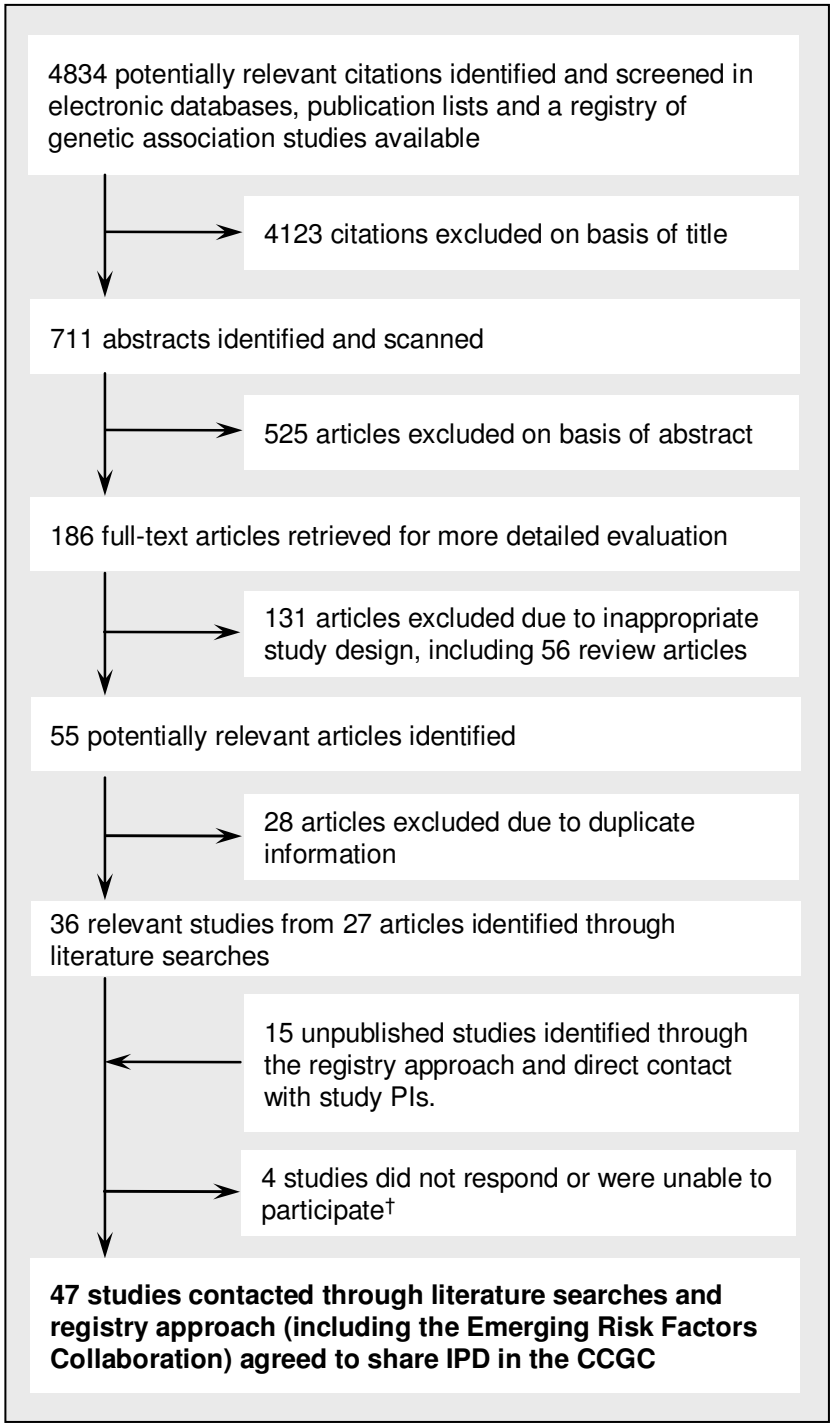
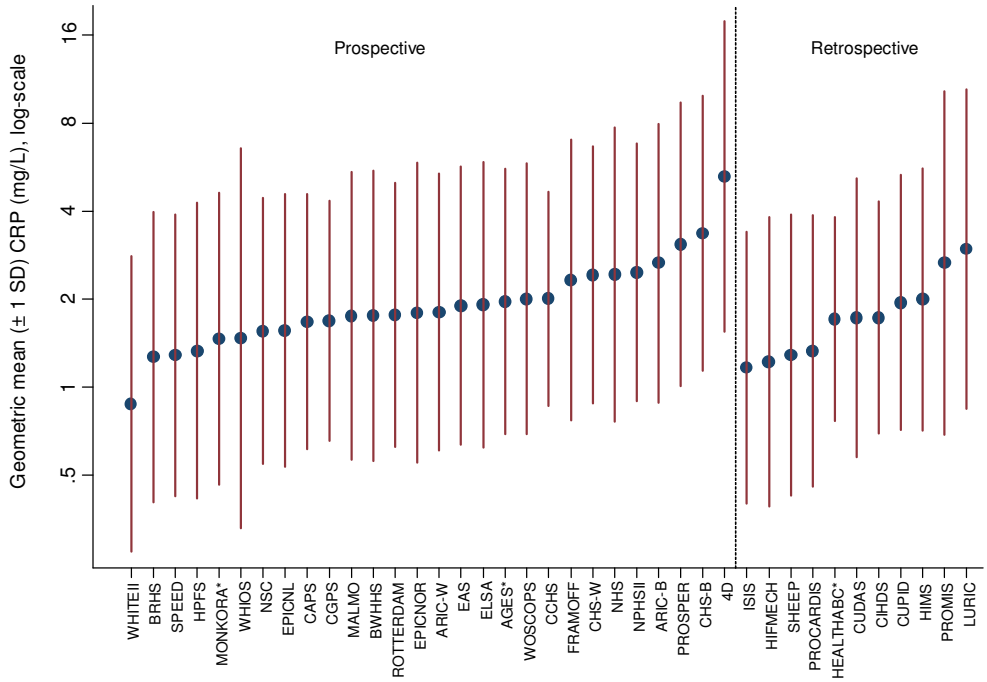
Appendix 3: Supplementary figures [posted as supplied by author]

Figure A. Flow chart summarizing search strategy for potential studies, updated regularly until July 2010.



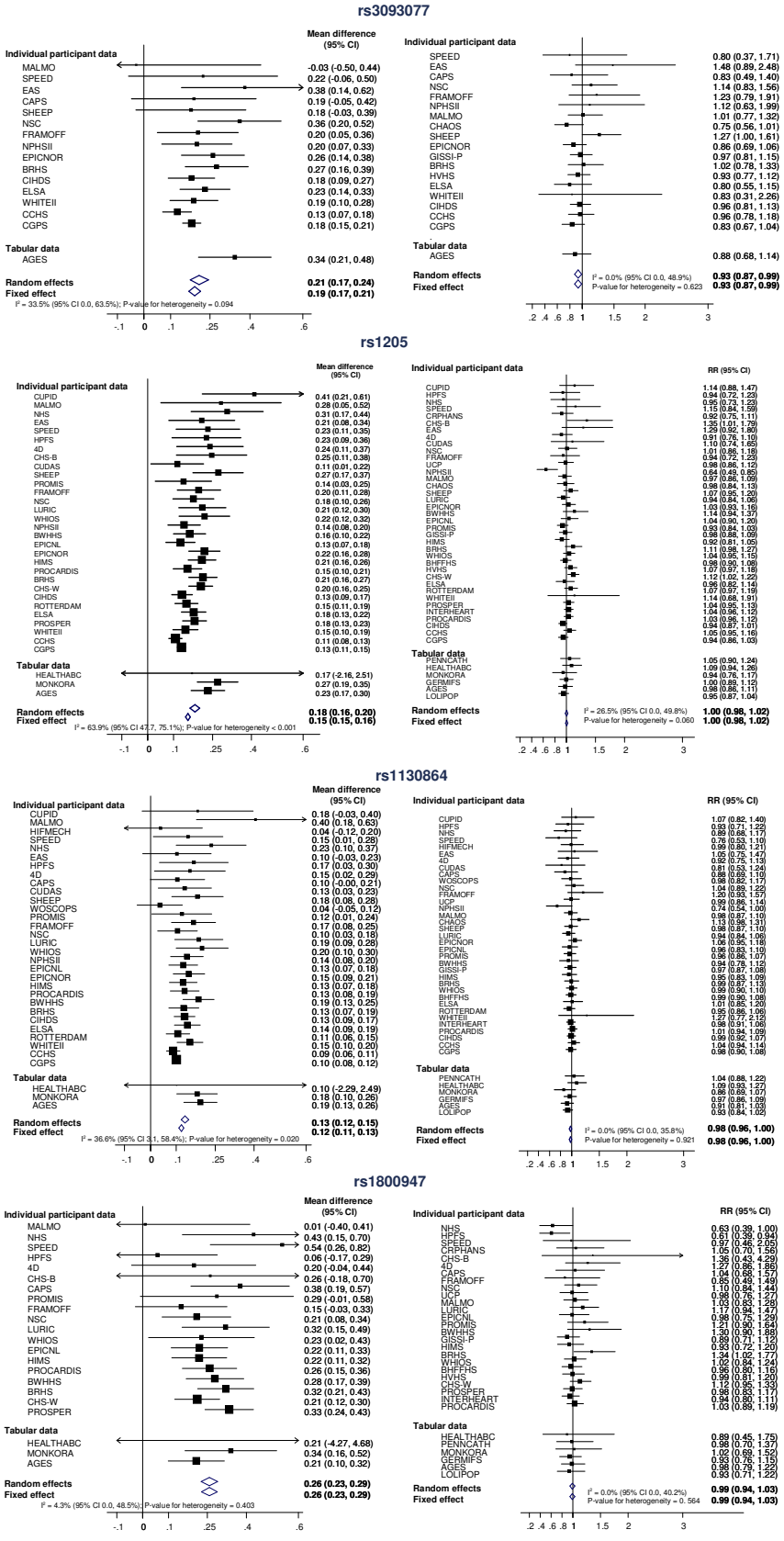
† Excluded studies, including the Physician's Health Study (PHS, Zee, R. *Atherosclerosis* 2002;162(1):217-219); Women's Genome Health Study (WGHS, Ridker, P. *Clin Chem* 2008;54(2):249-55); Pravastatin Inflammation / CRP Evaluation trial (PRINCE; Suk, H. *Atherosclerosis* 2005;178(1):139-145) and the Beijing Atherosclerosis Study (BAS, Chen, J. *J Mol Med.* 2005;83(1):72-78) comprising less than 1000 cases of CHD.

Figure B. Geometric mean CRP levels in according to study and design in 36 studies with CRP measurements in the CCGC.



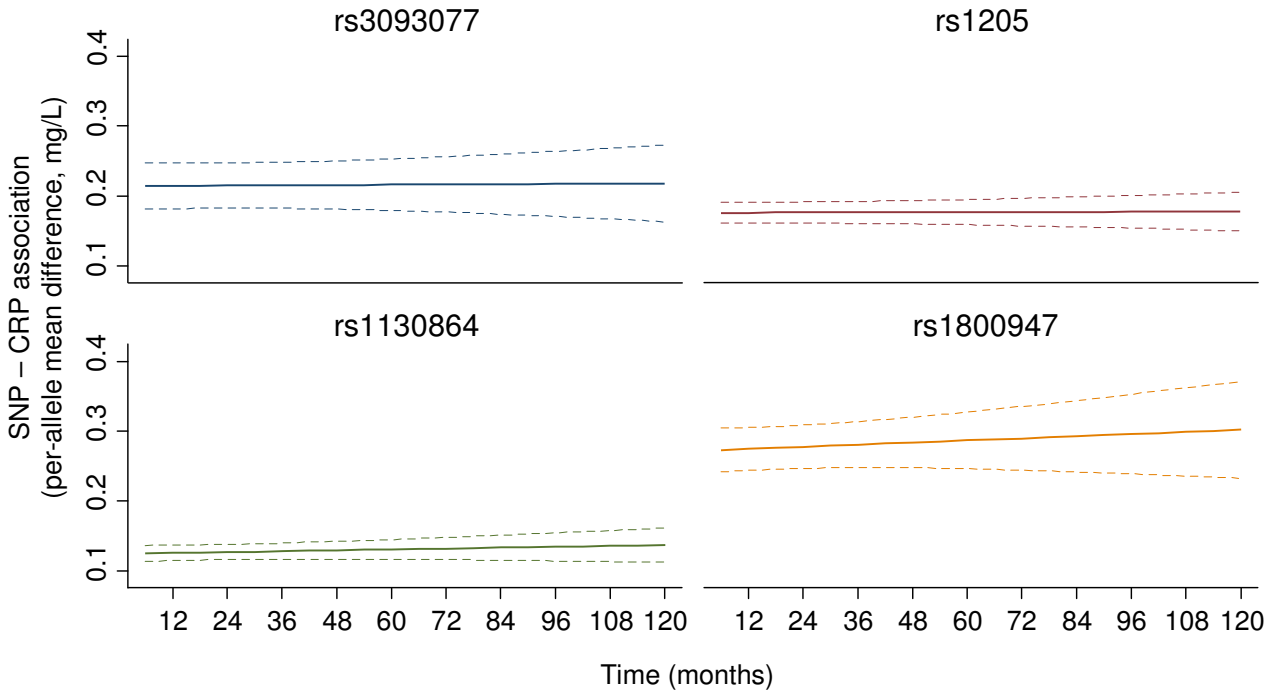
* These studies provided tabular data. Overall mean $\log_e$ CRP (SD) was 0.63 (1.057). SD = standard deviation; -W = European descent populations; -B = African descent populations; study abbreviations are listed in appendix 2.

Figure C. Study-specific estimates for per-allele higher CRP and per-allele risk of coronary heart disease.



CI indicates confidence interval. The sizes of data markers are proportional to the inverse of the variance of the risk ratios; analyses were stratified, where appropriate, or adjusted for sex, trial arm, and ethnicity. -W = European descent population; -B = African descent population; study abbreviations are listed in appendix 2.

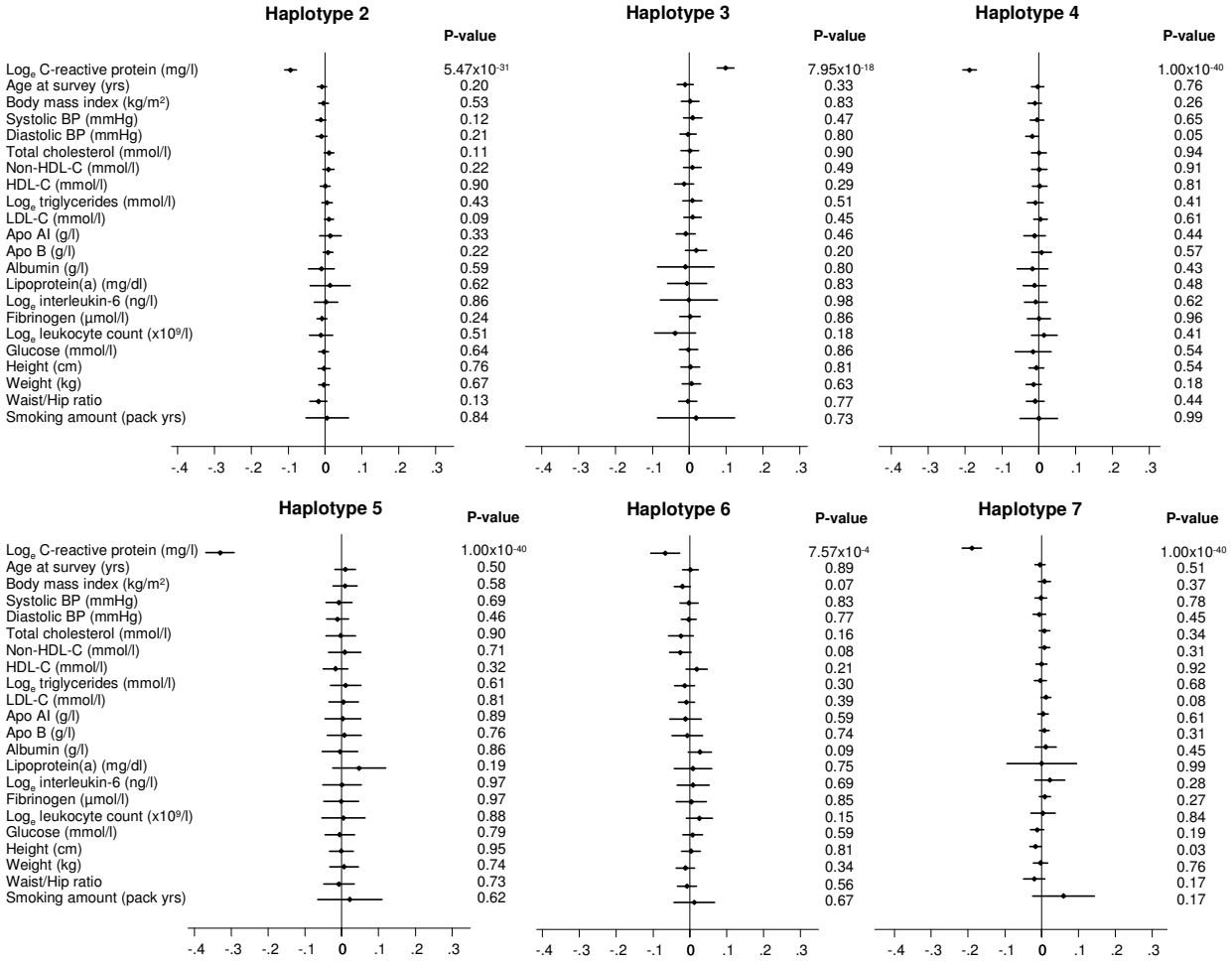
Figure D. Association of CRP SNPs with circulating CRP concentration over time, using repeat measures within individuals.



	Constant	SNP	Time	Interaction between SNP and time
	Beta (standard error)	Beta (standard error)	Beta (standard error)	Beta (standard error)
rs3093077	-1.469(0.083)	0.214 (0.017)	0.017 (0.008)	<0.001 (0.003)
rs1205	-1.666(0.091)	0.176 (0.008)	0.022 (0.008)	<0.001 (0.001)
rs1130864	-0.496 (0.277)	0.125 (0.006)	0.020 (0.009)	0.001 (0.001)
rs1800947	-1.366 (0.479)	0.271 (0.016)	0.020 (0.007)	0.007 (0.003)

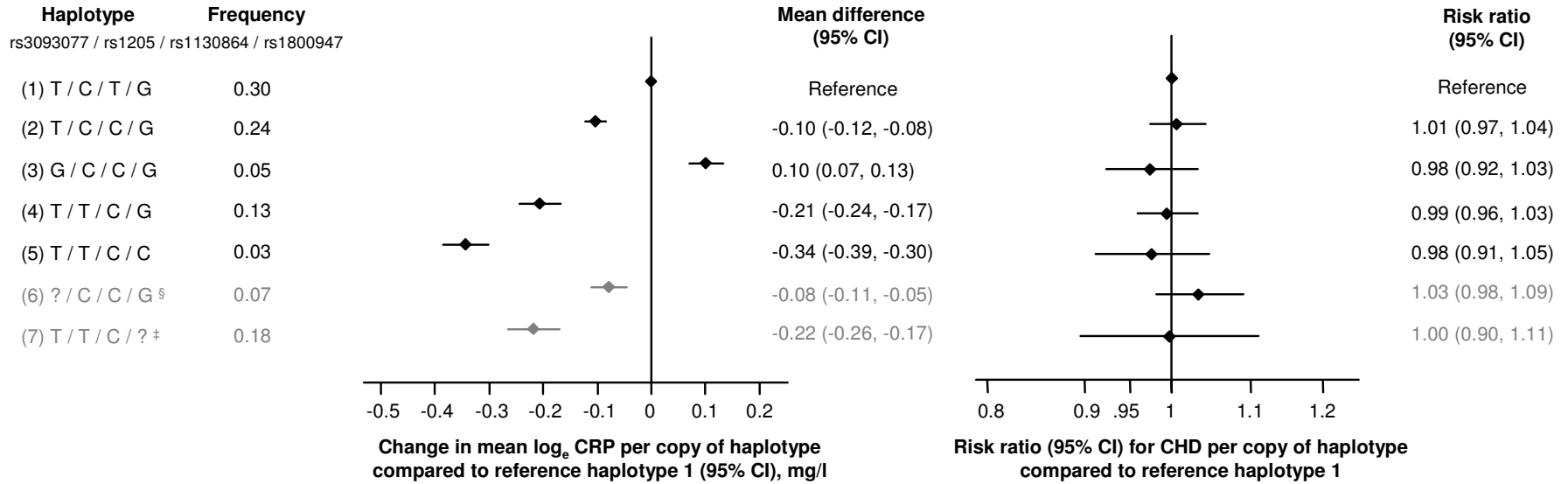
Dashed lines represent 95% confidence intervals; analyses were stratified, where appropriate, or adjusted for sex, trial arm, and ethnicity. 21,913 repeat measures of circulating CRP were available in 20,912 participants. Mean duration between repeat measurements was 2.9 (SD 1.9) years. Study-specific estimates of regression of $\log_e$ CRP on SNP, time, SNP*time adjusted for sex and ethnicity were combined using multivariate random effects meta-analysis. The SNP-CRP association is plotted over time using the combined regression coefficients.

Figure E. Associations of CRP-related haplotypes with various characteristics in individuals free of known coronary disease at time of measurement.



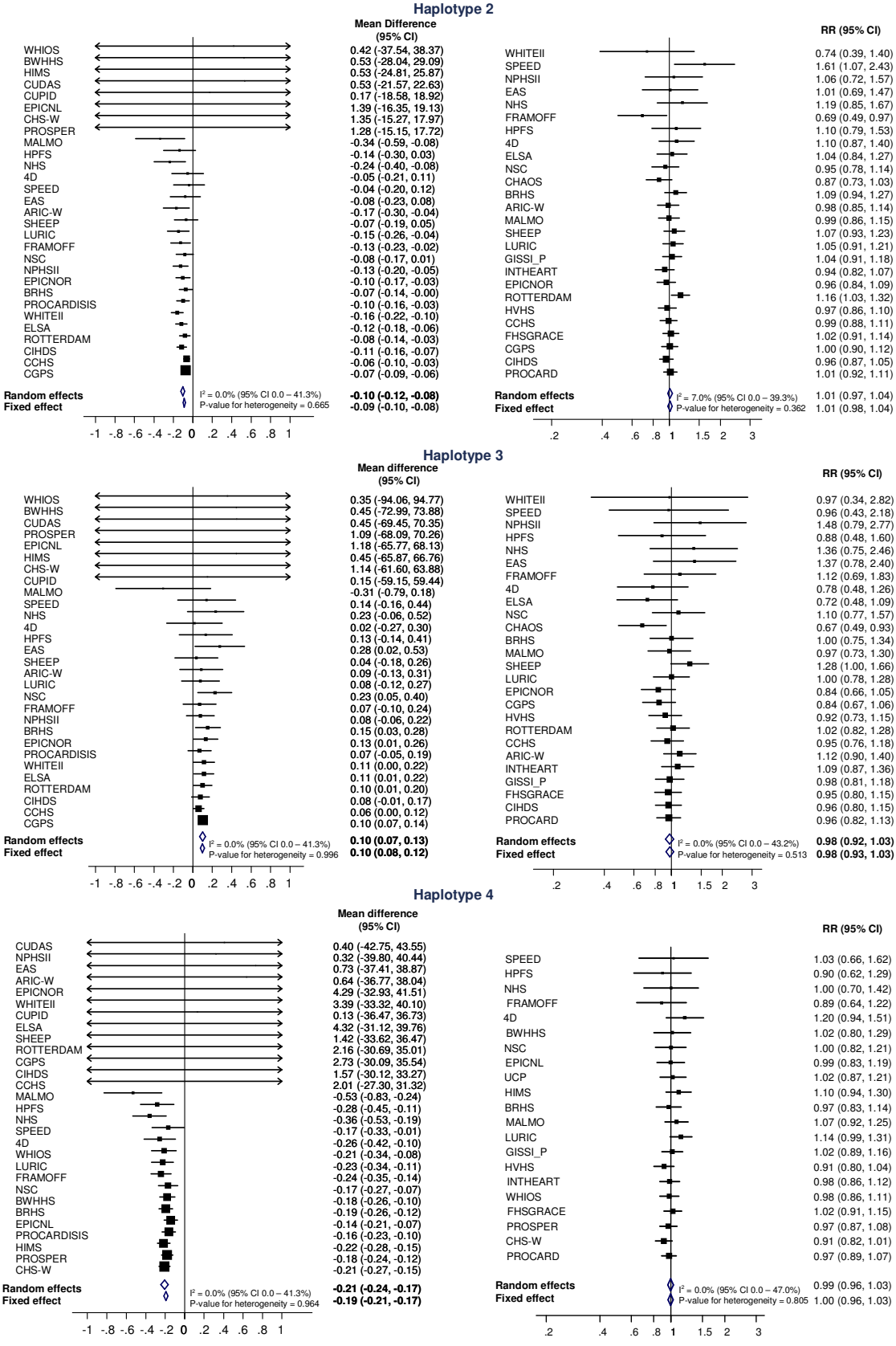
Estimates presented are based on a random-effects meta-analysis of study-specific associations of haplotypes with a panel of risk factors, assuming an additive model for haplotype effects, relative to reference haplotype 1; analyses were stratified, where appropriate, or adjusted for sex and trial arm; analyses are limited to European descent populations due to insufficient data to determine relevant haplotypes in African or Asian descent populations; CI = confidence interval; BP = blood pressure; HDL = high density lipoprotein, LDL = low density lipoprotein

Figure F. Estimates of association of each haplotype with usual levels of $\log_e$ CRP and coronary disease risk, compared to carrying two copies of reference haplotype 1.



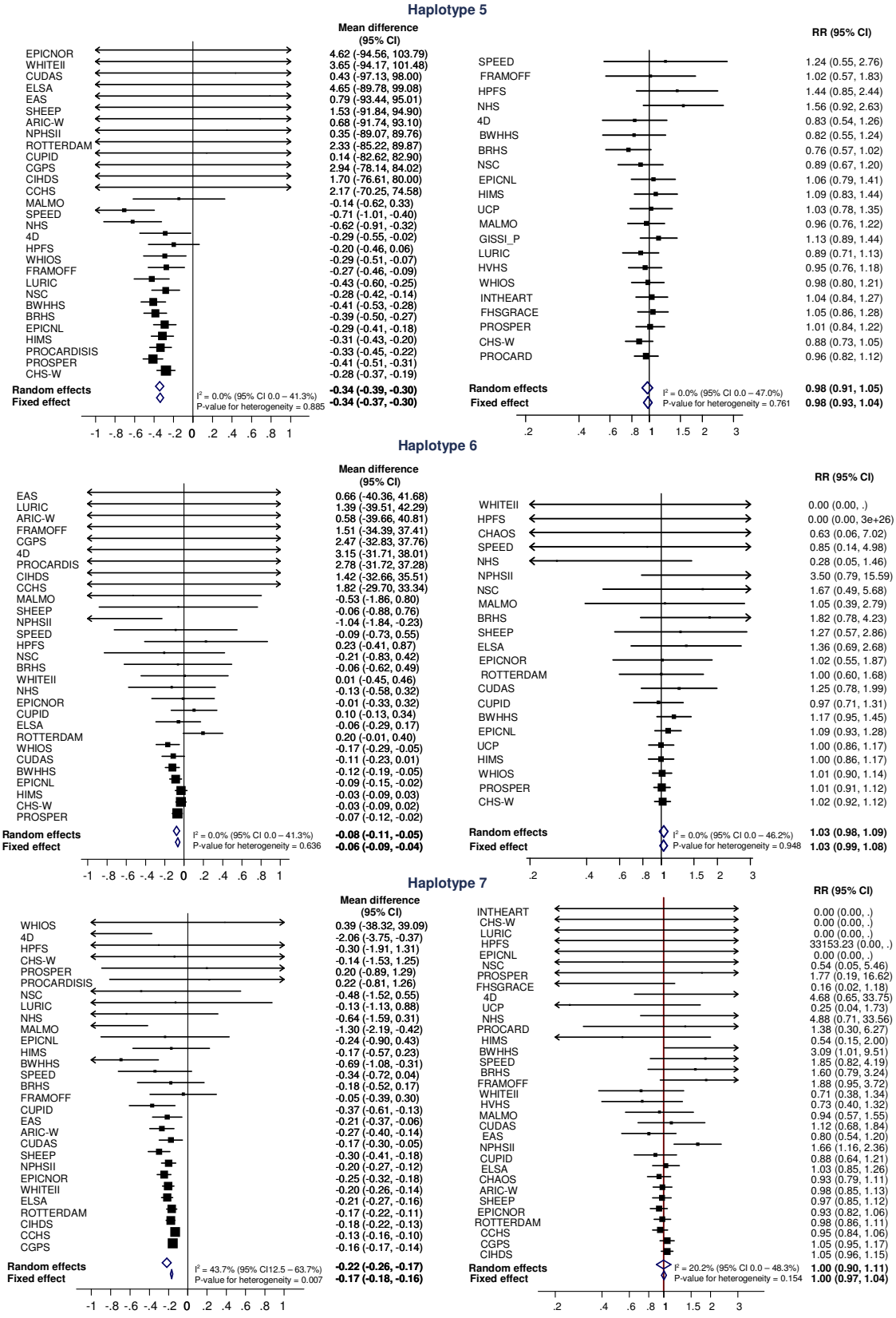
An additive haplotype model was used to estimate the effect of each haplotype relative to 2 copies of haplotype 1. CI = confidence intervals, depicted by error bars. § Haplotype 6 comprises participants who cannot be allocated to haplotypes 2 or 3 due to insufficient data on the following SNPs: rs3093077, rs3093068, rs3091244 and rs2794521. ‡ Haplotype 7 comprises participants who cannot be allocated to haplotypes 4 or 5 due to insufficient data on the rs1800947 SNP.

Figure G. Study-specific estimates for CRP and coronary heart disease risk per additional copy of haplotype compared to two copies of reference haplotype 1.



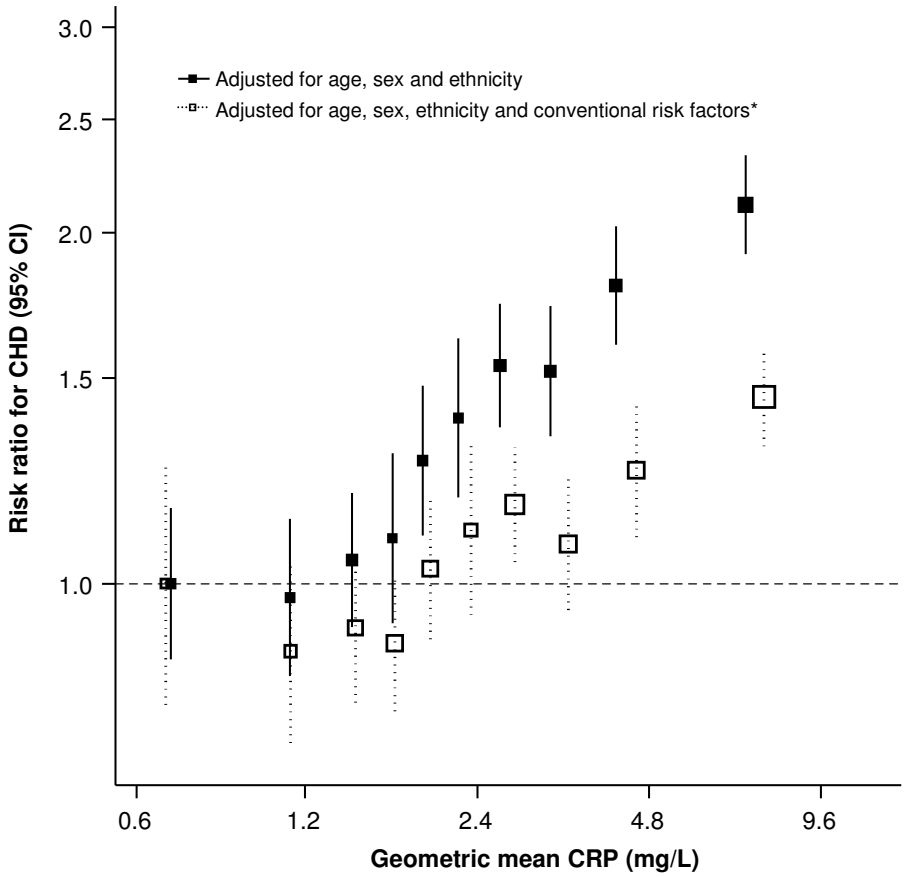
Change in $\log_e$ CRP per additional copy of haplotype (compared to two copies of haplotype 1)

Risk ratio for CHD per additional copy of haplotype (compared to two copies of haplotype 1)



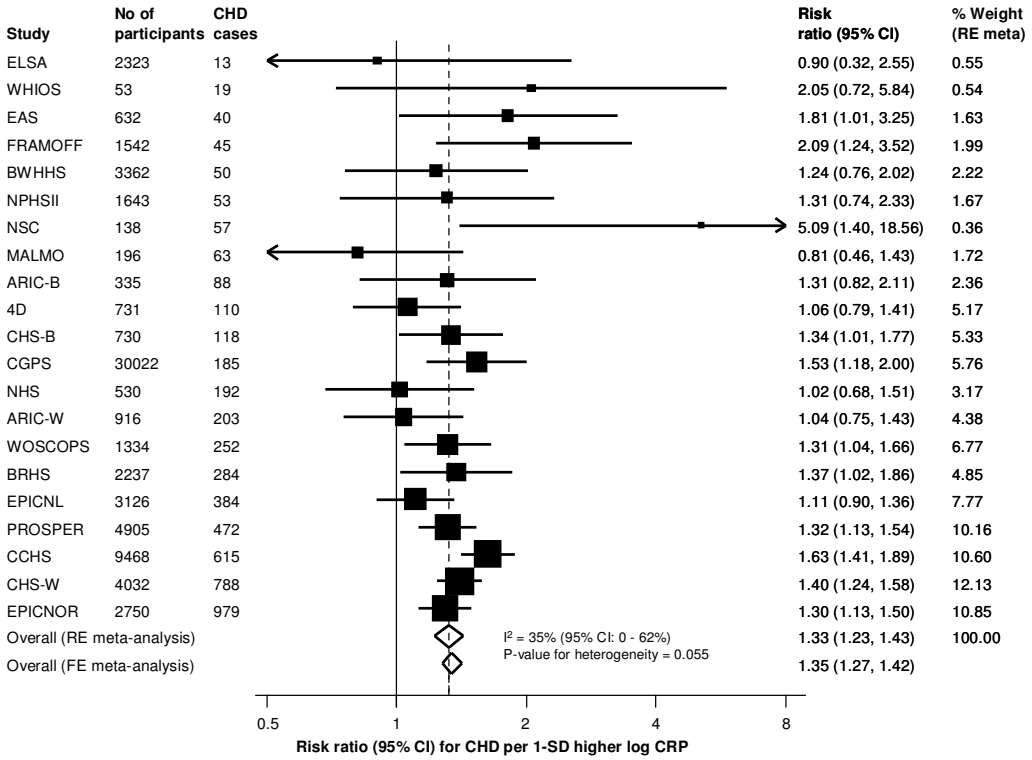
Analyses limited to participants of European descent. The sizes of data markers are proportional to the inverse of the variance of the log$_e$ risk ratios; analyses were stratified, where appropriate, or adjusted for sex and trial arm. CI = confidence interval; RR = risk ratio; study abbreviations are listed in appendix 2.

Figure H. Risk ratios for CHD across deciles of usual CRP.



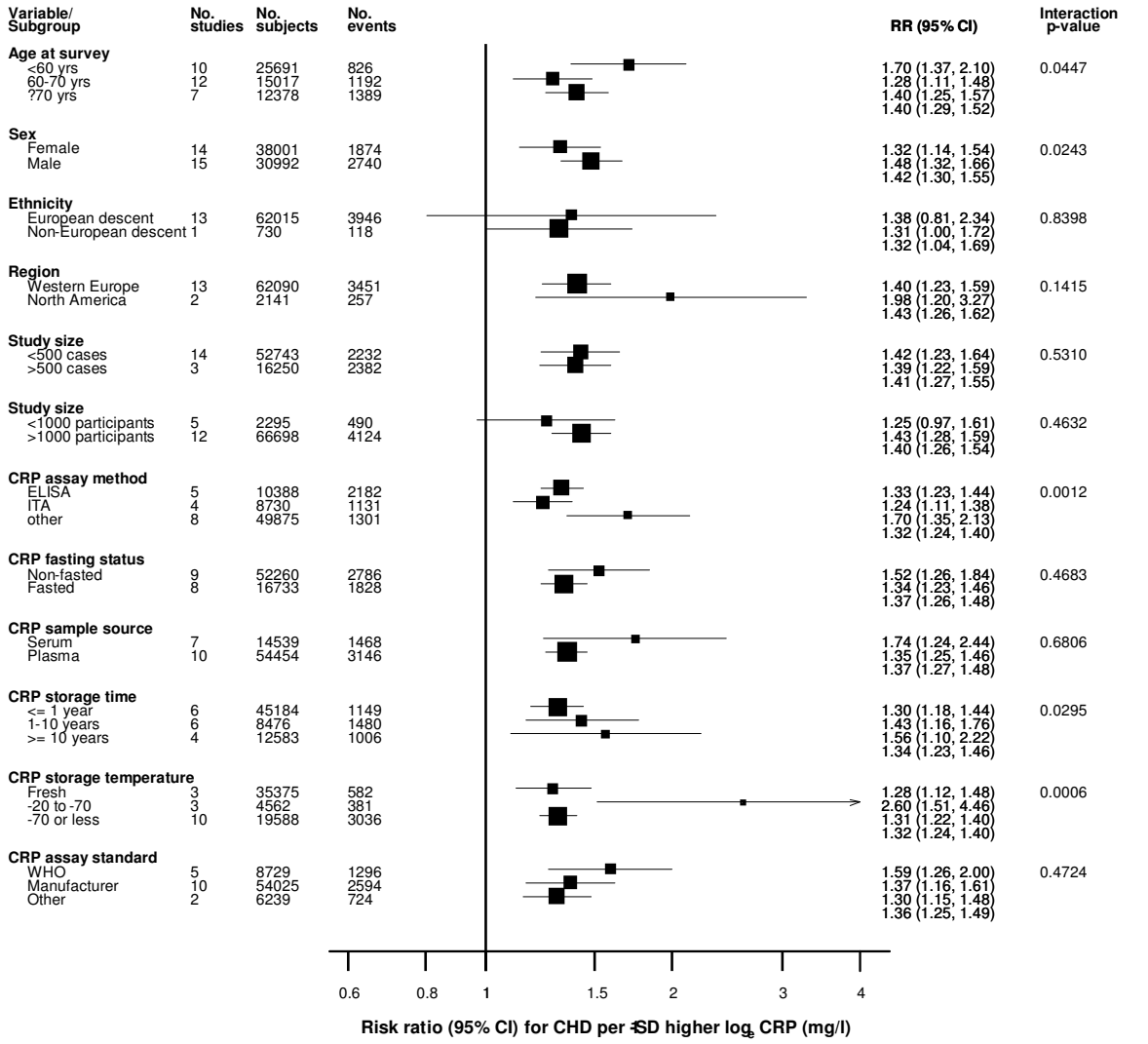
* Conventional risk factors include: systolic blood pressure, history of diabetes mellitus, body mass index, smoking status, HDL, non-HDL and triglycerides. Analyses for coronary heart disease were based on data from 71,005 participants (including 5028 cases) from 21 studies with complete data on CRP, age, sex and conventional risk factors. Sizes of data markers are proportional to the inverse of the variance of the $\log_e$ RRs. The y-axis is shown on a log scale. Referent groups are the lowest deciles of CRP. Confidence intervals (CI) were calculated using a floating absolute risk technique.

Figure I. Study-specific risk ratios for CHD per 1-SD higher usual CRP levels.



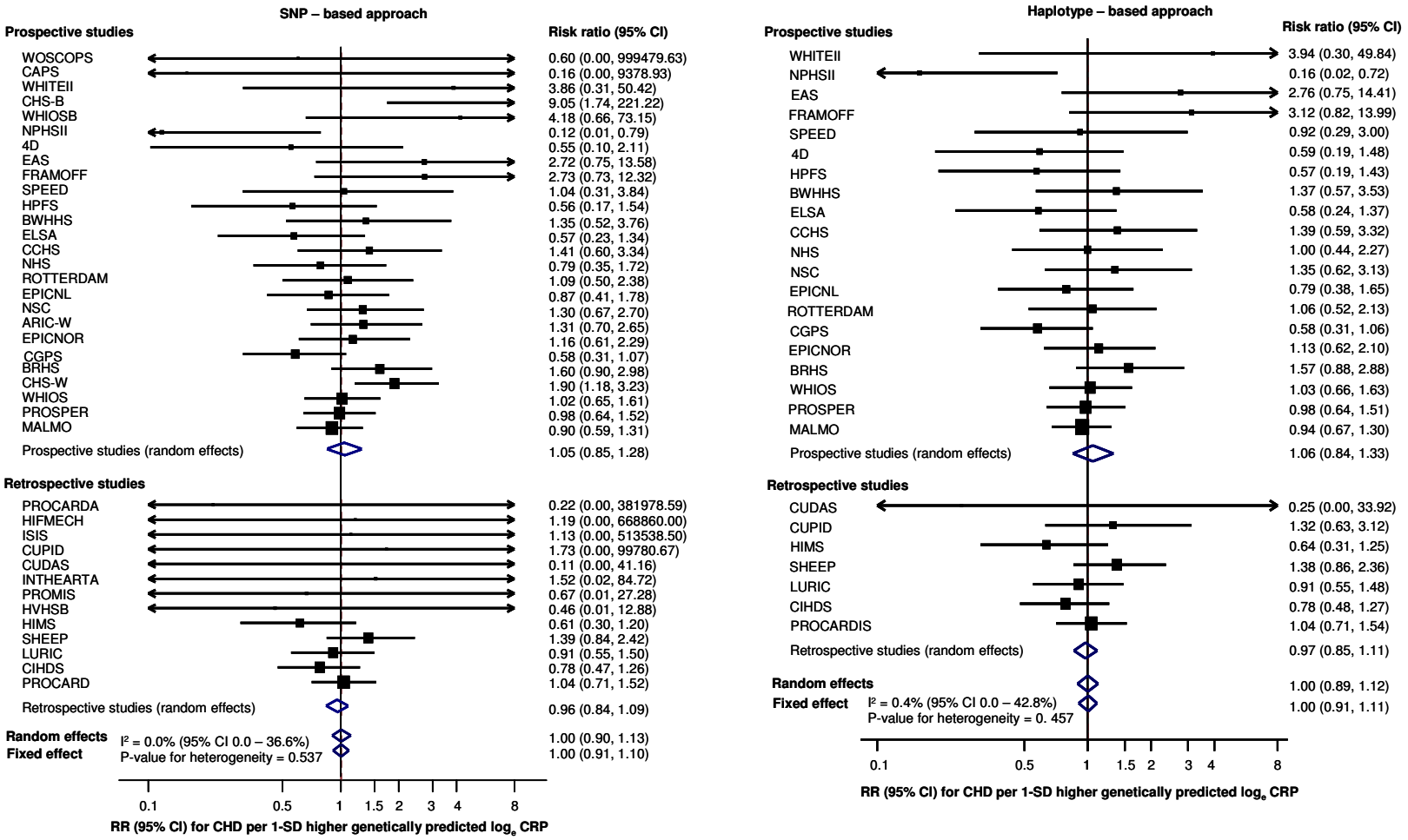
Usual levels of CRP adjusted for age, sex and usual levels of systolic blood pressure, smoking status, history of diabetes mellitus, body mass index, high density lipoprotein cholesterol (HDL-C), non-HDL-C and $\log_e$ triglyceride. The sizes of data markers are proportional to the inverse of the variance of the $\log_e$ risk ratios. CI = confidence interval; study abbreviations are listed in appendix 2.

Figure J. RRs for CHD per 1-SD higher CRP according to several individual and study level characteristics.



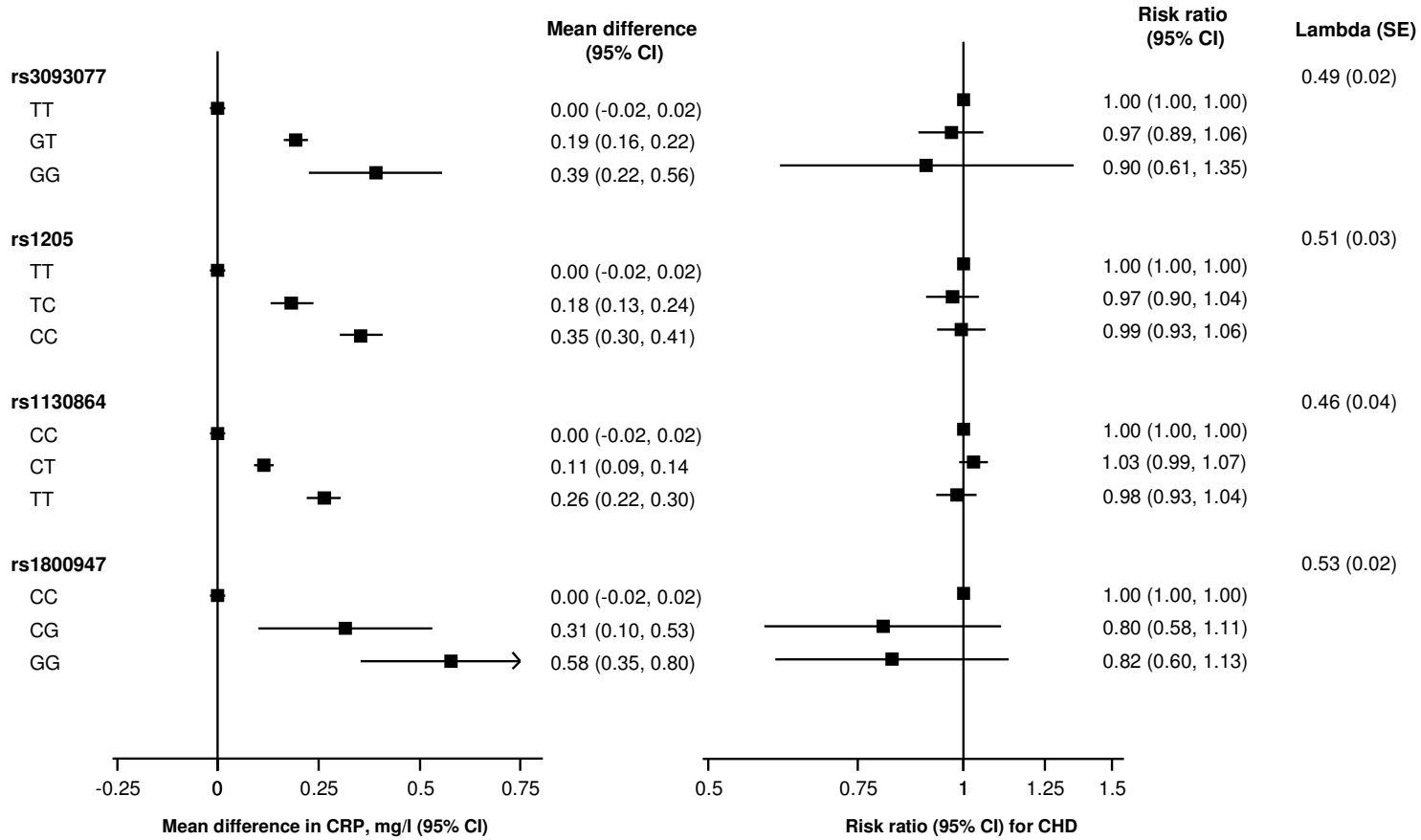
Study-specific risk ratios were adjusted for age, systolic blood pressure, smoking status, history of diabetes, body mass index, high density lipoprotein cholesterol (HDL-C), non-HDL-C and log$_e$ triglyceride and stratified, where appropriate, for sex, ethnicity and trial arm. Study-specific estimates were combined using random effects multivariate meta-analysis. Studies with fewer than 10 cases were excluded from the analyses. CI = confidence interval. The sizes of data markers are proportional to the inverse of the variance of the log$_e$ risk ratios.

Figure K. Study-specific RRs for CHD per 1-SD higher genetically predicted CRP levels using a SNP-based and a haplotype-based approach.



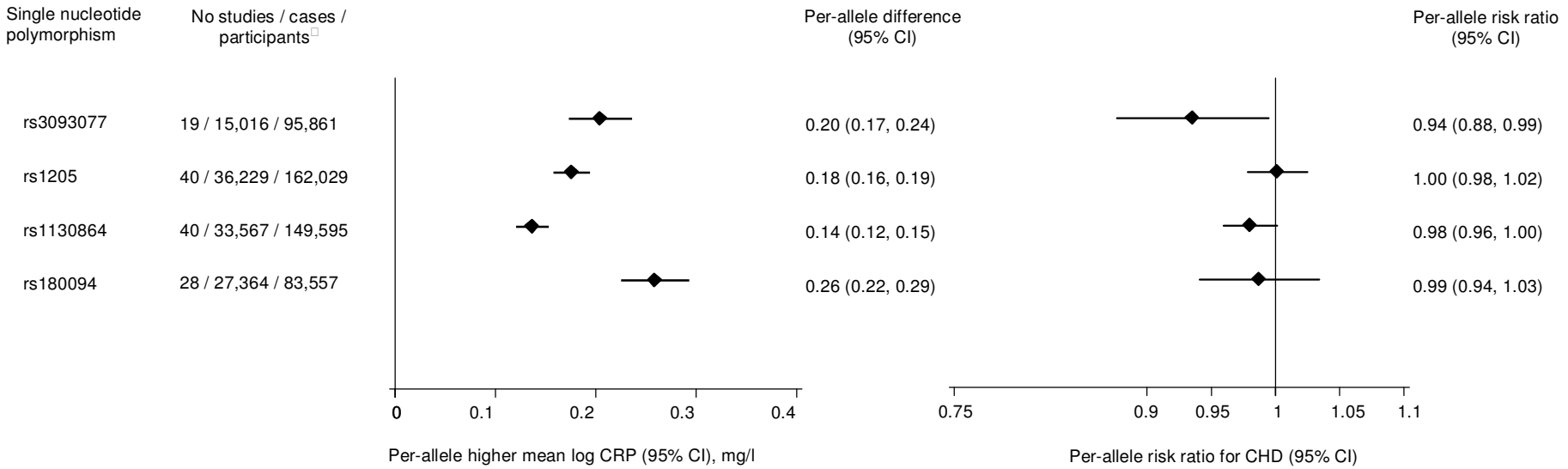
Study-specific estimates are only shown for studies with concomitant data on *CRP* variants, circulating CRP and CHD. Summary estimates presented here include data from additional studies that did not provide concomitant data. Analyses were stratified, where appropriate, or adjusted for sex, trial arm, and ethnicity. The sizes of data markers are proportional to the inverse of the variance of the risk ratios. CI = confidence interval. -W = European descent populations; -B = African descent populations, -A = Asian descent population; study abbreviations are listed in appendix 2.

Figure L. Estimates of association between each SNP and CRP and coronary disease using a model-free approach.



SNPs are coded for increased levels of circulating $\log_e$ CRP; Associations are presented for each genotype compared to a reference genotype with zero copies of the risk allele. CI indicates confidence intervals, depicted by error bars; analyses were stratified, where appropriate, or adjusted for sex, trial arm and ethnicity.

Figure M. Estimates of association of each SNP with levels of $\log_e$ CRP and coronary disease risk in individuals from European descent.



*Frequency of allele for increased levels of circulating $\log_e$ CRP (ie, risk allele). Associations are presented per additional copy of the risk allele. ‡ For SNP – CHD associations; Studies with fewer than 10 cases or fewer than 50 participants were excluded from analyses. Study-specific estimates were stratified, where appropriate, by sex, ethnicity and trial arm and combined using random effects models. Maximum available data on genetic variants, circulating CRP and coronary heart disease were used for analyses; sensitivity analyses restricted to participants with data on CRP SNPs, circulating CRP and coronary disease did not differ from the current analyses. CI = confidence intervals, depicted by error bars.