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Ancestry as a Determinant of Mean Population C-Reactive Protein Values

Implications for Cardiovascular Risk Prediction

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Background—Eligibility for rosuvastatin treatment for cardiovascular disease prevention includes a C-reactive protein (CRP) concentration >2 mg/L. Most observational studies of CRP and cardiovascular disease have been in Europeans. We evaluated the influence of ancestry on population CRP concentration to assess the implications for statin targeting in non-Europeans.

Methods and Results—In a systematic review and meta-analysis among 221 287 people from 89 studies, geometric mean CRP was 2.6 mg/L (95% credible interval, 2.27 to 2.96) in blacks resident in the United States ($n=18\ 585$); 2.51 mg/L (95% CI, 1.18 to 2.86) in Hispanics ($n=5049$); 2.34 mg/L (95% CI, 1.99 to 2.8) in South Asians ($n=1053$); 2.03 mg/L (95% CI, 1.77 to 2.3) in whites ($n=104\ 949$); and 1.01 mg/L (95% CI, 0.88 to 1.18) in East Asians ($n=39\ 521$). Differences were not explained by study design or CRP assay and were preserved after adjustment for age and body mass index. At age 60 years, fewer than half of East Asians but more than two thirds of Hispanics were estimated to have CRP values exceeding 2 mg/L. HapMap frequencies of CRP polymorphisms known to associate with CRP concentration but not coronary heart disease events differed by ancestry. In participant data from the Wandsworth Heart and Stroke Study including European, South Asian and African, and Caribbean-descent subjects, body mass index, systolic blood pressure, and smoking contributed to between-group differences in CRP, but the majority of the difference in CRP was unexplained.

Conclusions—Differences in CRP concentration in populations of diverse ancestry are sufficiently large to affect statin eligibility, based on a single CRP threshold of 2 mg/L, and only partially influenced by differences in variables related to cardiovascular risk. A single threshold value of CRP for cardiovascular risk prediction could lead to inequalities in statin eligibility that may not accurately reflect underlying levels of cardiovascular risk. (*Circ Cardiovasc Genet.* 2010;3:436-444.)

Key Words: C-reactive protein ■ risk factor ■ cardiovascular risk prediction ■ statins

Primary prevention of cardiovascular events currently involves targeting interventions to people at high absolute risk, identified using risk-prediction instruments such as the Framingham equation, that integrate information on established risk factors.¹ However, a large proportion of events occur among individuals with near-average levels of continuous risk factors² or at intermediate Framingham risk. With emerging evidence on the role of inflammation in atherosclerosis, there is interest in the potential predictive

utility of C-reactive protein (CRP), a sensitive circulating biomarker of inflammation.^{3,4}

Clinical Perspective on p 444

Nearly 40 reports from prospective cohort studies and 3 meta-analyses in European individuals⁵⁻⁷ indicate a highly consistent, moderate association of CRP with later coronary heart disease (CHD) events among clinically healthy subjects. However, when evaluated using appropriate metrics for

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assessing predictive utility,^{8,9} CRP performed only modestly well, and its performance as a predictor for coronary disease was similar to blood pressure (BP) and low-density lipoprotein (LDL) cholesterol, whose use in isolation for assessment of cardiovascular risk has been abandoned in many healthcare settings in favor of risk scores (<http://www.sign.ac.uk/pdf/sign97.pdf>; <http://www.nice.org.uk/nicemedia/pdf/CG67FullGuideline1.pdf>; <http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-CVD-prevention-ES-FT.pdf>). Moreover, most observational studies examining the association of CRP with cardiovascular risk have been based on studies in Europeans.

Nevertheless, in 2003, consensus statements from population, laboratory science, and clinical practice expert committees convened by the American Heart Association/Centers for Disease Control (AHA/CDC) indicated that “CRP may be used at the discretion of the physician as part of a global coronary risk assessment in adults without known cardiovascular disease” and that a CRP value above a cut-point of 3 mg/L was indicative of subjects at high risk.¹⁰ More recently, the Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)¹¹ evaluated the efficacy of statins in participants considered to be at risk because of a CRP value of >2 mg/L. On the basis of the findings of the trial, the US Food and Drug Administration (FDA) recently licensed rosuvastatin for primary prevention of cardiovascular disease in men over age 50 years and women over age 60 years, 1 other risk factor, and CRP >2 mg/L.

If general differences exist in average CRP concentrations between populations of different ethnic or ancestral background, it may affect the eligibility for treatment, based on the new FDA license. We conducted a systematic review to precisely evaluate differences in CRP between populations of differing geographical and ancestral background to consider the implications for risk prediction in non-Europeans. We investigated genetic and nongenetic determinants of the interethnic CRP differences using the human HapMap and SeattleSNPs databases and a participant level analysis in the multiethnic Wandsworth Heart and Stroke Study (WHSS).

Methods

Systematic Review

We conducted a systematic review of studies of healthy populations reporting CRP concentration in any ethnic group up to November 2009. Two electronic data bases (Medline and EMBASE) were searched using the MeSH terms (“C-reactive protein” OR “CRP”) AND (“ethnicity” OR “ethnic groups,” OR “ancestry” OR “race”). The search was limited by the terms “human” and “English language.” Geographical location was used as a proxy for ancestry, with studies divided into those investigating white, black, Hispanic, South Asian, and East Asian groups.

We extracted study-specific values reported for arithmetic or geometric mean CRP, or median CRP values, together with any measure of dispersion (including standard deviation [SD], approximate SD, or range). Because there is no exact way to transform between scales and geometric mean, CRP best follows the normal assumptions necessary for the meta-analysis model we used. Our main analysis utilized geometric mean values for CRP, but we also conducted a subsidiary analysis restricted to those studies reporting arithmetic means. Given that the distribution of CRP concentration is right-skewed, CRP values were log-transformed. Where no measure

of dispersion was reported, for both geometric and arithmetic analyses, we used a conservative replacement using the highest pooled SD from all ethnicities. We also extracted information on sample size, study design, CRP assay, age, sex, body mass index (BMI), and other physical measures.

We conducted a regression analysis using log-CRP as a continuous variable and ethnicity as a categorical fixed-effects predictor, taking the white group as baseline. Random intercepts were fitted for each study. We further evaluated to what extent any differences in CRP by ancestral group were accounted for by systematic differences in study design or assay type. In addition, we sought to examine whether differences in CRP across ancestral groups were still present after adjustment for age and what the probability would be that an individual in each ancestral group would have a CRP value above the JUPITER cut-point value of 2 mg/L. By analyzing the data with a bayesian hierarchical model using R and WinBUGs, it was possible to infer this probability from the resulting posterior samples of the linear predictor (ie, the probability from the bayesian analysis). Standard normal distribution (mean, 0; variance, 0.00001) and γ distribution (shape, 0.001; rate, 0.001) priors were used for the regression coefficients and between study variability, respectively. We ran 1 000 000 iterations and checked convergence by running different chains and inspecting diagnostic plots. For all analyses, this number of iterations resulted in chain plots indicating very satisfactory convergence for all parameters and identical inference between chains.

Sensitivity to prior specifications was checked using alternative uninformative priors for regression coefficients and between study variability. Further, sensitivity to small study bias was investigated by repeating the main analysis of geometric mean data after excluding all studies with a total number of subjects <500. All sensitivity analyses lead to equivalent inference (see online-only Data Supplement Figure 1).

Data From HapMap and SeattleSNPs

We consulted the International HapMap Project (<http://www.hapmap.org>) (data release 27) and Programs for Genomic Applications (PGA) SeattleSNPs (<http://pga.gs.washington.edu/data/crp/>) databases (location chromosome 1, position: 157 946 209 to 157 953 498 bp) for information on the frequency and range of common single nucleotide variation in the *CRP* gene in individuals of differing ancestry.

WHSS Population

The WHSS population of 1577 individuals comprises approximately equal numbers of European, black African (West African and Caribbean), and South Asian individuals (age, 40 to 59 years), recruited from the lists of general practices in South London.^{12,13} Ethnic group was recorded at the time of interview, based on the answers to a combination of questions in the administered questionnaire, which included place and country of birth, language, religion, history of migration, and parental country of birth. For the present study, we selected the 705 individuals without diabetes or hypertension and excluded those on lipid-lowering medication, oral contraceptive pill, or hormone replacement therapy and those with any history of ischemic heart disease or stroke. The local ethics committee approved the study, and all participants gave their informed consent to participate.

BP was recorded using standard methods as described previously.¹³ Fasting blood was taken in the seated position without stasis. Biochemical measurements were performed using standardized methods, as described previously.¹⁴ CRP was measured in thawed plasma K-EDTA (IL Coagulation Systems on ACL9000, IL, Milan, Italy), using a latex particle-enhanced immunoturbidimetric high-sensitivity assay. Genotyping of the triallelic *CRP* SNP rs3091244 (−286C/T/A) was performed using a pyrosequencing method using the forward primer 5′ TGA TTT GGG CTG AAG TAG GTG 3′, the reverse primer 5′ TGG CTA TCT ATC CTG CGA AAA T 3′, and the sequencing primer 5′ ACC CAG ATG GCC ACT 3′.

Table. Summary of Studies Identified in the Systematic Review and Included in the Main Analysis

	White (Non-Hispanic)	Black	East Asian	Hispanic	South Asian	All
Total No. of studies	73	27	20	15	9	89
Total No. of participants	137 524	24 086	48 600	9567	1510	221 287
Study design: General population	67	24	16	13	7	78
Control subjects from nested case-control studies	3	0	4	0	1	7
Other	5	3	0	2	1	6
Reported CRP geometric mean (studies/participants)	41/104 949	19/18 585	15/39 521	9/5049	4/1053	50/169 157
Reported CRP approximate SD (studies/participants)	30/82 889	16/15 895	15/39 521	7/3143	4/1053	39/142 501
Reported CRP arithmetic mean (studies/participants)	14/14 439	3/3092	4/8565	3/3069	2/100	20/29 265
Reported CRP arithmetic SD (studies/participants)	12/8206	3/3092	3/7217	3/3069	2/100	17/21 684
Reported age (studies/participants)	61/118 507	22/18 730	18/41 669	10/5251	8/1454	76/185 611
Reported BMI (studies/participants)	51/92 210	15/12 721	14/29 520	6/1435	6/1139	62/137 025
Assay type: ELISA	20	6	2	2	5	23
Turbidometric immunoassay	13	6	4	2	1	16
Nephelometry	34	14	11	9	2	40
Other CRP assay	9	1	3	2	1	13

Statistical Analysis in WHSS

We first conducted univariable regressions of log-CRP on age, BMI, and systolic BP as continuous variables and ethnicity, sex, smoking, and genotype for a triallelic *CRP* SNP ($-286C/T/A$) as categorical predictors. The European ancestry was used as baseline and the CC category as the baseline genotype. For ethnicity and $-286C/T/A$ genotype, joint Wald tests were used to test the variable as a whole. Further, for the $-286C/T/A$ SNP, genotype frequencies in the WHSS were compared with those expected under the Hardy-Weinberg equilibrium assumption by χ^2 analysis.

We also conducted multivariable regression; first including ethnicity, age, and sex as predictors; second including all nongenetic predictors; and the third with the addition of CRP genotype for the $-286C/T/A$ SNP. Adjusted r^2 values were compared between the models, which correspond to the percentage of explained variation in log-CRP, adjusted for the number of parameters used.

Results

Systematic Review

CRP Concentration in Groups of Diverse Ancestry

The primary search identified 102 studies ($n=252\,906$ participants), of which 3 were excluded because they reported data already included from another study, and 2 were excluded because CRP values could not be extracted from the publication. We excluded ethnic groups in which there was only 1 published study. Thus, information on African and Caribbean people resident outside North America (2725 individuals), South African people (102 individuals), Ab-origines (430 individuals), Native Americans (45 individuals), and Inuit (180 individuals), comprising 3482 individuals in all, were excluded. The remaining 89 studies provided information on 221 287 individuals from 5 ancestral groups (Table). Of 89 studies included in our analysis, 50 studies ($n=169\,157$) reported on the geometric scale, 20 studies ($n=29\,265$) on the arithmetic scale, and the rest reported medians (Table).

An unadjusted meta-regression on ethnicity inferred geometric mean CRP values of 2.6 mg/L (95% confidence interval [CI], 2.27 to 2.96) in blacks (18 585 subjects), 2.51

mg/L (95% CI, 1.18 to 2.86) in Hispanics (5049 subjects), 2.34 mg/L (95% CI, 1.99 to 2.8) in South Asians (1053 subjects), 2.03 mg/L (95% CI, 1.77 to 2.3) in whites (104 949 subjects), and 1.01 mg/L (95% CI, 0.88 to 1.18) in East Asians (39 521 subjects) (Figure 1). The findings were consistent in analyses restricted to studies reporting data on the arithmetic scale (online-only Data Supplement Figure 2). There were no systematic differences in study design (categorized as general population, control subjects from nested case-control studies, or other) across ethnic groups (Fisher exact test, $P=0.41$), nor in assay type (categorized as ELISAs, turbidometric immunoassays, and nephelometry, excluding other types of assays due to small numbers) (Fisher exact test, $P=0.12$).

The mean age of participants was strongly associated with log-geometric mean CRP (weighted correlation coefficient, $r=0.6$, $P<0.0001$). To explore the possibility that the observed differences in CRP by ancestry might be affected by differences in mean age between the studies, the analyses were repeated, adjusted for mean age, among the studies in which this was reported. In these analyses, the differences in log-CRP between ancestral groups were preserved (Figure 2). Black and Hispanic individuals had age-adjusted geometric mean CRP values of 2.99 mg/L (95% CI, 2.58 to 3.53) and 2.77 mg/L (95% CI, 2.35 to 3.3), respectively, white and South Asian subjects had age-adjusted geometric mean CRP values of 2.26 mg/L (95% CI, 1.95 to 2.66) and 2.63 mg/L (95% CI, 2.21 to 3.15), respectively, and East Asian individuals had mean age-adjusted CRP values of 0.97 mg/L (95% CI, 0.83 to 1.15) (Figure 2). Again, results were consistent in the arithmetic data. Similarly, a mean BMI-adjusted analysis was carried out among studies in which this was reported. As expected, mean BMI did explain part of the variation in CRP by ethnicity; however, differences remained suggesting that the CRP-ethnicity association is not simply due to ethnic differences in BMI (online-only Data Supplement Figure 3).

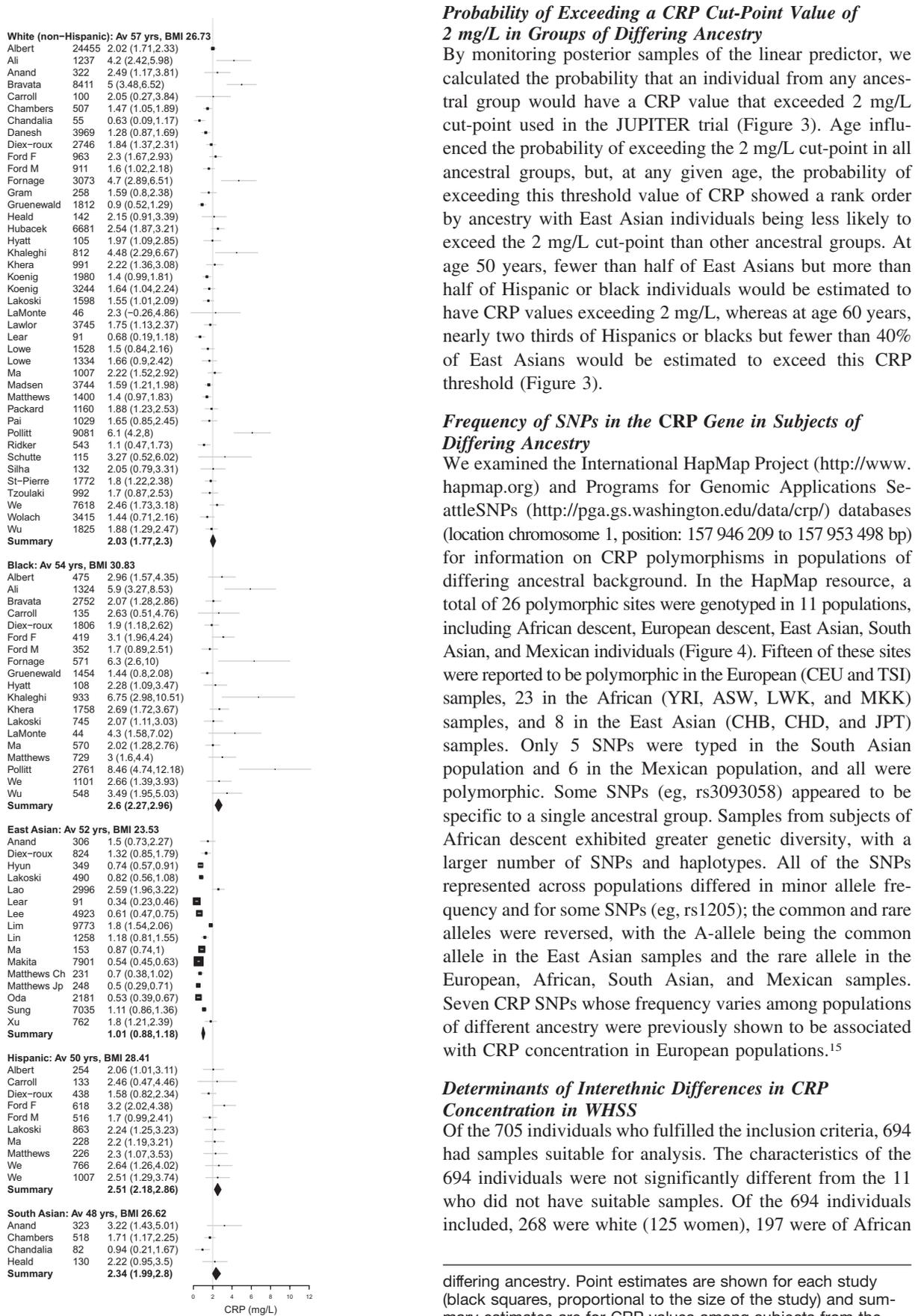


Figure 1. Forest plot showing meta-regression of studies reporting unadjusted geometric mean CRP values among populations of

Probability of Exceeding a CRP Cut-Point Value of 2 mg/L in Groups of Differing Ancestry

By monitoring posterior samples of the linear predictor, we calculated the probability that an individual from any ancestral group would have a CRP value that exceeded 2 mg/L cut-point used in the JUPITER trial (Figure 3). Age influenced the probability of exceeding the 2 mg/L cut-point in all ancestral groups, but, at any given age, the probability of exceeding this threshold value of CRP showed a rank order by ancestry with East Asian individuals being less likely to exceed the 2 mg/L cut-point than other ancestral groups. At age 50 years, fewer than half of East Asians but more than half of Hispanic or black individuals would be estimated to have CRP values exceeding 2 mg/L, whereas at age 60 years, nearly two thirds of Hispanics or blacks but fewer than 40% of East Asians would be estimated to exceed this CRP threshold (Figure 3).

Frequency of SNPs in the CRP Gene in Subjects of Differing Ancestry

We examined the International HapMap Project (<http://www.hapmap.org>) and Programs for Genomic Applications SeattleSNPs (<http://pga.gs.washington.edu/data/crp/>) databases (location chromosome 1, position: 157 946 209 to 157 953 498 bp) for information on CRP polymorphisms in populations of differing ancestral background. In the HapMap resource, a total of 26 polymorphic sites were genotyped in 11 populations, including African descent, European descent, East Asian, South Asian, and Mexican individuals (Figure 4). Fifteen of these sites were reported to be polymorphic in the European (CEU and TSI) samples, 23 in the African (YRI, ASW, LWK, and MKK) samples, and 8 in the East Asian (CHB, CHD, and JPT) samples. Only 5 SNPs were typed in the South Asian population and 6 in the Mexican population, and all were polymorphic. Some SNPs (eg, rs3093058) appeared to be specific to a single ancestral group. Samples from subjects of African descent exhibited greater genetic diversity, with a larger number of SNPs and haplotypes. All of the SNPs represented across populations differed in minor allele frequency and for some SNPs (eg, rs1205); the common and rare alleles were reversed, with the A-allele being the common allele in the East Asian samples and the rare allele in the European, African, South Asian, and Mexican samples. Seven CRP SNPs whose frequency varies among populations of different ancestry were previously shown to be associated with CRP concentration in European populations.¹⁵

Determinants of Interethnic Differences in CRP Concentration in WHSS

Of the 705 individuals who fulfilled the inclusion criteria, 694 had samples suitable for analysis. The characteristics of the 694 individuals were not significantly different from the 11 who did not have suitable samples. Of the 694 individuals included, 268 were white (125 women), 197 were of African

differing ancestry. Point estimates are shown for each study (black squares, proportional to the size of the study) and summary estimates are for CRP values among subjects from the specified ethnic group obtained from meta-regression (black diamonds).

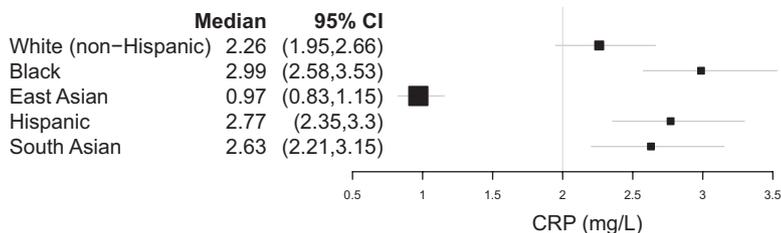


Figure 2. Estimated median CRP and 95% CIs of posterior samples, using an age adjusted model. Vertical line indicates the JUPITER 2 mg/L cut-point. The weighted average age across all studies is 55.4 years.

origin (106 women), and 229 were of South Asian origin (105 women). People of African origin were all first generation immigrants resident in the United Kingdom.

The geometric mean (approximate SD) CRP values among individuals of European, South Asian, and African and Caribbean individuals in the WHSS were 1.23 (2.59), 1.51 (2.61), and 1.11 (2.48), respectively (online-only Data Supplement Table 1). These were all somewhat lower than the corresponding point estimates from the meta-analysis but all well within the range of summary values reported by published studies contributing information to the meta-analysis. Differences in summary estimates between studies from the same ethnic group could arise because of differences in mean age, CRP assay used, or exposure to different risk factors. However, our previous adjustment for age, assay, and mean BMI did not alter the association of ethnicity with CRP.

There were significant differences in CRP by ancestral group in univariable analyses (online-only Data Supplement Table 1). In an adjusted model, ancestry ($P=0.016$), BMI ($P<0.001$), age ($P=0.017$), and smoking ($P=0.004$) were all independent predictors of log-CRP, together explaining 18.6% of the variance, of which 16.3% was explained by BMI. Although not a statistically significant predictor in this modestly sized data set, there were differences observed in mean log-CRP values between the CC, TT, and CA genotypes of the triallelic SNP, which are consistent with previous publications.¹⁵

Discussion

In this systematic review involving 221 287 individuals from 89 published studies, conducted to provide more reliable estimates, we found substantial differences in CRP concentration across diverse ancestral groups that could have a major impact on eligibility for rosuvastatin treatment, based on a CRP cut-point value of 2 mg/L. These differences were

unrelated to study design or assay type and were robust to group-level adjustment for mean age and BMI. There was indirect evidence that differences in smoking prevalence, BMI, and the frequency of polymorphisms in the CRP gene could influence the between-group variation in CRP in populations of differing ancestry, but most of the variation in CRP values between groups of differing ancestry was unexplained by these factors.

The well-studied and robust association of CRP with risk of CHD has engendered interest in the possibility that CRP might be causally involved in the development of cardiovascular disease or that its measurement might serve as a predictive test that could supersede or augment established risk assessment tools such as the Framingham risk equation. Recent evidence from animal models and human genetic studies (using the mendelian randomization principle) indicate that CRP is unlikely to be causally involved in atherosclerosis,^{16–22} therefore narrowing the focus of interest around measurement of CRP for its possible predictive function. In the randomized, controlled JUPITER trial, in which individuals were enrolled on the basis of a CRP value >2 mg/L and an LDL-C concentration <130 mg/dL (<3.4 mmol/L), rosuvastatin reduced the risk of cardiovascular events by 44%, leading to the proposal that a CRP cut-point of 2 mg/L might be applied as a threshold to facilitate the targeting of statins for the primary prevention of cardiovascular disease.¹¹ This finding was reflected in the recent amendment to the FDA license for rosuvastatin. Although median CRP concentrations have been reported previously to vary among populations of differing ancestry,²³ individual studies have been too small in size to estimate these differences precisely. If substantial, as we now confirm, this could lead to ethnicity being an impor-

Posterior probability that an individual is above 2mg/L for different ages and ethnic groups

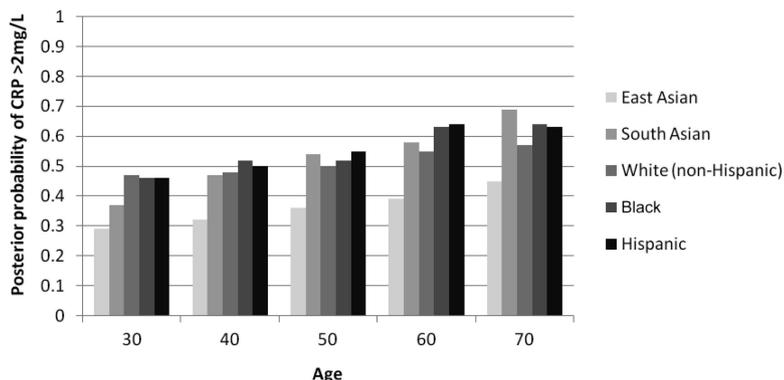
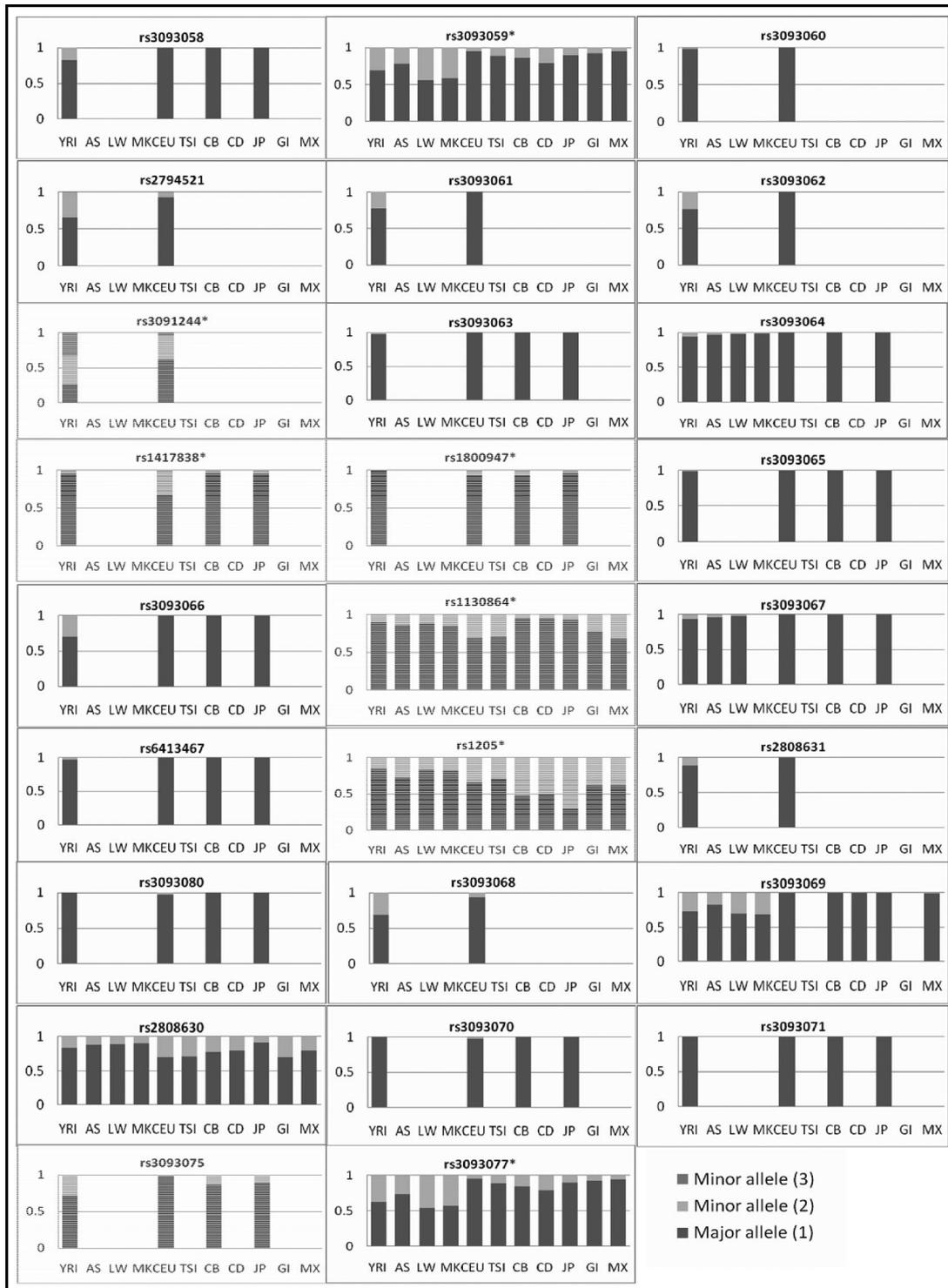


Figure 3. Posterior probability of exceeding the JUPITER 2 mg/L cut-point for CRP in groups of different ancestry. All analyses are stratified by age.



YRI: Yoruban in Ibadan, Nigeria, **AS:** African ancestry in Southwest USA, **LW:** Luhya in Webuye, Kenya, **MK:** Maasai in Kinyawa, Kenya, **CEU:** Utah residents with Northern and Western European ancestry from the CEPH collection, **TSI:** Tuscans in Italy, **CB:** Han Chinese in Beijing, China, **CD:** Chinese in Metropolitan Denver, Colorado, **JP:** Japanese in Tokyo, Japan, **GI:** Gujarati Indians in Houston, Texas, **MX:** Mexican ancestry in Los Angeles, California. *SNP associated with CRP concentration in European

Figure 4. Allele frequencies of SNPs in the *CRP* gene among diverse ethnic groups. Information is based on HapMap and SeattleSNPs, using the European population as the reference population (see text for details).

tant influence on eligibility for statin treatment based on a CRP cut-point value.

Although a large number of studies contributing to this systematic review reported cross-sectional analyses of CRP in populations of different ancestry, direct evidence on the

prospective relationship between CRP and risk of cardiovascular events among non-European subjects is very limited. Two recent studies of Japanese residents in Japan reported similar relative associations of CRP with coronary risk to those observed in Europeans, but at lower absolute values of

CRP, and in the context of the low absolute risk of cardiovascular disease in Japan.^{24,25} Multi-ethnic cohort studies in the United States have reported similar overall relative associations of CRP with cardiovascular disease as those cohorts that included exclusively European descent individuals and have not reported evidence of any modifying effect of ancestry on the overall association.^{26–30}

However, both the absolute risk of cardiovascular disease and the population exposure to risk factors (which influences the attributable risk) will differ substantially by ethnicity/ancestry. Absolute rather than relative risk is preferred for the purposes of cardiovascular risk prediction because absolute risk determines the absolute benefit and therefore the cost-effectiveness and risk-benefit balance of any preventative intervention.³¹ Thus, the combination of a likely homogeneous relative association of CRP with cardiovascular events across populations, but the different absolute values of CRP and absolute risks of cardiovascular events in the different ethnic/ancestral groups, means that a single universal CRP threshold for the designation of high risk individuals will capture a different proportion of the adult population, depending on their ancestral origin.

There are additional reasons for being cautious about the consideration of CRP value in isolation. First, bearing in mind the limitations of the population statistic data, CVD mortality rates among different US ethnic groups do not relate clearly to the estimated mean CRP value from the current analysis (online-only Data Supplement Table 2). Second, even in European populations, where the association of CRP with incident cardiovascular events has been extensively analyzed, previous overviews and primary studies have indicated that CRP, like other individual measures including the causally relevant risk factors BP and cholesterol discriminates cases of CHD poorly. CRP has also been found in several studies and overviews to add little or no incremental information to risk models based on established risk factors, whether assessed using recalibration or reclassification.^{8,32–34} Moreover, any individual CRP value (just like any individual cholesterol value) can be compatible with very wide range of absolute risks of cardiovascular disease.

Current AHA/CDC task force recommendations from 2003 consider individuals with CRP >3 mg/L to be at high risk,¹⁰ currently without acknowledgement of the ethnic differences in CRP values, or the paucity of evidence in on its utility as a risk marker in non-Europeans. Since then, the FDA has granted approval for rosuvastatin for primary prevention of cardiovascular disease on the basis of age and a CRP cut-point of 2 mg/L, also without acknowledgement of ethnic differences in CRP. It was estimated that approximately 5 million hs-CRP tests were ordered in the United States in 2007, even before the recent FDA decision, presumably by clinicians concerned with the estimation of cardiovascular risk. The recent FDA decision is likely to increase the number of hs-CRP tests ordered annually. On the basis of our findings, clinicians may now wish to take ethnicity into account in their interpretation of a CRP value. There is also a need to better delineate the relationship of CRP to cardiovascular events in the major non-European populations, in both absolute as well as relative terms, so that clinicians are better

informed on the utility or otherwise of a CRP measurement for risk prediction in these groups. This is particularly important since the proportion of non-Hispanic European descent individuals as a share of the US population is likely to fall in the next few decades (US Census Bureau; <http://www.census.gov/population/www/projections/2009projections.html>).

Limitations of the Study

Our study was limited to aggregate rather than participant level data and to published studies. However, the group level differences in CRP values in populations of different ethnicity were consistent and substantial. Because most of the data came from studies evaluating a different question to that considered in the current analysis, small study and publication bias are also unlikely to have affected the findings.

Previous studies have shown that CRP is also associated with proatherogenic lipoproteins (ApoB), higher levels of abdominal obesity (indicated by waist-to-hip ratio), increased prevalence of diabetes, or metabolic syndrome, alcohol, and low birth weight.^{35–43} Conversely, the frequency of protective risk factors such as physical activity, HDL-C, or Apo-A1 and consumption of fruits and vegetables also tend to be less prevalent in such individuals.⁴⁴ CRP concentrations also exhibit association with sociodemographic indicators measured across the lifetime⁴³; however, it was not possible to examine these associations as they had not been reported in the majority of studies included in the systematic review.

There were many more observations for Europeans than other populations. However, there was no evidence of substantial between study variability, suggesting that what we observed may be reasonably representative of each population. In the systematic review, only studies with black subjects resident in the United States were included to preserve homogeneity of the population. There were not enough studies to examine Africans and Caribbeans as separate groups, and information from these populations was therefore excluded from the current analysis. Previous studies have shown differences both in relation to risk profile and in relation to cardiovascular outcomes⁴⁵ among African American individuals living in North America, and individuals of African and Caribbean ancestry living in Britain that may be due to differences in environment, socioeconomic factors and degree of admixture.

In addition, there was inconsistency in how CRP values were reported (geometric mean, arithmetic mean, or median), which meant that not all identified studies could be analyzed together. However, for analysis of geometric data, which best fits the normality assumptions of the meta-analysis model, there were still 169 157 participants from 50 data sets available.

Conclusion

A one size-fits-all threshold value of CRP for risk prediction or statin targeting could diminish the opportunity to receive a statin in individuals from certain ethnic backgrounds while increasing this opportunity among others. This policy could lead to inequalities in statin eligibility that do not closely relate to underlying levels of risk.

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CLINICAL PERSPECTIVE

Circulating C-reactive protein (CRP) concentration has been proposed as a biomarker for cardiovascular risk prediction and as a selection marker for initiating statin treatment. Most observational studies of CRP and cardiovascular disease have been conducted in Europeans, but average CRP concentrations are thought to differ in populations of non-European ancestry. We conducted a systematic review of published studies to precisely quantify circulating CRP levels in populations of diverse ancestry. Population average CRP values were higher in black and Hispanic individuals, and lower in South and East Asian individuals in comparison with Europeans. The differences were not explained by study design or by the type of CRP assay, and were preserved after adjustment for age and body mass index. At age 60, we estimated that 39% of East Asians but 65% of Hispanics have CRP values exceeding 2 mg/L, the cut point used to define eligibility for rosuvastatin treatment for primary prevention of cardiovascular disease in men over 50 years and women over 60 years. Differences in blood CRP concentration in populations of diverse ancestry are sufficiently large to impact statin eligibility based on a single CRP threshold of 2 mg/L, and may be only partially influenced by differences in variables related to cardiovascular risk. A single threshold value of CRP for cardiovascular risk prediction could potentially lead to inequalities in statin eligibility that may not accurately reflect the underlying levels of cardiovascular risk, a premise that warrants further study.

SUPPLEMENTAL MATERIAL

Ancestry as a determinant of mean population C-reactive protein values: implications for cardiovascular risk prediction

Supplementary Table 1. Characteristics of individuals in the WHSS by ethnic group.

Supplementary Table 2. Cardiovascular mortality among different US ethnic groups and their estimated mean CRP value.

Supplementary Figure 1. Forest plot of studies with more than 500 subjects reporting unadjusted geometric mean CRP values among populations of differing ancestry. Point estimates are shown for each study and summary estimates are for CRP values among subjects from the specified ethnic group.

Supplementary Figure 2. Forest plot of all studies with unadjusted arithmetic mean CRP values with summary estimates across ethnic groups.

Supplementary Figure 3. BMI-adjusted CRP values across ethnic groups.

Supplementary Table 1. Characteristics of individuals in the WHSS by ethnic group.

	European	South Asian	African and Caribbean	P-value*
Total number	268	229	197	
Age (years)	49 (5.6)	47.9 (5.5)	50.5 (6.1)	<0.001
Gender: Male (N)	143	124	91	
Gender: Female (N)	125	105	106	
BMI	25.6 (4.4)	25.3 (4.3)	27.4 (4.1)	<0.001
Systolic BP (mm Hg)	123.4 (17.8)	124.6 (17.8)	128.2 (18.0)	0.014
CRP (mg/L)	1.23 (2.59)	1.51 (2.61)	1.11 (2.48)	0.002
Smoking: Current (N)	83	38	32	
Smoking: Ex (N)	99	15	23	
Smoking: Never (N)	85	176	142	
-286 SNP: CC	114	96	38	
-286 SNP: CT	99	72	49	
-286 SNP: TT	18	17	14	
-286 SNP: CA	18	29	39	
-286 SNP: TA	0	0	0	
-286 SNP: AA	0	0	22	

Unadjusted mean values and (SD).

*P-values from univariable analyses.

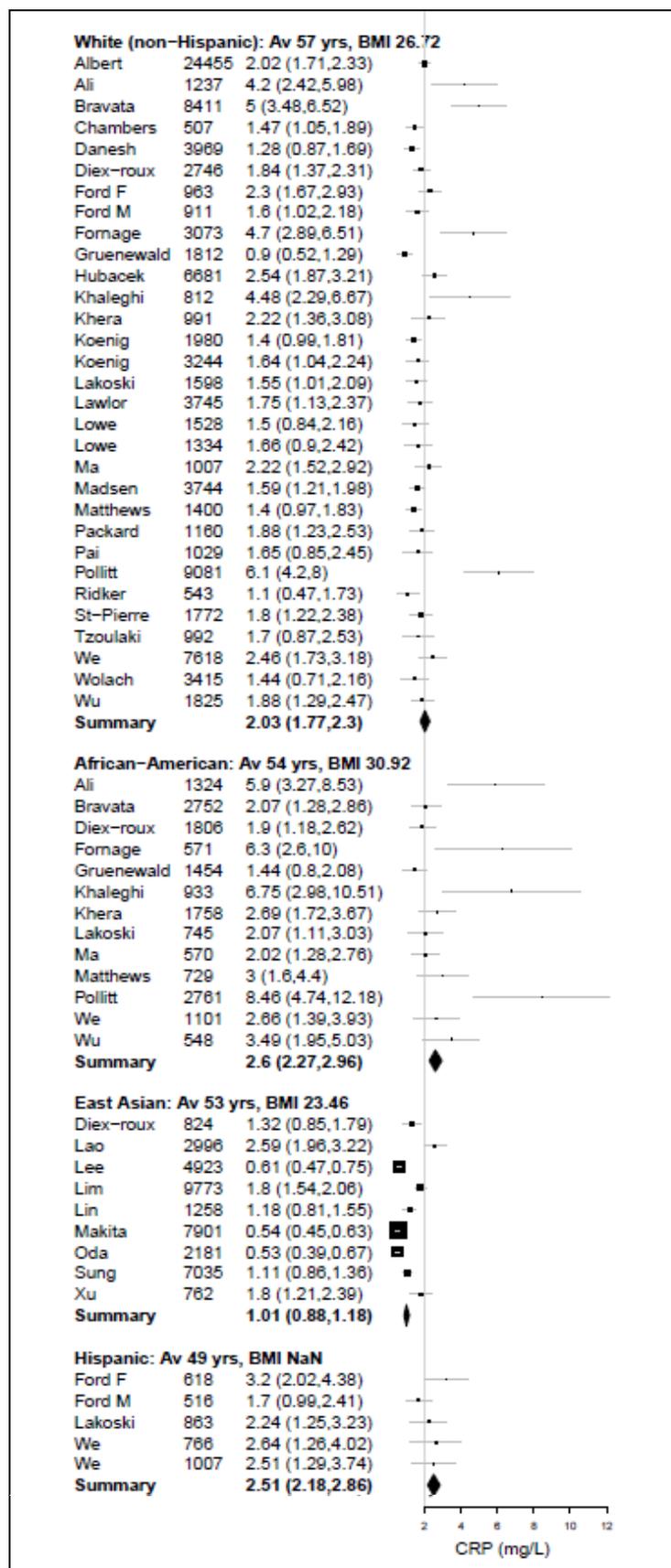
Supplementary Table 2. Cardiovascular mortality among different US ethnic groups and their estimated mean CRP value.

	Source	Ancestry							
		White		Black		Hispanic and Latino		Asian or Pacific islander**	
		Male	Female	Male	Female	Male	Female	Male	Female
Cardiovascular disease (% total deaths including congenital heart disease)	NCHS/NHLBI* US 2006	33.3	35.3	32.3	35.9	27.0.0	31.5	34.5	34.8
CRP (geometric mean and 95% credible interval)	This study	2.03 (1.77-3		2.6 (2.27-2.96)		2.51 (1.18-2.26)		2.34 (1.99-2.8) [South Asian] 1.01 (0.88-1.18) [East Asian]	

*Heart Disease and Stroke Statistics—2010. *Circulation* 2010; 121: e46-215. Charts 2-12-2-14.

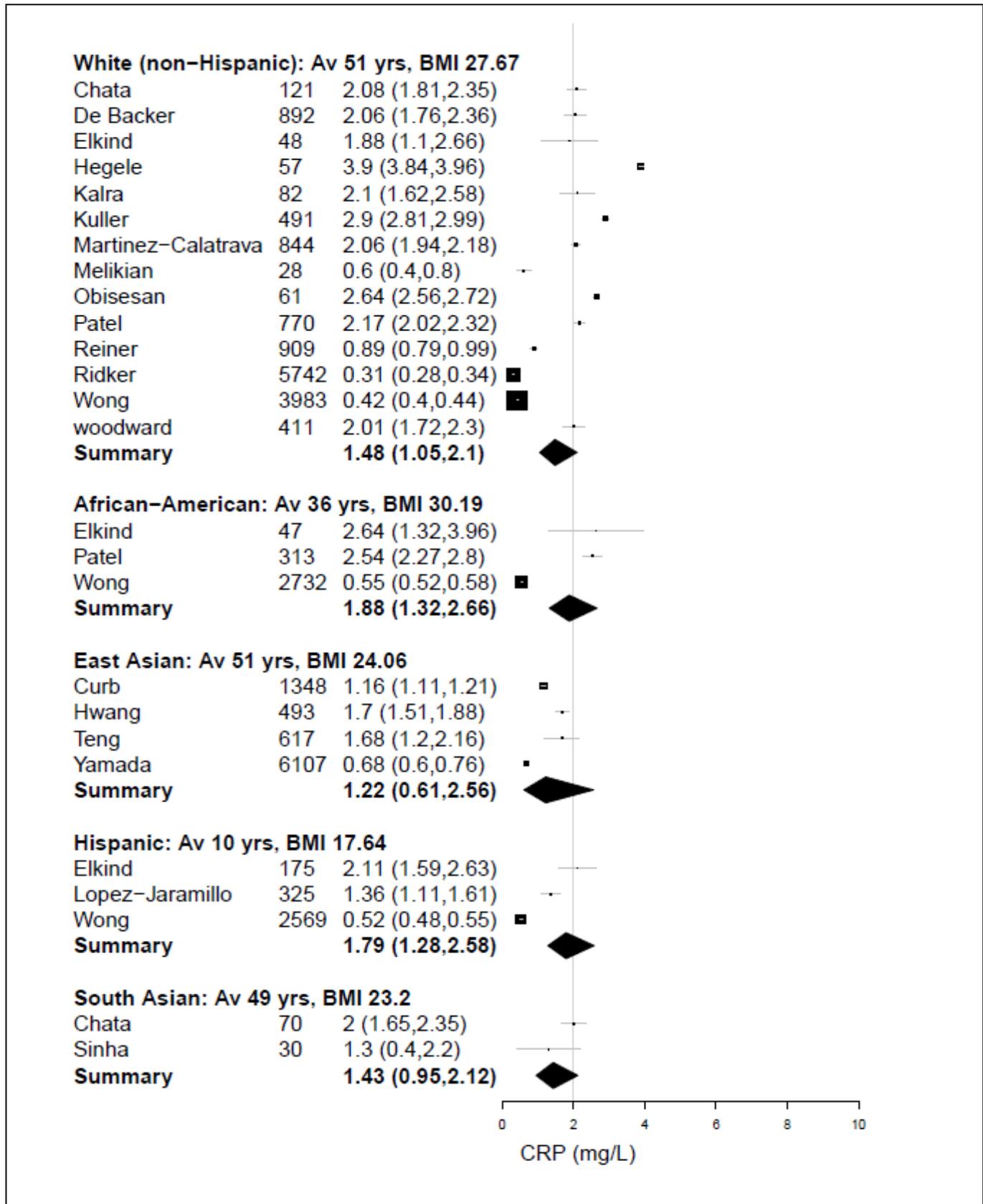
**Includes South Asian, Japanese and Pacific Islanders

Supplementary Figure 1. Forest plot of studies with more than 500 subjects reporting unadjusted geometric mean CRP values among populations of differing ancestry. Point estimates are shown for each study and summary estimates are for CRP values among subjects from the specified ethnic group.



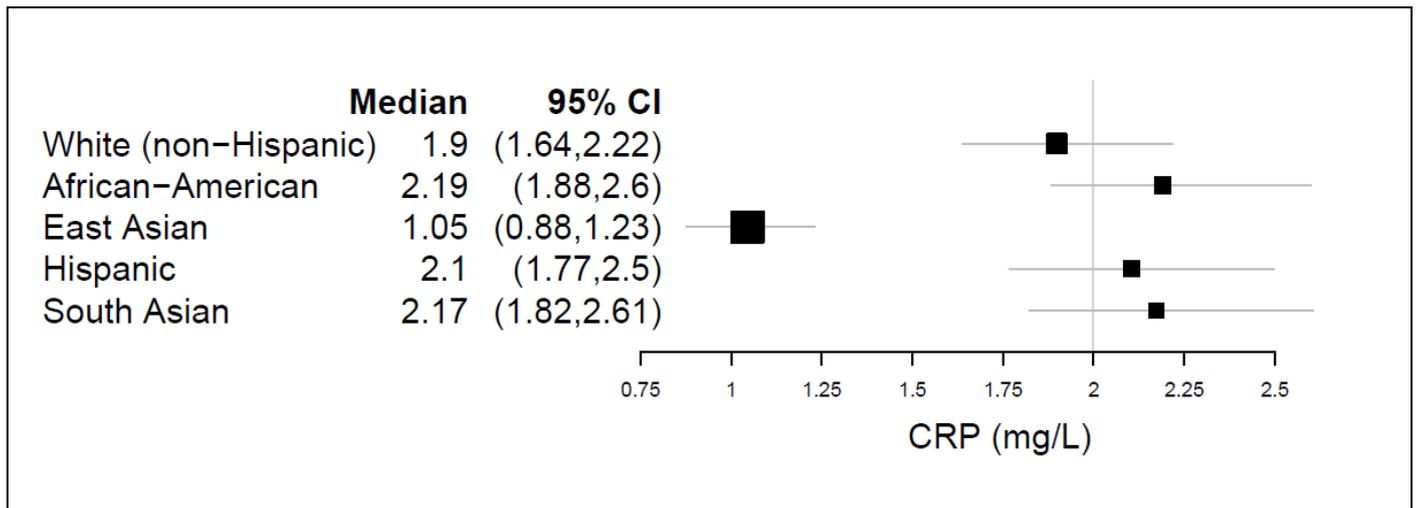
Studies with South Asian individuals are not included in this analysis as only one study had more than 500 subjects (Chambers et al, N=518).

Supplementary Figure 2. Forest plot of all studies with unadjusted arithmetic mean CRP values with summary estimates across ethnic groups.



The vertical line in the forest plot indicates the JUPITER 2mg/L cutpoint.

Supplementary Figure 3. BMI-adjusted CRP values across ethnic groups.



These are based on medians and 95% credible intervals of posterior samples drawn from the BMI adjusted model used for the analysis of geometric mean CRP. The vertical line indicates the JUPITER 2mg/L cutpoint. The weighted average BMI across all studies is 26.42.