiovascular mortality by stratifying on additional factors. Hazard ratios less than one for HapB and early cardiovascular mortality were present in both black men and women, though confidence intervals were wider (black men: 0.50, 95 percent CI 0.12, 2.17; black women: 0.22, 95 percent CI 0.05, 0.89). Associations of HapA with early cardiovascular mortality were similar in both white men and women (white men: 0.54, 95 percent CI 0.22, 1.32; white women 0.56, 95 percent CI 0.21, 1.52).

Since the differences in the association between CRP haplotypes and cardiovascular mortality by timing of death in blacks might reflect the effect of age, we additionally stratified on age. The associations between CRP haplotypes and cardiovascular mortality, on the whole, did not differ according to median age at baseline ($p = 0.18$ for global test of interaction). Additionally, results were similar when individuals with the highest 1% of CRP values were excluded, though the interaction with time on all-cause mortality did not reach statistical significance in whites.

Causes of noncardiovascular mortality in blacks

Based on the observed association between CRP haplotypes and noncardiovascular mortality in blacks, an exploratory analysis of specific causes of noncardiovascular mortality was conducted. Because power was limited by small numbers of specific causes of noncardiovascular death, haplotype associations were assessed for HapB compared to all other haplotypes combined. Each additional copy of HapB was associated with a significantly increased risk of total cancer death, relative to one fewer copy (Table 5; HR: 1.68, 95 percent CI: 1.18, 2.39). Similar results were observed for the two most common cancers (lung cancer and prostate cancer), though results were not statistically significant.

Discussion

In this longitudinal study of 5324 older adults in the Cardiovascular Health Study, common CRP polymorphisms previously shown to be associated with CRP levels were not associated with overall all-cause mortality or number of years or healthy years lived in either whites or blacks. Our results suggest that common genetic variation within the CRP gene does not influence overall longevity or mortality risk in older adults. However, the association between CRP haplotypes and all-cause mortality differed according to time scale, with a tendency toward decreased relative risks of early total death associated with the baseline haplotype. Additionally, there was some evidence of race-specific associations between CRP haplotypes and cause-specific mortality. In blacks, HapB, bearing the 3872A allele (rs1205) associated with decreased CRP levels, was associated with an increased risk of noncardiovascular mortality (HR for each additional copy, relative to all other haplotypes combined: 1.42, 95 percent CI: 1.07, 1.87), particularly cancer deaths. Finally, the association between CRP haplotypes and cardiovascular mortality in blacks differed by time scale, suggesting that hazard ratios stratified on early versus late follow-up were more appropriate than an overall hazard ratio. Relative to all other haplotypes combined, HapB was associated with a decreased risk of early deaths from cardiovascular disease in blacks (HR for each additional copy: 0.29, 95 percent CI: 0.11, 0.78), but was not associated with decreased risk of late cardiovascular deaths (HR: 1.29, 95 percent CI: 0.88, 1.87). Results were similar but nonsignificant in whites for HapA, bearing the 2667C (rs1800947) allele.

In a previous analysis of incident MI and stroke, Lange, et al.⁹ reported that each additional copy of HapE, bearing the 1919T allele (rs1417938) associated with higher CRP levels, was associated with the largest relative risk of stroke and fatal CVD events in whites. Here, we assessed the association between CRP genotypes and mortality more broadly than Lange, et al., by including all participants regardless of a previous MI or stroke, and by broadening the definition of cardiovascular mortality to include all cardiovascular-related deaths, rather than just coronary heart disease and cerebrovascular deaths. As a result, the global association between CRP haplotypes and cardiovascular mortality was not statistically significant in whites, and individual HR's were attenuated. Our preliminary findings of an increased association of HapB with cancer deaths in blacks are consistent with a recent report in adults over the age of 55²¹. Overall, these results suggest that polymorphisms within the CRP gene may influence both cardiovascular and non-cardiovascular outcomes related to aging and

mortality in specific ways, rather than having a more generalized influence on the process of aging or healthy aging in older adults.

The observation that CRP haplotypes associated with higher CRP levels were associated with an increased relative risk of early rather than late total deaths in both races and cardiovascular death in blacks was consistent with the direction of the relationship between plasma CRP level and mortality reported by Jenny, et al.¹⁰. That short-term and not longer-term cardiovascular deaths were associated with CRP haplotypes may reflect the involvement of plasma CRP levels in more severe pathological events occurring proximate to mortality²². Previous studies suggest that older adults accumulate vascular burden over the lifespan²³, and CRP is known to exacerbate inflammation, leading to further atherothrombotic disease²⁴. Alternately, plasma CRP may simply be a marker of advanced vascular burden. This study was unable to distinguish between the role of plasma CRP as a cause or a consequence of complex atherothrombotic or other forms of disease, but both possibilities may be true to some extent²⁴. A related limitation is that the interaction between study time and CRP haplotypes on cardiovascular mortality in blacks was independent of age. We did not observe an interaction between CRP haplotypes and age, though age strongly predicts both atherosclerotic and inflammatory burden^{23, 24}.

The current study performed in a large, population-based, longitudinal cohort of white and black older adults has several strengths. The CRP gene was interrogated in a comprehensive manner by assessing haplotypes comprised of known common variants in whites and blacks. Previously, data on the genetics of human longevity in populations of African descent have been limited. In addition, most genetic association studies of human longevity have been performed in cross-sectional samples comparing individuals of different ages (for example centenarians vs. younger adults). Such cross-sectional studies may suffer from the lack of an appropriate control group, and also do not allow analyses of specific causes of death²⁵. Longitudinal cohort studies may allow more accurate analysis of genetic influences on longevity, including assessment of both overall and cause-specific mortality. As suggested by the upper and lower 95% confidence limits, this study suggested that differences in longevity associated with CRP genotype were no larger than about 0.2 years in whites and 0.5 years in blacks. Similarly, differences in relative risk of cause-specific mortality associated with CRP genotype were likely to be no larger than about 20% in whites and 30–50% in blacks.

Several additional limitations of this study should be noted. First, the role of chance in explaining our results cannot be excluded, particularly in the context of multiple testing, multiple subgroup analyses, and the relatively smaller size of the self-identified black sample. We did not formally adjust for multiple comparisons among the correlated SNPs or outcomes, which places this study in a hypothesis-generating rather than hypothesis-confirming role. Next, if CRP haplotypes were associated with cardiovascular mortality by influencing plasma CRP, adjustment for CRP levels might be expected to attenuate the observed hazard ratios. Adjustment did not materially alter our results. Potential explanations include measurement error in a single baseline measure of CRP or alternate mechanisms. The proportion of variance in CRP levels explained by the polymorphisms genotyped here was modest (2.4 percent in whites, 5.6 percent in blacks). Other polymorphisms within the CRP gene not genotyped directly or indirectly in this study may also be associated with CRP levels and mortality. Third, we observed that HapB, relative to all other haplotypes, was associated with a decreased risk of early cardiovascular mortality and an increased risk of noncardiovascular mortality in blacks. High mortality rates among older adults may limit the ability to assess cause-specific mortality due to the presence of competing risks.

Finally, another limitation was the simplistic categorizations of self-identified race. Data on proportion of individual African ancestry were available for self-identified blacks¹⁷, but additionally adjusting for these estimates did not materially alter the results. Also, given the

very low prevalence of the 790T allele in a younger white population⁷, the 790 SNP was genotyped only in blacks, which limited our ability to combine the two groups for analysis. Given recent concerns that the relationship between genetics and race may be interpreted as deterministic²⁶, we emphasize that the differences in results according to race are not intuitive and may reflect chance findings, differences in SNPs genotyped, proportion of variance explained by these SNPs or underlying pathology of cardiovascular mortality²⁷ rather than race itself.

Our study suggests that CRP genetic variants may be associated with both cardiovascular and noncardiovascular causes of death, and that the strength of these findings differs by race and timing of death. These results should be regarded as hypothesis-generating and should be interpreted cautiously, particularly with regard to the smaller numbers of deaths in blacks. That genetic polymorphisms do not vary over time within an individual, but the associations might, suggests a need for similar studies across a broad age spectrum. Replication of these findings and additional studies clarifying the degree to which CRP genotype is causally related to the specific causes of death will be key in explaining the race- and time-specific results.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of study participants, by self-identified race.

	Overall (n = 5324)	Whites (n = 4512)	Blacks (n = 812)
Age, mean (SD)	72.8 (5.6)	72.8 (5.6)	72.8 (5.6)
Male, %	42.4	43.2	37.8*
BMI, kg/m ² , mean (SD)	26.7 (4.7)	26.4 (4.5)	28.5 (5.5)
Diabetes, %	16.1	14.5	24.8*
Hypertension, %	47.7	44.2	67.1*
Treated hypertension, %	38.1	34.8	55.9*
Lipid-lowering medication, %	5.6	5.4	6.5
Current smoking, %	11.7	11.0	15.8*
Ever diagnosed with cancer, %	14.1	15.1	8.6*
History of CHD, %	19.6	19.6	19.2
Occupation, %			
Managerial/professional/admin.	50.0	52.2	37.5*
Farmer/laborer	18.4	16.6	28.7
Housewife/other	31.6	31.3	33.8
Annual income, %			
<\$8000	14.3	10.2	37.3*
\$8000–34,999	62.5	64.2	53.0
>\$35,000	23.2	25.7	9.8
Education, %			
Up to grade 9	18.9	17.0	29.5*
High school/GED	37.7	37.9	36.4
Vocational/technical/graduate	43.4	45.1	34.1
Years of life at 10-year follow-up visit (YOL10), mean (SD)	8.5 (2.5)	8.6 (2.5)	8.3 (2.8)*
Years of healthy life at 10-year follow-up visit (YHL10), mean (SD)	6.4 (3.4)	6.6 (3.3)	5.2 (3.5)*
CRP level, median, mg/L (interquartile range)	2.5 (3.2)	2.4 (3.0)	3.4 (5.8)*

Unless otherwise indicated, characteristics were ascertained at baseline.

* p < 0.05 for blacks compared to whites. For occupation, income and education, p < 0.05 for the comparison of all categories of the variable between races.

Table 2

Association of CRP haplotypes with longevity.

Whites		1919	2667	3872	5237	Frequency, %	Average difference in YOL10	95% CI	Average difference in YHL10	95% CI
Haplotype										
HapA	A	C	A	A	A	6.8	0	Ref.	0	Ref.
HapB	A	G	A	A	A	27.2	-0.03	(-0.22, 0.17)	0.18	(-0.09, 0.45)
HapC	A	G	G	A	A	8.1	0.09	(-0.14, 0.32)	0.25	(-0.08, 0.57)
HapD	A	G	G	G	G	27.6	-0.02	(-0.21, 0.17)	0.29	(-0.02, 0.55)
HapE	T	G	G	A	A	30.2	-0.08	(-0.27, 0.11)	0.14	(-0.12, 0.41)
global test							p = 0.42		p = 0.20	
Blacks										
Haplotype		790	2667	3872	5237	Frequency, %	Average difference in YOL10	95% CI	Average difference in YHL10	95% CI
HapB	A	A	G	A	A	18.0	0	Ref.	0	Ref.
HapC	A	A	G	G	A	31.1	0.05	(-0.34, 0.44)	0.48	(0.02, 0.94)
HapD	A	A	G	G	G	18.9	0.25	(-0.15, 0.65)	0.10	(-0.37, 0.58)
HapE	A	T	G	G	A	13.9	0.29	(-0.13, 0.70)	0.22	(-0.30, 0.73)
HapF	T	A	G	G	A	16.6	-0.03	(-0.47, 0.42)	0.23	(-0.28, 0.73)
global test							p = 0.48		p = 0.31	

Minor alleles are shaded. Estimates are for each additional copy of the haplotype, relative to the reference haplotype, and are adjusted for age, recruitment community, diabetes, cancer, CHD, treated hypertension, current smoking, income, education, occupation and, in blacks, % African ancestry.

Table 3

CRP haplotypes and cause-specific mortality.

Whites		All-cause		HR (95% CI)		NonCV		HR (95% CI)	
Hap	n	n events, 0/1/2 copies	n events, 0/1/2 copies	n events, 0/1/2 copies	n events, 0/1/2 copies	n events, 0/1/2 copies	n events, 0/1/2 copies	n events, 0/1/2 copies	n events, 0/1/2 copies
HapA	1919	2667	3872	5237	1798 / 253 / 12	A	A	1037 / 160 / 5	I
HapB	A	C	A	A	1108 / 815 / 140	A	A	637 / 470 / 94	0.97 (0.81, 1.15)
HapC	A	G	A	A	1743 / 301 / 19	G	A	1016 / 175 / 11	0.94 (0.77, 1.16)
HapD	A	G	G	G	1081 / 844 / 138	G	G	633 / 492 / 76	0.93 (0.79, 1.11)
HapE	T	G	G	A	973 / 891 / 199	G	A	580 / 513 / 108	0.97 (0.82, 1.15)
global test									p = 0.57
Blacks		All-cause		HR (95% CI)		NonCV		HR (95% CI)	
Hap	790	1919	3872	5237	208 / 93 / 12	A	A	111 / 60 / 8	I
HapB	A	A	A	A	147 / 135 / 31	G	A	84 / 72 / 22	0.80 (0.57, 1.12)
HapC	A	A	G	G	209 / 94 / 10	G	G	124 / 53 / 2	0.58 (0.41, 0.82)
HapD	A	A	G	G	239 / 67 / 6	G	A	138 / 38 / 2	0.66 (0.45, 0.96)
HapE	A	T	G	A	214 / 88 / 11	G	A	124 / 49 / 6	0.79 (0.54, 1.14)
HapF	T	A	G	A					p = 0.02
global test									p = 0.21

HR's and 95% CI's are for each additional copy of the haplotype, relative to the reference haplotype, and are adjusted for age, recruitment community, diabetes, cancer, CHD, treated hypertension, current smoking, income, education, occupation and, in blacks, % African ancestry.

Table 4

CRP haplotypes and all-cause mortality, by timing of death.

Whites		1919	2667	3872	5237	< 3 years n events, 0/1/2 copies	HR	95% CI	> 3 years n events, 0/1/2 copies	HR	95% CI
Hap							1	Ref.		1	Ref.
HapA	A	A	C	A	A	235 / 20 / 1	1.76	1.09, 2.84	1563 / 233 / 11	0.91	0.79, 1.05
HapB	A	A	G	A	A	126 / 109 / 21	1.27	0.74, 2.17	982 / 706 / 119	0.94	0.79, 1.12
HapC	A	A	G	G	A	224 / 29 / 3	1.69	1.06, 2.68	1519 / 272 / 16	0.93	0.80, 1.07
HapD	A	A	G	G	G	124 / 112 / 20	1.49	0.94, 2.36	957 / 732 / 118	1.00	0.87, 1.15
HapE	T	T	G	G	A	124 / 113 / 19		0.10	849 / 778 / 180		
global test for interaction						0.031					0.21
Blacks											
Hap							1	Ref.		1	Ref.
HapB	A	A	G	A	A	53 / 17 / 0	1.32	0.77, 2.29	155 / 76 / 12	0.78	0.59, 1.04
HapC	A	A	G	G	A	31 / 31 / 7	1.33	0.76, 2.34	115 / 104 / 24	0.66	0.48, 0.90
HapD	A	A	G	G	G	43 / 26 / 1	0.89	0.44, 1.83	166 / 68 / 9	0.74	0.53, 1.04
HapE	A	T	G	G	A	58 / 11 / 1	2.10	1.20, 3.69	181 / 56 / 6	0.73	0.53, 1.00
HapF	T	A	G	G	A	39 / 26 / 5		0.028	175 / 62 / 6		0.093
global test for interaction						0.011					

HR's and 95% CI's are for each additional copy of the haplotype, relative to the reference haplotype, and are adjusted for age, recruitment community, diabetes, cancer, CHD, treated hypertension, current smoking, income, education, occupation and, in blacks, % African ancestry.

Table 5

CRP haplotypes and causes of noncardiovascular deaths in blacks.

Cause of death	N, cause-specific deaths, 0/1/2 copies of HapB	N, persons without cause-specific death, 0/1/2 copies of HapB	HR (95% CI)
Cancer, total	41 / 29 / 5	507 / 207 / 23	1.68 (1.18, 2.39)
Lung cancer	13 / 11 / 1	535 / 225 / 27	1.60 (0.89, 2.87)
Prostate cancer	5 / 5 / 0	543 / 231 / 28	1.95 (0.82, 4.68)
Other cancers	23 / 13 / 4	525 / 223 / 24	1.73 (1.04, 2.90)
Dementia	13 / 4 / 0	535 / 232 / 28	0.75 (0.27, 2.09)
Respiratory	8 / 6 / 0	540 / 230 / 28	1.41 (0.67, 2.98)
Infectious	15 / 4 / 1	533 / 232 / 27	0.93 (0.35, 2.46)
Renal failure	8 / 2 / 0	540 / 234 / 28	0.52 (0.13, 2.02)

HR's are for each additional copy of HapB, relative to one fewer copy and are adjusted for age and gender.