Quantile-dependent expressivity of serum high sensitivity C-reactive protein concentrations, gene-environment interactions, and genetic effects during acute phase reaction

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Background: "Quantile-dependent expressivity" occurs when the effect size of a genetic variant depends upon whether the phenotype (e.g. C-reactive protein, CRP) is high or low relative to its distribution. We have previously shown that the heritabilities (h^2) of pulmonary function, adiponectin, adiposity, lipoproteins, postprandial lipemia, and coffee and alcohol consumption are quantile-specific. Whether CRP heritability is quantile-specific remains to be determined. **Methods** Serum high sensitivity CRP concentrations from 6144 offspring-parent pairs and 2036 sibships from the Framingham Heart Study were analyzed. Quantile-specific heritability from offspring-parent (β_{OP}, $h^2=2\beta_{OP}/(1+r_{spouse})$) and full-sib regression slopes (β_{FS}, $h^2=\{(1+8r_{spouse}\beta_{FS})^{0.05}-1\}/(2r_{spouse})$) were robustly estimated by quantile regression with nonparametric significance assigned from 1000 bootstrap samples. **Results***:* Quantile-specific h^2 (±SE) increased with increasing percentiles of the offspring's age- and sex-adjusted CRP distribution when estimated from β_{OP} ($P_{trend}=0.0004$): 0.02±0.01 at the 10th, 0.04±0.01 at the 25th, 0.10±0.02 at the 50th, 0.20±0.05 at the 75th, and 0.33±0.10 at the 90th percentile, and when estimated from β_{FS} ($P_{trend}=0.0008$): 0.03±0.01 at the 10th, 0.06±0.02 at the 25th, 0.14±0.03 at the 50th, 0.24±0.05 at the 75th, and 0.53±0.21 at the 90th percentile. **Conclusion**: Heritability of serum CRP concentration is quantile-dependent, which may explain or contribute to the inflated CRP differences between *CRP* (rs1130864, rs1205, rs1800947, rs2794521 rs3091244), *FGB* (rs1800787), *IL-6* (rs1800795, rs1800796, rs8192284), *IL6R* (rs8192284), *TNF-α* (rs1800629) and *APOE* genotypes following CABG surgery, stroke, TIA, curative esophagectomy, intensive periodontal therapy, or acute exercise; during acute coronary syndrome or *Staphylococcus aureus* bacteremia; or in patients with chronic rheumatoid arthritis, diabetes, peripheral arterial disease, obesity or inflammatory bowel disease or who smoke.

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Running title: Quantile-specific CRP heritability

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Abbreviation key

AFT3	Activating transcription factor
APOA2	Apolipoprotein A2
APOE	Apolipoprotein E
β_{FS}	Full-sib regression slope
β_{OM}	Offspring mid-parental regression slope
β_{OP}	Offspring-parent regression slope
BMI	Body mass index
CABG	Coronary Artery Bypass surgery
CHD	Coronary Heart Disease
CLOCK	Circadian locomotor output cycles kaput
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
FGB	Fibrinogen beta-chain
GWAS	Genome-wide association studies
h^2	Heritability in the narrow sense
HNF1A	hepatic nuclear factor-1α
IL-6	Interleukin-6
IBD	Inflammatory bowel disease
NHLBI	National Heart Lung and Blood Institute
Q-Q plot	Quantile-quantile plot
RANK	Receptor activator of nuclear factor κB
RANKL	Receptor activator of nuclear factor κB ligand
SD	Standard deviation
SE	Standard error
SNP	Single nucleotide polymorphism
TIA	Transient Ischemic Attack
TNF-α	Tumor necrosis factor α
T2DM	Type 2 diabetes mellitus

Abstract

Background: "Quantile-dependent expressivity" occurs when the effect size of a genetic variant depends upon whether the phenotype (e.g. C-reactive protein, CRP) is high or low relative to its distribution. We have previously shown that the heritabilities (h^2) of pulmonary function, adiponectin, adiposity, lipoproteins, postprandial lipemia, and coffee and alcohol consumption are quantile-specific. Whether CRP heritability is quantile-specific remains to be determined.

Methods Serum high sensitivity CRP concentrations from 6144 offspring-parent pairs and 2036 sibships from the Framingham Heart Study were analyzed. Quantile-specific heritability from offspring-parent (β_{OP}, $h^2=2\beta_{OP}/(1+r_{spouse})$) and full-sib regression slopes (β_{FS}, $h^2=\{(1+8r_{spouse}\beta_{FS})^{0.05}-1\}/(2r_{spouse})$) were robustly estimated by quantile regression with nonparametric significance assigned from 1000 bootstrap samples.

Results*:* Quantile-specific h^2 (±SE) increased with increasing percentiles of the offspring's age- and sex-adjusted CRP distribution when estimated from β_{OP} ($P_{trend}=0.0004$): 0.02±0.01 at the 10th, 0.04±0.01 at the 25th, 0.10±0.02 at the 50th, 0.20±0.05 at the 75th, and 0.33±0.10 at the 90th percentile, and when estimated from β_{FS} ($P_{trend}=0.0008$): 0.03±0.01 at the 10th, 0.06±0.02 at the 25th, 0.14±0.03 at the 50th, 0.24±0.05 at the 75th, and 0.53±0.21 at the 90th percentile.

Conclusion: Heritability of serum CRP concentration is quantile-dependent, which may explain or contribute to the inflated CRP differences between *CRP* (rs1130864, rs1205, rs1800947, rs2794521 rs3091244), *FGB* (rs1800787), *IL-6* (rs1800795, rs1800796, rs8192284), *IL6R* (rs8192284), *TNF-*α (rs1800629) and *APOE* genotypes following CABG surgery, stroke, TIA, curative esophagectomy, intensive periodontal therapy, or acute exercise; during acute coronary syndrome or *Staphylococcus aureus* bacteremia; or in patients with chronic rheumatoid arthritis, diabetes, peripheral arterial disease, obesity or inflammatory bowel disease or who smoke.

C-reactive protein (CRP) concentrations are reflective of low-grade systemic inflammation. Higher basal concentrations are associated with increasing age, obesity, smoking, disease (Alzheimer's, cardiovascular, Type 2 diabetes mellitus (T2DM)) and female sex [1]. Prospectively, plasma CRP-concentrations predict de novo atherothrombotic cardiovascular events [2]. Basal CRP concentrations are also in part genetic, with an estimated heritability of about 35%, but with individual estimates varying greatly [3]. CRP concentration may increase by 500-fold following an acute-phase stimulus due to enhanced hepatic transcription, primarily in response to the proinflammatory cytokine interleukin 6 [4,5]. Clinically, CRP concentrations are used for the diagnosis and monitoring of inflammatory processes [4] in rheumatologic disease [6,7,8], ankylosing spondylitis [9], inflammatory bowel disease [10], pancreatitis, cardiovascular disease [5,11], cancer, and other infections [4].

"Quantile-dependent expressivity" postulates that the effects of genetic variants on phenotypes may depend on the whether the phenotype (e.g., CRP concentration) is high or low relative to its distribution. The heritability of adiposity [12,13]; plasma concentrations of triglyceride [12,14], high-density lipoproteins [12,15,16], and adiponection [17]; pulmonary function [18]; and intakes of alcohol [19] and coffee [20] are quantile dependent, whereas height and the intakes of other macronutrients are not [12,13,19]. A particularly compelling case for quantile-dependent expressivity is the linear increases in the effect sizes of single nucleotide polymorphisms (SNP) with postprandial increases in triglyceride [21] and adiponectin [17] concentrations during lipemia–compelling because their concordant increases are demonstrable within individuals and within hours, exclusive of other sources of temporal and between-subject variation. Many purported examples of gene-environment interactions may be attributable to quantile-dependent expressivity when subjects are selected for conditions that distinguish high vs. low phenotype values [16]. With respect to precision-medicine, genetic markers for identifying patients most likely to benefit from medications or diet may also be artifacts of quantile-dependent expressivity when the markers simply track the change heritability associated with drug-, diet-, or behavior-induced changes in the average phenotype value [15,14,21].

It is not known whether CRP heritability is quantile dependent or whether the CRP gene-environment interactions reported by others are consistent with quantile-dependent expressivity.

Therefore, quantile-dependent expressivity of CRP was investigated by applying quantile regression [22,23] to sibships and offspring-parent pairs from the Framingham Study [24,25] to estimate heritability in the narrow sense (h^2 [26]) at different quantile of the CRP distributions. Heritability of untransformed CRP concentrations was studied because only a small proportion of CRP variation is attributable to specific SNPs [27], because quantile regression does not require statistical normality [22,23], and because no biological justification for logarithmic transforming CRP concentrations has heretofore been provided. The discussion furthers this investigation by re-examining published examples of CRP gene-environment interactions from the perspective of quantile-dependent expressivity. Of particular interest are the effects of genetic variants on CRP concentrations during its acute phase response to infections, trauma, and surgery because these may exceed basal CRP levels by over 100-fold [4,28,29]. Quantile-dependent expressivity hypothesizes that genetic effects on CRP concentrations should increase in accordance with changing CRP concentrations during intermediate and peak increases in it's acute phase concentrations.

Methods

The Framingham Study data were obtained from the National Institutes of Health FRAMCOHORT, GEN3, FRAMOFFSPRING Research Materials obtained from the National Heart, lung, and Blood (NHLBI) Biologic Specimen and Data Repository Information Coordinating Center. The hypothesis tested not considered as part of the initial Framingham Study design and is exploratory. The Framingham Heart Study included three cohorts. The Original Cohort includes 5209 thirty to fifty-nine year old men and women who lived in Framingham, Massachusetts. The Offspring Cohort is made up of the 5,124 adult children of the Original Cohort and their spouses. They were initially examined between 1971 and 1975, reexamined eight years later, and then every three to four years thereafter [24]. The Third Generation Cohort are the children of the Offspring Cohort [25]. Subjects used in the current analyses were at least 16 years of age and were self-identified as non-Hispanic white. Phlebotomy was performed on fasting participants who had rested for 5 to 10 minutes in a supine position, typically between 8 and 9 AM. Specimens were stored at −80°C without freeze-thaw

cycles until assay. Serum high-sensitivity CRP concentrations were measured with a Dade Behring BN100 nephelometer (Deerfield, IL) with a Kappa statistic of 0.95 for 146 samples run in duplicate [30]. Plasma CRP concentrations were measured for examinations 2, 6, 7, 8, and 9 of the Offspring Cohort, and examinations 1 and 2 of the Third Generation Cohort.

Our analyses of these data were approved by Lawrence Berkeley National Laboratory Human Subjects Committee (HSC) for protocol "Gene-environment interaction vs. quantile-dependent penetrance of established SNPs (107H021)" LBNL holds Office of Human Research Protections Federal wide Assurance number FWA 00006253. Approval number: 107H021-13MR20. All surveys were conducted under the direction of the Framingham Heart Study human use committee guidelines, with signed informed consent from all participants or parent and/or legal guardian if <18 years of age.

Statistics Age and sex adjustment was performed in each cohort separately using standard least-squares regression with female (0,1), age, age^2, female x age, and female x age^2 as dependent variables. Individual subject values were taken as the average of the age and sex-adjusted concentrations over all available exams. Offspring-parent regression slopes (β_{OP}) were computed using parents from the Offspring Cohort and their children from the Third Generation Cohort. Sibships were identified from the Offspring and Third Generation Cohorts. Full-sibling regression slopes (β_{FS}) for were obtained by forming all $k_i(k_i-1)$ sibpair combinations for the k_i siblings in sibship i and assigning equal weight to each sibling [31].

Simultaneous quantile regression was performed using the sqreg command of Stata (version. 11, StataCorp, College Station, TX). One thousand bootstrap samples were drawn to estimate the variance-covariance matrix for the 91 quantile regression coefficients between the 5th and 95th percentiles of the offspring's distribution [23]. Post-estimation procedures (test and lincom) were used to test linear combinations of the slopes after estimation with Σk_i-2 degrees of freedom for offspring-parent regression slopes and $\Sigma(k_i-1)$ degrees of freedom for sibship regression slopes. Quantile-specific expressivity was assessed by: 1) estimating quantile-specific β-coefficients (±SE) for the 5th, 6th,…, 95th percentiles of the sample distribution; 2) plotting the quantile-specific β coefficient vs. the quantile of the trait distribution; and 3) testing whether the resulting

graph was constant, or changed as a linear, quadratic, or cubic functions of the percentile of the trait distribution using orthogonal polynomials [32]. Falconer and Mackay's formula [26] equates heritability in the narrow sense (h^2) to $h^2= 2\beta_{OP}/(1+r_{spouse})$, where r_{spouse} is the spouse correlation and to $h^2= \{(1+8\beta_{FS}r_{spouse})^{0.5}-1\}/2r_{spouse}$ under specific restrictive assumptions. "Quantile-specific heritability" refers to the heritability statistic, whereas "quantile-specific expressivity" is the biological phenomenon of the trait expression being quantile-dependent.

The results from other studies were re-interpreted from the perspective of quantile-dependent expressivity using genotype-specific mean CRP concentrations presented in the original articles or by extracting these values from graphs using the Microsoft Powerpoint formatting palette (version 12.3.6 for Macintosh computers, Microsoft corporation, Redmond WA) as previously described [21]. Almost every paper presents median or geometric means computed from back-transformed logarithmic CRP-concentrations. The weighted average of the median values or geometric means were used to approximate average concentration by condition or pooled genotypes.

Data availability: The data are not being published in accordance with the data use agreement between the NIH National Heart Lung, and Blood Institute and Lawrence Berkeley National Laboratory. However, the data that support the findings of this study are available from NIH National Heart Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center directly through the website https://biolincc.nhlbi.nih.gov/my/submitted/request/ [33]. Restrictions apply to the availability of these data, which were used under license for this study. Those wishing a copy of the data set should contact the Blood Institute Biologic Specimen and Data Repository Information Coordinating Center at the above website, where they can find information on human use approval and data use agreement requiring signature by an official with signing authority for their institute. The public summary-level phenotype data may be browsed at the dbGaP study home page [34].

Results

208

209 *Traditional estimates of familial concordance and heritability* Table 1, which displays the
210 sample characteristics, shows that average CRP were significantly higher in women than men.
211 As expected CRP-concentrations were correlated positively with BMI (r=0.38) and were higher
212 in smokers than nonsmokers (difference±SE: 0.54±0.18, P=0.008) when age and sex adjusted.
213 The spouse correlation for adjusted CRP concentrations was negligible (r_{spouse}=-0.0013) for
214 untransformed CRP and weak (r_{spouse}=0.0482) for log CRP. There were 1718 offspring with one
215 parent and 1232 offspring with two parents. The offspring-parent regression slope for adjusted
216 CRP concentrations (β_{OP}±SE: 0.06±0.01) corresponds to a heritability (h^2) of 0.11±0.02. There
217 were 5703 full-sibs in 2036 sibships with age and sex-adjusted CRP concentrations, whose full-
218 sib regression slope (β_{FS}) was 0.08±0.02, which from Falconer's formula, corresponds to a
219 heritability of h^2=0.15±0.03. Heritability in female offspring was somewhat greater than in male
220 offspring whether computed from β_{OP} (0.13±0.03 vs. 0.08±0.03) or β_{FS} (0.20±0.06 vs.
221 0.10±0.06), but not significantly so. Heritabilities for log CRP derived from β_{OP} (0.43±0.03) or
222 β_{FS} (0.37±0.03) were consistent with published reports [3].
223
224 *Quantile-dependent expressivity*. The offspring-parent regression slopes at the 10th, 25th, 50th,
225 75th, and 90th percentiles of the offspring's CRP distribution are presented in Figure 1A, along
226 with their corresponding heritability estimates. The slopes get progressively greater with
227 increasing percentiles of the CRP distribution. The heritability at the 90th percentile was 0.33 or
228 nearly 18-fold greater than the heritability at the 10th percentile ($P_{difference}$=0.001). Figure 1B,
229 which presents these slopes with those of the other percentiles between the 5th and 95th
230 percentiles, shows heritability increased linearly (i.e., slope±SE: 0.0038±0.0010, P_{linear}=0.0004)
231 with increasing percentiles of the offspring's distribution. There was no statistically significant
232 evidence of nonlinearity (i.e., $P_{quadratic}$=0.09; P_{cubic}=0.31). Quantile-specific heritability was
233 individually significant (P≤0.04) for all percentiles between the 17th and 92nd percentiles of the
234 offspring's distribution. If the heritabilities over all quantiles were constant, then the line
235 segments in Figure 1A would be parallel, and Figure 1B would show a flat line with zero slope.
236 Figure 1C displays the quantile regression analysis for h^2 estimated from full-sib regression
237 slopes (β_{FS}). Each one-percent increase in the CRP distribution was associated with a

238 0.0054±0.0016 increase in heritability and a 0.0027±0.0008 increase in the full-sib regression
239 slope (P_{linear}=0.0008).
240
241 Figure 2 presents quantile-specific heritability for logarithmically transformed CRP. The
242 transformation replaced the significant linear trend for a quadratic trend showing the greatest
243 heritability near the median and declining heritability moving away from the median when
244 estimated from offspring-parent pairs ($P_{quadratic}$=0.001) and full siblings ($P_{quadratic}$=0.06).
245
246 Discussion
247
248 Our analyses of the Framingham Heart Study provide consistent evidence for quantile-specific
249 heritability of untransformed serum CRP concentrations from both offspring-parent and full-sib
250 age- and sex-adjusted values. Heritability at the 90th percentile of the CRP distribution
251 (0.33±0.10) was 18-fold greater at the 10th percentile (0.02±0.01) when estimated from
252 offspring-parent pairs, and 15-fold greater when estimated from full sibs. These are substantial
253 differences that exceed those reported for high-density lipoprotein cholesterol (48% h^2 increase
254 in going from the 10th to 90th percentile) [15], adiponectin (72%) [17], or triglycerides
255 concentrations (13-fold) [14], or BMI (3.1-fold) [13]. We analyzed heritability because it
256 represents 30% to 50% of CRP additive the genetic variance vis-à-vis the 5% of the CRP
257 variance attributable to 18 specific loci identified by Dehghan et al. as genomewide significant
258 [27].
259
260 There are, however, important limitations to our analysis of familial phenotypes: 1) heritability
261 lacks the specificity of directly measured genotypes; and 2) Falconer's formula probably do not
262 adequately address the true complexity CRP genetics. These concerns may be partly addressed
263 by re-evaluating other published studies that measured genetic variants directly, from the
264 perspective of quantile-dependent expressivity. A number of examples presented below show
265 larger genetic effect sizes in association with the higher CRP concentrations of low-level
266 inflammation, consistent with quantile-dependent expressivity. Additional examples are
267 presented that suggest the phenomenon may extend to CRP acute phase reaction. To the best of
268 our knowledge, quantile-specific heritability has never been formally acknowledged fundamental

property of CRP genetics, although several authors do point out that genetic variant affecting acute phase CRP response are also evident for basal CRP concentrations [29,35,6].

The CRP gene is located on chromosome 1q32 and includes two exons and one intron. *CRP* genetic variants that are reported to affect CRP concentrations include rs2794521 (−717A>G), rs3091244 (−286C>T>A), rs1800947 (+1059G>C), rs1130864 (+1444C>T) and rs1205 (+1846G>A). Rs2794521 and rs3091244 are located in the promoter region, rs1800947 in exon 2, rs1130864 in the 3' untranslated region, and rs1205 occur in the 3′ flanking region [36]. Rs3091244 has been shown to affect CRP transcriptional activity in vitro [37]. Rs1800947 is silent [38]. Higher basal CRP concentrations are reported for the rs3091244 A-allele, rs1800947 GG-homozygotes, rs1130864 T-allele, and the rs1205 G-allele [29]. Interleukin-6 (IL-6), the primary inflammatory cytokine stimulus for CRP [39], has two polymorphisms whose minor alleles are reported to increase CRP concentrations: rs1800795 (−174G>C) [40] and rs1800796 (-572G>C) [41]. The tumor necrosis factor α (TNF-α) rs1800629 (G-308A) polymorphism has been shown to increased TNF-α production in vitro [42], and in turn, stimulate hepatic CRP production [43]. Carriers of the APOE ε4 allele have lower CRP-concentrations than non-carriers [44,45,46,47].

Adiposity BMI, waist circumference and fat body mass are associated with significantly higher CRP concentrations, accounting for five to seven percent of log CRP variation [48]. Visceral adipose tissue in particular promotes higher IL-6 concentrations [49] and low-grade CRP inflammation [50,51]. CRP concentrations decrease an average of 0.13 mg/L per kg of weight loss [52].

Consistent with quantile-dependent expressivity and the higher CRP concentrations of obese subjects, Friedlander et al. [53] reported that the heritability of untransformed CRP was nearly three-fold greater in obese than nonobese subjects (0.670 vs. 0.256). In addition, data reported by Farup et al. [54] showed that CRP difference between non-carriers and carriers of the *APOE* ε4-allele decreased linearly as average CRP concentrations decreased in morbidly obese patients undergoing weight loss (Figure 3A). Specifically, the genotype difference was greatest at baseline (ε4- vs. ε4+: 8.2 vs. 5.3 mg/L, p=0.004) when average CRP was highest, intermediate

six months later (5.2 vs. 3.1 mg/L, p=0.007) for the lower average CRP from losing 3.0 kg/m^2 on a conservative weight loss program, and smallest (1.3 vs. 0.7 mg/L, p=0.03) when average CRP was least after losing an additional 10.7 kg/m^2 during the year following bariatric surgery.

Cross-sectional data support these results. Pramudji et al. [55] reported that CRP concentrations increased with the number of C-alleles of the IL-6 rs1800795 polymorphism for obese (P=0.02) but not non-obese Indonesians (P=0.64), consistent with the higher average CRP concentrations of those who were obese (2.26 vs. 0.49 mg/L, Figure 4A). Teng et al. [56] reported that the effects of obesity on Taiwanese CRP concentrations differed significantly by rs2794521 ($P_{interaction}$=0.03, Figure 4B histogram) and rs1800947 ($P_{interaction}$=0.02, Figure 4C histogram), and possibly rs1205 (Figure 4D histogram). Correspondingly, average CRP levels were approximately twice as high in the obese than non-obese subjects, and as shown in the associated line graphs, the interactions could be attributed to a larger genetic effect size at higher average CRP concentrations. Studies by Eiriksdottir et al. [48], Todenti et al. [57], and Wang et al. [58] all present results consistent with a larger rs1205 genotype differences at the higher average CRP concentrations of those who are more overweight. Eiriksdottir et al. reported that the log CRP difference between rs1205 G-carriers and AA homozygotes increased as CRP levels increased with increasing BMI in both men ($P_{interaction}$=0.05) and women ($P_{interaction}$=0.09) [48].

Smoking The Speedwell Survey of British men reported that average CRP increased significantly from those who never smoked (1.13 mg/L), to those who averaged 1-14 (1.87 mg/L), 15-24 (2.32 mg/L), and greater than 25 cigarettes/day (2.05 mg/L) [59]. Consistent with quantile-dependent expressivity, Friedlander et al. [53] reported that the heritability of untransformed CRP was 4-fold larger in smokers than nonsmokers (0.863 vs. 0.193), and Retterstol et al [60] reported a higher MZ twin correlation in smokers than nonsmokers (r=0.49 vs. r=0.34).

Luetragoon et al. [61] reported a significant CRP difference between smokers and nonsmokers in the *CRP* rs1800947 CC homozygotes (P=0.03) but not G-allele carriers (P=0.67, Figure 4E histogram), corresponding to a larger genotype difference for the higher CRP concentrations of the smokers vs. nonsmokers (2.57 vs. 1.34 mg/L, P=0.009 line graph). Shin et al. [62] reported a significant interaction between smoking and the IL-6 rs1800796 promoter polymorphism in their

effect on CRP concentrations ($P_{interaction}$=0.04). Whereas the Figure 4F histogram shows that the effect of smoking on CRP was greater in GG homozygotes, the line graph suggests that the results could also be interpreted in part as a larger genetic effect size at the higher CRP concentrations of the smokers. Data presented by Gander et al. in their figure 1 [63] showed a greater smoking effect in carriers of the A-allele than GG homozygotes of the TNF-α rs1800629 polymorphism (Figure 5A), corresponding to a larger difference between genotypes at the higher average concentrations of the smokers.

Physical activity. Brull et al. [64] reported overall mean CRP concentrations in British army recruits increased significantly following an intensive 48-hour final military endurance exercise (1.14 post-exercise vs. 0.59 mg/L at baseline). Figure 5B shows that the exercise-induced CRP increases were over 2.5-fold greater in rs1130864 TT homozygotes than C-allele carriers (histogram), and that the difference between genotypes was two-fold greater 2 hours post exercise than at baseline (1.28 vs. 0.49 mg/L difference) corresponding to the higher post-exercise mean concentrations (line graph).

Diet. A Mediterranean-style diet that is rich in monounsaturated fat, polyunsaturated fat, and fiber was reported to significantly decrease CRP concentrations relative to a prudent diet [65]. In T2DM, Keramet et al. [66] reported a greater effect of monounsaturated fat intake on CRP concentrations in CC homozygotes of the APOA2 rs5082 polymorphism than in carriers of the T-allele (Figure 5C histogram, $P_{interaction}$=0.02). The line graph suggests there were greater genotype differences and average CRP concentrations below vs. above median intake of monounsaturated fatty acids.

Our analysis of Carvalho-Wells et al. data suggest that *APOE* ε3ε3 subjects who switched from an 8-wk low fat to an 8-wk high fat diet had somewhat greater increases in CRP than ε3ε4 subjects [67]. Figure 5D shows a larger difference between genotypes at the significantly higher CRP concentrations of the high-fat vis-à-vis the low-fat diet. Supplementing the high-fat diet with 3.45 g of DHA-rich oil eliminated the genotype difference (not displayed).

Gomez-Delgado et al. [68] reported that decreases in CRP concentrations from switching from the basal to a low-fat diet were greater in CC-homozygotes of the circadian locomotor output cycles kaput (CLOCK) rs4580704 polymorphism than in carriers of the G-allele ($P < 0.001$). Cross-sectionally, the histogram of Figure 5E shows that the CRP difference between consuming a low fat diet vs. a Mediterranean diet for one year was greater for carriers of the G-homozygotes (histogram), while the line graph shows that the difference between rs4580704 genotypes was greater for the higher CRP concentrations of the low-fat diet than for the lower CRP concentrations of the Mediterranean diet.

Elevated Coronary Heart Disease (CHD) risk Zee and Ridker [69] reported that baseline median CRP concentrations in healthy men who experienced their first arterial thrombosis (nonfatal MI, nonfatal stroke, or cardiovascular death) during 8.6-year follow-up were significantly higher than matched controls who remained event free (1.43 vs. 1.23 mg/L, $P=0.006$). The CRP difference between those experiencing and not experiencing thrombosis was greater in rs1800947 GG homozygotes than GC heterozygotes (Figure 5F histogram), which corresponded to a larger genotype difference at the higher median baseline CRP concentrations of those with a thrombotic destiny (Figure 5F line graph) [69].

Myocardial infarction survivors. Data reported by Kovacs et al. [70] showed that the CRP difference between carriers and non-carriers of the rs3091244 A-allele was greater in myocardial infarction survivors ($P<0.02$) than matched controls (NS), consistent with the higher median concentrations of the survivors (1.46 vs. 0.96 mg/L, Figure 6A).

Stroke Ben-Assayag et al. [71] reported that CRP differences between G-allele carriers and AA homozygotes of the rs2794521 polymorphism were significant at admission following a stroke or transient ischemic attack (2.02 vs. 1.73 mg/L, $P=0.03$) when average CRP concentrations were elevated (1.71 g/L) but not six-months later (1.44 vs. 1.43 mg/L, $P=0.98$) when average CRP concentrations were lower (1.43 g/L). The CRP change between admission and six-month follow-up was significantly greater in the G-allele carriers than AA homozygotes ($P=0.05$).

Type 2 diabetes mellitus Subclinical systemic inflammation contributes to the etiology of insulin resistance [72], which may explain the increased diabetes risk associated with elevated CRP concentrations prospectively [73]. The missense variant rs8192284 of the interleukin-6 receptor (IL6R) gene is reported to be strongly associated with IL-6 and CRP concentrations in genomewide association studies [74]. Qi et al. reported a significant interaction ($P_{interaction}$=0.03) between diabetes and rs8192284 in their affect on CRP concentrations (Figure 6B histogram) [74]. However, diabetic had higher CRP concentrations than non-diabetics, and the interaction could be due to the larger genetic effect size at the higher average CRP concentrations of the T2DM (Figure 6B line graph).

Peripheral arterial disease (PAD) The IL-6 rs1800795 polymorphism has been suggested to affect IL-6 expression and influence the development of PAD, a vascular pathology associated with T2DM [75]. Data reported by Libra et al. [75] showed that the CRP difference between T2DM patients with and without PAD was greater in GG homozygotes than C-allele carriers (2.0±0.34 vs. -0.16±0.26 mg/L, Figure 6C histogram). Average CRP concentrations were higher in the PAD+ than PAD- patients (3.22±0.16 vs. 2.06±0.13 mg/L), and correspondingly, the difference between genotypes was greater for PAD+ than PAD- (3.25±0.32 vs. 1.09±0.28 mg/L).

Sex Females have higher CRP concentrations than men, which may be hormonal, i.e., female CRP concentrations correlate positively with esterdiol levels, and the odds of CRP falling above the median doubles with each standard deviation increment in endogenous esterdiol [76]. Higher female CRP may explain the greater estimated heritability we observed in female than male offspring (0.13 vs. 0.08) and female than male sibling (0.20 vs. 0.10), the greater heritability of untransformed CRP in females than males reported by Friedlander et al. (0.352 vs. 0.150) [53], and the higher within-pair correlations in female than male MZ twins reported by Retterstol et al. (r=0.44 vs. r=0.31) [60].

Race CRP concentrations tend to be higher in Blacks than other racial groups [77], i.e., mean CRP concentrations estimated from meta-analysis are 2.61 mg/L for African-Americans, 2.51 for Hispanics, 2.03 for White Americans, and 1.01 for East Indians [78]. European ancestry is negatively correlated with age-adjusted CRP in both African-Americans ($p<0.0001$) and

Hispanic Americans (p=0.001) [79]. Quantile-dependent expressivity may contribute to the higher heritability of lnCRP in Blacks than whites (53% vs. 31%) reported by Wu et al. [80]

Acute phase response Rapid hepatic synthesis of CRP occurs as part of the acute phase response to infection, injury or trauma [4,28]. The increase can be 1000-fold [4,28]. Consistent with quantile-dependent expressivity, several SNPs show effects on CRP that are greatly accentuated during acute phase response vis-à-vis their basal concentrations, and intermediate effects during intermediate transitional concentrations.

Coronary artery bypass grafting (CABG) surgery produces a strong inflammatory response with substantially increased CRP, fibrinogen, and IL-6 circulating concentrations [81,64]. Wypasek et al. [81] reported that CRP increased from a pre-operative concentration of 4.3±0.1 mg/L to 62.5±4.2 mg/L five to seven days following CABG surgery ($P < 0.0001$). Consistent with quantile-dependent expressivity, the line graph of Figure 6D shows that the increase in mean concentrations coincided with substantially greater post-operative CRP differences between carriers and non-carriers of the C allele of the fibrinogen beta-chain (*FGB*) -148C>T rs1800787 polymorphism (70.4±5.0 vs. 51.6±4.25 mg/L, p=0.005) vis-à-vis their much smaller pre-operative difference (7.49±1.2 vs. 4.26±1.0 mg/L, p=0.04). Another report by Wypasek et al. [82] showed that post-operative CRP concentrations were significantly higher in C-allele carriers than non-carriers of the IL-6 rs1800795 polymorphism (56.39±4.27 versus 36.60±7.78 mg/L, P =0.03) when average CRP concentrations were elevated (54.92±35.02 mg/L), which was substantially greater than the pre-operative difference between genotypes (4.1 ± 0.35 vs. 2.4 ± 0.59 mg/L, P =0.02) when average CRP concentrations were much lower (3.71±4.11, Figure 6E).

Mathew et al. [83] reported a substantial increase in mean CRP concentrations following CABG and cardiopulmonary bypass that was significantly affected by the rs1800947 polymorphism (Figure 6F, P=0.01). Twenty-four hour post cross-clamp CRP levels were significantly higher in GG homozygotes than CC homozygotes and CG heterozygotes ($P<0.001$). The greater post-operative CRP increase in GG than C-allele carriers (histogram) corresponds to a small pre-operative genotype difference when the average CRP concentration was 3.4 mg/L vs. a large postoperative genotype difference at 45.3 mg/L.

Perry et al. [84] reported that median peak CRP went from 1.2 mg/L preoperatively to 293.3 mg/L postoperatively following CABG surgery. The rs3091244 T-allele was associated with higher peak postoperative CRP ($P = 2.1\times10^{-3}$), whilst the rs1800947 C-allele of was associated with lower peak postoperative levels ($P = 2.4\times10^{-4}$). Compared to their most common haplotype (rs1800947G/rs3091244C), the peak postoperative levels were significantly lower for haplotype 4 (CC, P=0.004) and significantly higher for haplotype 2 (GT, P=0.03). Figures 3B and 3C show that the postoperative genotype differences increased with increasing CRP concentrations, consistent with quantile-dependent expressivity.

Brull et al. [64] reported an 83-fold increase in average CRP, from a preoperative 1.97±0.36 mg/L to a post-operative 167.2±5.0 mg/L, seventy-two hours after CABG surgery, and that CRP concentrations remained significantly elevated through post-operative day five. The rs1130864 TT-homozygotes had significantly higher CRP levels than C-allele carriers at all time points >24 hours post-operation, but not before. Our analysis of their figure 2A suggests that rs1130864 genotype differences were significantly related to average CRP concentrations during the acute phase response (Figure 3D, P=0.02).

Intensive periodontal therapy also causes sharp rises in CRP and IL-6 that peak by 24 h and remain elevated for up to 7 days [85]. D'Aiuto et al. [35] reported significantly higher CRP concentrations in rs1130864 TT homozygotes than C-allele carriers one (21.10 vs. 12.37 mg/L, P=0.02) and seven-days (4.89 vs. 3.08 mg/L, P<0.01) during the inflammatory stimulus of periodontal intensive therapy. Correspondingly, the geometric means of CRP concentrations were elevated one (13.64 mg/L) and seven days (3.35 mg/L) relative to baseline (1.93 mg/L), such that the intermediate 7-day genotype difference was as predicted by linear interpolation using the 7-day average CRP concentration relative to baseline and day one average concentrations (Figure 3E). Similarly, Motoyama et al.'s [86] data showed that the CRP difference between rs1800947 GG homozygotes than C-allele carriers after curative esophagectomy was linearly related to average CRP concentrations, and that the intermediate 12 hours genotype difference was almost exactly predicted by it's intermediate average concentration by linear interpolation (Figure 3F).

CRP concentrations also increase substantially during acute ischemia and return to near basal levels during the chronic stable phase after ischemia is resolved [36]. Recurrent myocardial infarction and cardiovascular death are strongly related to CRP increases during acute coronary syndrome [36]. Suk Danil et al. [36] reported that rs3091244 AA homozygotes had the highest (76.6 mg/L) median concentrations during the acute rise in plasma CRP-concentrations following an acute coronary syndrome whereas the median concentration in noncarriers was 11.1 mg/L. Figures 7A-7C show that during both acute coronary syndrome and the chronic stable phase one month later, CRP concentrations were significantly higher in rs3091244 A-allele carriers than non-carriers (P=0.0005 and P=0.0008, respectively), rs1800947 GG-homozygotes than C-allele carriers (both P<0.0001), and per dose of the rs1205 G-allele (both P<0.0001). Consistent with quantile-dependent expressivity, the line graphs show greater genotype differences during acute coronary syndrome when median CRP concentrations were substantially elevated vis-a-vis the chronic stable phase. Results reported by Kovacs et al. [70] for rs3091244 are consistent with Suk Danil's results (Figure 7D).

Infection Molkanen et al. [87] reported greater differences in CRP concentrations between carriers and non-carriers of the rs3091244 A-allele at peak CRP concentrations (103 mg/L difference, P=0.004) during the first week of a *Staphylococcus aureus* bacteremia when average CRP was approximately 190 mg/L, than 7-days after diagnosis (5 mg/L difference, P=0.77) when average CRP concentrations had decreased to approximately 43 mg/L (Figure 7E).

Chronic rheumatoid arthritis Ammitzboll et al. [7] reported that rs1205 TT homozygotes had 50% lower CRP concentrations than CC homozygotes at baseline (P=0.005) when average concentrations were approximately 16.6 mg/L in patients with untreated early chronic rheumatoid arthritis, but not after 1-year (P=0.38) when antirheumatic drug and steroid treatment had decreased average CRP concentrations to approximately 4.1 mg/L (Figure 7F). Another study of rheumatoid arthritis patients by Rhodes et al. [6] compared CRP concentrations across genotypes using erythrocyte sedimentation rate (ESR) as an independent measure of inflammation. Their data showed larger estimated CRP differences between genotypes at an ESR of 80 vs. 40 for rs1800947 (CC/GC/GG: 19.4/28.6/42.2 vs. 12.0/17.7/26.1 mg/L), rs1205

(AA/GA/GG: 27.6/35.5/45.7 vs. 17.0/21.9/28.2 mg/L), and rs11265257 (AA/GA/GG: 29.2/37.3/47.6 vs. 17.9/22.9/29.2 mg/L), which quantile-dependent expressivity would attribute to the higher average CRP when ESR was 80 than 40 (approximately 40 vs. 24 mg/L). Wielińska et al. [8] reported larger differences between genotypes for genes coding for receptor activator of nuclear factor κB (RANK rs8086340) and its ligand (RANKL rs7325635) in rheumatoid arthritis patients prior to 12 week of anti-TNF treatment when average CRP concentrations were high (23.6 mg/L), than after treatment when average concentrations were lower (9.84 mg/L, Figure 8A, 8B).

Inflammatory bowel disease (IBD) TNF-α is both a major regulator of hepatic CRP production and a key inflammatory mediator in IBD pathophysiology [88]. Data presented by Vatay et al. [10] show median CRP concentrations were substantially higher in GA heterozygotes than GG homozygotes of the TNF-α rs1800629 polymorphism for the high CRP concentrations of active phase IBD, but not for the low CRP concentrations of matched healthy controls (Figure 8C).

Ankylosing spondylitis Ankylosing spondylitis is a spinal inflammation whose severity, clinical progression, and treatment response are indicated by elevated CRP concentrations. Etanercept, a TNF-α inhibitor, is one of the few treatment options for ankylosing spondylitis. Xu et al. [9] reported that rs3091244 AA homozygotes have higher CRP concentrations than carriers of the G allele both before and after 12-week etanercept treatment, but that this difference in genotypes was over two-fold greater prior to treatment when average CRP was high vis-à-vis post-treatment concentrations (Figure 8D).

Dilated cardiomyopathy Proinflammatory cytokines may contribute to dilated cardiomyopathy, a condition distinguished by dilatation and impaired contraction of the left or both ventricles. Liaquat et al. [89] reported that differences in CRP concentrations between idiopathic dilated cardiomyopathy patients and healthy controls increased with the number of A-alleles of the TNF-α rs1800629 polymorphism (Figure 8E histogram), and were greater in C-allele carriers of the IL-6 rs1800629 polymorphism (Figure 8F histogram). Consistent with quantile-dependent expressivity, the line graphs show that the effects of the genotypes were greater for the higher mean concentrations of the patients than controls.

546

547 *Kawasaki disease* Kawasaki disease is an inflammation of the walls of medium-size artery that
548 occurs affecting children. Kim et al. [90] reported that the CRP promoter rs12068753 showed
549 greater CRP differences between genotypes in patients with Kawasaki disease than controls in
550 accordance with the cases' higher average CRP concentrations (8.9 vs. 0.3 mg/L, Figure 9).
551
552 *Exceptions* Contrary to expectations: 1) Wu et al. [91] reported that the significant interaction
553 between activating transcription factor (AFT3) rs10475 and obesity on CRP concentrations
554 ($P_{interaction}$=0.006) was due to a significant difference between genotypes (P=0.001) in non-obese
555 subjects having lower overall CRP concentrations and not obese subjects (P=0.27) whose CRP
556 concentrations were higher; 2) Keramat et al. [66] reported significantly greater APOA2 rs5082
557 genotype differences for the lower average CRP concentrations of low saturated fat intake than
558 for the higher average CRP concentrations above median saturated fat intake: 3) Hsu et al's [92]
559 report of significantly greater genotype differences for hepatic nuclear factor-1α (HNF1A)
560 rs1920792, rs2464196, and rs1169310 polymorphisms in nonobese than obese subjects despite
561 the higher average CRP the obese; 4) Eklund et al's [93] report that CRP differed between IL6
562 rs1800795 genotypes after weight loss when average CRP concentrations were decreased but not
563 before when average concentrations were higher; F) Retterstol et al. report of a larger MZ
564 correlation below the median BMI than above (r_{MZ}=0.42 vs. 0.31) despite the positive correlation
565 between BMI and CRP [60]. These exception to quantile-dependent expressivity may make them
566 noteworthy in themselves, however, most reported gene-environment interactions are
567 unreplicated, and it is expected that at least some of the reported interactions could be spurious.
568
569 *Conclusion:* Heritability of serum CRP concentration is quantile-dependent, which may explain
570 or contribute to the inflated CRP differences between *CRP* (rs1130864, rs1205, rs1800947,
571 rs2794521 rs3091244), *FGB* (rs1800787), *IL-6* (rs1800795, rs1800796, rs8192284), *IL6R*
572 (rs8192284), *TNF-α* (rs1800629) and *APOE* genotypes following CABG surgery, stroke, TIA,
573 curative esophagectomy, intensive periodontal therapy, or acute exercise; during acute coronary
574 syndrome or *Staphylococcus aureus* bacteremia; or in patients with chronic rheumatoid arthritis,
575 diabetes, peripheral arterial disease, obesity or inflammatory bowel disease or who smoke.
576

Quantile-dependent expressivity is a novel concept, and unsurprisingly, the majority of articles do not provide the data in a form necessary to evaluate its applicability, namely genotype-specific CRP concentrations stratified by characteristics affecting average CRP concentrations. Although it is reported that CRP concentrations are higher in patients with abdominal aortic aneurysm [94], poor cognitive performance and cognitive decline over time [95], anxiety disorders [46], and Alzheimer's disease [96], it is not known whether these conditions affect the genetic effect of CRP-related genetic variants.

Finally, we note that quantile regression and its bootstrap-derived standard errors do not require a normal distribution, and provide insights into CRP inheritance heretofore unstudied. The decision to logarithmically transform CRP concentration has been exclusively based on the theoretical requirement of the parametric statistical testing rather than a biological rationale. All the major genomewide association studies were performed on log CRP, as were virtually all tests of association or gene-environment interaction. This statistical accommodation may work against the goal of identifying some SNPs affecting CRP concentrations given our results suggesting the largest genetic effects are at the highest concentrations.

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Figure legends

Figure 1. A) Offspring-parent regression slopes (β_{OP}) for selected quantiles of the offspring's untransformed CRP concentrations from 6144 offspring-parent pairs, with corresponding estimates of heritability ($h^2=2\beta_{OP}/(1+r_{spouse})$ [26], where the correlation between spouses was $r_{spouse}=-0.0013$. The slopes became progressively greater (i.e., steeper) with increasing quantiles of the CRP distribution. B) The selected quantile-specific regression slopes were included with those of other quantiles to create the quantile-specific heritability function in the lower panel. Significance of the linear, quadratic and cubic trends and the 95% confidence intervals (shaded region) determined by 1000 bootstrap samples. C) Quantile-specific full-sib regression slopes (β_{FS}) from 5703 full-sibs in 2036 sibships, with corresponding estimates of heritability as calculated by $h^2=\{(8r_{spouse}\beta_{FS}+1)^{0.5}-1\}/(2r_{spouse})$ [26].

Figure 2. Quantile-specific offspring-parent (β_{OP}) and full-sib regression slopes (β_{FS}) for the offspring's logarithmically transformed CRP concentrations with corresponding estimates of heritability [26], where the correlation between spouses was $r_{spouse}=0.0482$.

Figure 3. Simple regression analysis of showing larger genotype differences associated with higher estimated average CRP response for: A) Farup et al.'s [54] 2020 report on the *APOE* CRP differences (non-carriers minus carriers of ε4-allele) in morbidly obese patients losing weight; B) Perry et al.'s [84] 2009 report on the rs3091244 CRP difference (T-allele carrier minus noncarrier) post CABG surgery ($P_{linear}=0.08$); C) Perry et al.'s [84] 2009 report on the rs1800947 CRP difference (GG homozygotes minus C-allele carrier) post CABG surgery ($P_{linear}=0.11$); D) Brull et al.'s [64] 2003 report on the rs1130864 CRP difference (TT homozygotes minus C-allele carriers) pre- and post CABG surgery ($P_{linear}=0.02$); E) D'Aiuto et al.'s [35] 2005 report on the rs1130864 CRP difference (TT homozygotes minus C-allele carriers) following periodontal intensive therapy ($P_{linear}=0.002$); F) Motoyama et al.'s [86] 2009 report on the rs1800947 CRP difference (GG homozygotes minus C-allele carriers) following esophagectomy surgery ($P_{linear}=0.07$).

Figure 4. Precision medicine perspective of genotype-specific CRP differences (histogram inserts) vs. quantile-dependent expressivity perspective (line graphs showing larger genetic effect size when average fibrinogen concentrations were high) for: A) Pramudji et al. [55] of the CRP difference between obese and non-obese subjects by the -174 G>C *IL-6* polymorphism; B) Teng et al.'s [56] 2009 report on the CRP difference between obese and non-obese subjects by the rs2794521 genotypes ($P_{interaction}$=0.034); C) Teng et al.'s [56] 2009 report on the CRP difference between obese and non-obese subjects by the rs1800947 genotypes ($P_{interaction}$=0.02); D) Teng et al.'s [56] 2009 report on the CRP difference between obese and non-obese subjects by the rs1205 genotypes ($P_{interaction}$=0.02); E) Luetragoon et al.'s [61] 2017 report on the CRP difference between smokers and nonsmokers by *CRP* 1800947 genotypes; F) Shin et al.'s [62] 2007 report on the CRP difference between smokers and nonsmokers by *CRP* rs1800796 genotypes.

Figure 5. Precision medicine perspective of genotype-specific CRP differences (histogram inserts) vs. quantile-dependent expressivity perspective (line graphs showing larger genetic effect size when average CRP concentrations were high) for: A) Gander et al.'s [63] 2004 report on the CRP difference between smokers and nonsmokers by *CRP* rs1800629; B) Brull et al.'s [64] 2003 reported on the effect of 48-hour military endurance exercise on CRP concentrations by rs1130864 genotypes; C) Keramet et al.'s [66] 2017 report on the affect of monounsaturated fat intake on CRP concentrations by *APOA2* rs5082 genotypes; D) Carvalho-Wells et al.'s [67] 2012 report on the effect of a high fat diet by *APOE* isoform; E) Gomez-Delgado et al.'s [68] 2015 report on the affect of a lowfat diet by *CLOCK* rs4580704 genotypes; F) Zee and Ridker's [69] report on the CRP difference between men experiencing vs. not experiencing their first arterial thrombosis during 8.6 year follow-up by *CRP* rs1800947 genotypes.

Figure 6. Precision medicine perspective of genotype-specific CRP differences (histogram inserts) vs. quantile-dependent expressivity perspective (line graphs showing larger genetic effect size when average fibrinogen concentrations were high) for: A) Kovacs et al. [70] 2005 reported on the effect of myocardial infarction by *CRP* rs3091244 genotypes cross-sectionally; B) Qi et al.'s [74] 2007 report on the effect of T2DM by interleukin-6 receptor (*IL6R*) rs8192284 genotypes ($P_{interaction}$=0.03); C) Libra et al.'s [75] 2006 report on the CRP difference between

T2DM with (PAD+) and without (PAD-) peripheral arterial disease by *IL-6* G(-174)C rs1800795 genotypes; D) Wypasek et al. [81] 2012 reported on the effects of coronary artery bypass grafting (CABG) surgery on CRP by fibrinogen beta-chain (*FGB*) -148C>T genotypes (rs1800787); E) Wypasek et al. [82] 2010 reported on the effects of CABG surgery on CRP by -174G>C *IL-6* (rs1800795) genotypes; F) Mathew et al. [83] 2007 report on the effects of CABG with cardiopulmonary bypass by *CRP* +1059G>C (rs1800947) genotypes.

Figure 7. Precision medicine perspective of genotype-specific CRP differences (histogram inserts) vs. quantile-dependent expressivity perspective (line graphs showing larger genetic effect size when average fibrinogen concentrations were high) for: A) Suk Danil et al. [36] 2006 report on the effect of acute coronary syndrome by *CRP* rs3091244 genotypes; B) Suk Danil et al. [36] 2006 report on the effect of acute coronary syndrome by *CRP* rs1800947 genotypes; and C) Suk Danil et al. [36] 2006 report on the effect of acute coronary syndrome by *CRP* rs1800947 genotypes; D) Kovacs et al's [70] 2005 report on the effect of myocardial infarction by *CRP* rs3091244 genotypes longitudinally; E) Mölkänen et al. [87] 2010 reported on the effect of *Staphylococcus aureus* bacteremia by rs3091244 genotypes; F) Ammitzboll et al. [7] 2014 report on the effect of early chronic rheumatoid arthritis by *CRP* rs1205; E) Qi et al's [74] 2007 report on the effect of T2DM by *IL6R* rs8192284 genotypes.

Figure 8. Precision medicine perspective of genotype-specific CRP differences (histogram inserts) vs. quantile-dependent expressivity perspective (line graphs showing larger genetic effect size when average fibrinogen concentrations were high) for: A) Wielińska et al. [8] 2020 report on the effect of anti-TNF treatment by *RANK* rs8086340 genotypes; B) Wielińska et al.'s [8] 2020 report on the effect of anti-TNF treatment by *RANKL* rs7325635 genotypes; C) Vatay et al's [10] 2003 report on the CRP difference between active phase inflammatory bowel disease and healthy controls by tumor necrosis factor alpha (*TNF-α*) G-308A (rs1800629) promoter polymorphism; D) Xu et al.'s [9] 2020 report on the effect of etanercept treatment in Ankylosing spondylitis patients by *CRP* rs3091244 genotypes; E) Liaquat et al. [89] on the effect of idiopathic dilated cardiomyopathy by *TNF-α* (rs1800629) -308G>A genotypes; F) Liaquat et al. [89] on the effect of idiopathic dilated cardiomyopathy by *IL-6* rs1800795 (–174 G>C) genotypes.

1133

1134 Figure 9. Precision medicine perspective of genotype-specific CRP differences (histogram
1135 inserts) vs. quantile-dependent expressivity perspective (line graphs showing larger genetic
1136 effect size when average fibrinogen concentrations were high) for Kim et al. [90] 2014 report on
1137 the effect of Kawasaki disease by *CRP* promoter rs12068753 genotypes.

1138

Table 1(on next page)

Table 1. Sample characteristics

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2
3

Table 1. Sample characteristics				
	Males		Females	
	Offspring Cohort	Third generation cohort	Offspring Cohort	Third generation cohort
Sample size	1232	1851	1340	2108
Age, years	56.54 (8.74)	40.42 (8.72)	55.64 (9.10)	39.99 (8.77)
BMI, kg/m^2	28.08 (3.90)	28.43 (4.79)	26.65 (5.22)	26.50 (6.11)
Waist/ht	0.58 (0.06)	0.56 (0.07)	0.56 (0.09)	0.55 (0.10)
CRP mg/mL-all	3.58 (5.83)	2.15 (3.12)	3.84 (4.97)	3.05 (4.57)
Waist/ht 1st tertile	3.25 (7.91)	1.34 (2.60)	2.63 (3.72)	1.37 (2.32)
Waist/ht 2nd tertile	3.16 (4.54)	1.79 (2.53)	3.34 (3.37)	2.58 (3.97)
Waist/ht 3rd tertile	4.22 (5.36)	3.26 (3.79)	5.64 (6.55)	5.23 (5.81)

4
5 CRP was measured at visits 2, 6, 7, 8, and 9 of the offspring cohort, and

Figure 1

Quantile-specific offspring-parent (β_{OP}) and full-sib regression slopes (β_{FS}) for untransformed CRP concentrations

Figure 1. (A) Offspring-parent regression slopes (β_{OP}) for selected quantiles of the offspring's untransformed CRP concentrations from 6144 offspring-parent pairs, with corresponding estimates of heritability ($h^2=2\beta_{OP}/(1+r_{spouse})$ [26], where the correlation between spouses was $r_{spouse}=-0.0013$. The slopes became progressively greater (i.e., steeper) with increasing quantiles of the CRP distribution. (B) The selected quantile-specific regression slopes were included with those of other quantiles to create the quantile-specific heritability function in the lower panel. Significance of the linear, quadratic and cubic trends and the 95% confidence intervals (shaded region) determined by 1000 bootstrap samples. (C) Quantile-specific full-sib regression slopes (β_{FS}) from 5703 full-sibs in 2036 sibships, with corresponding estimates of heritability as calculated by $h^2=\{(8r_{spouse}\beta_{FS}+1)^{0.5}-1\}/(2r_{spouse})$ [26].

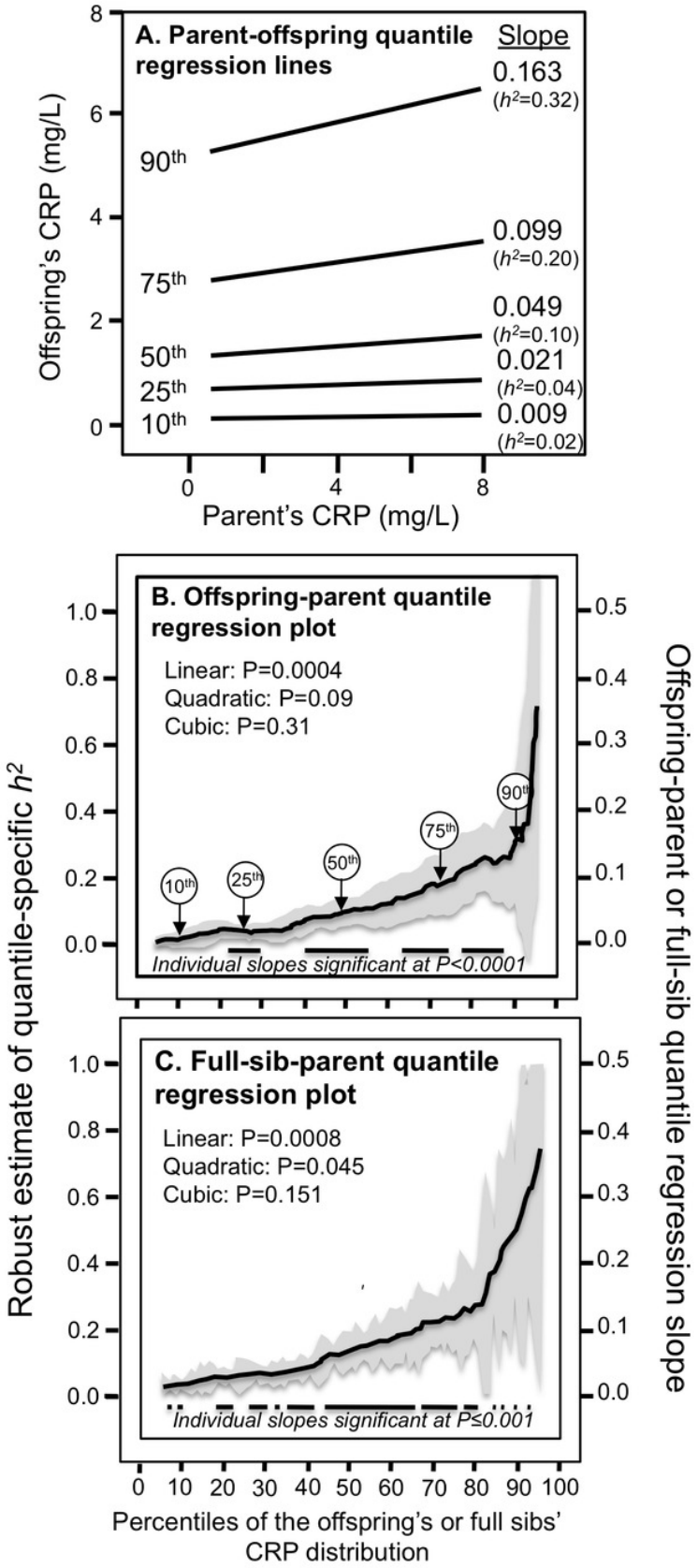
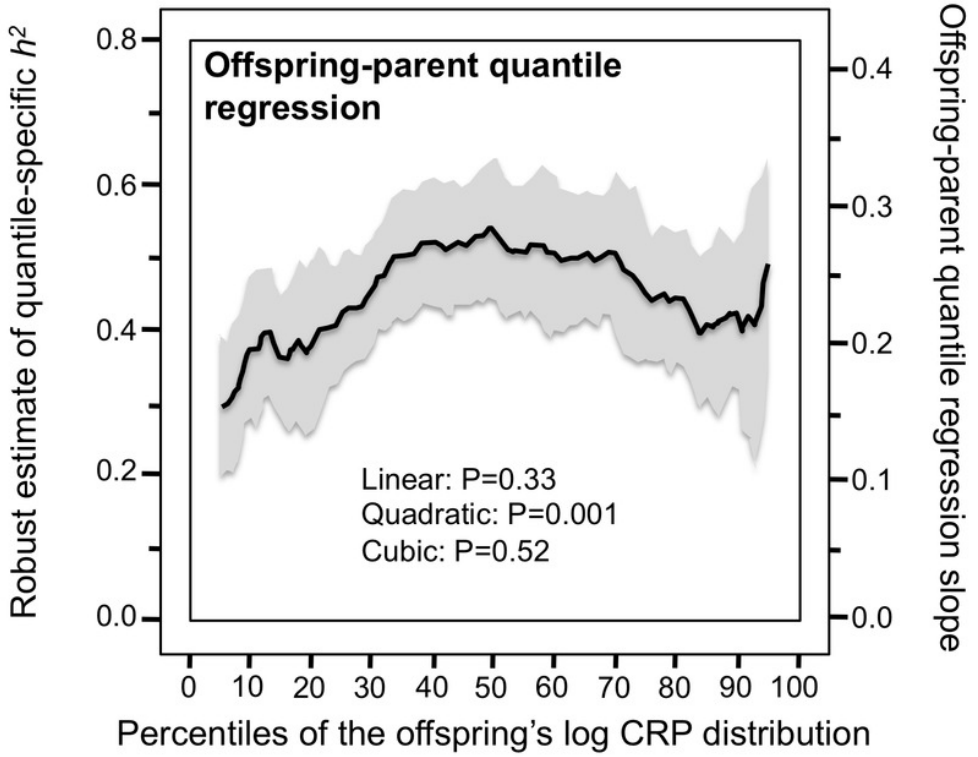

A. Parent-offspring quantile regression lines
Slope
0.163
(h^2=0.32)
90th
0.099
(h^2=0.20)
75th
0.049
(h^2=0.10)
50th
0.021
(h^2=0.04)
25th
0.009
(h^2=0.02)
10th
Offspring's CRP (mg/L)
Parent's CRP (mg/L)
B. Offspring-parent quantile regression plot
Linear: P=0.0004
Quadratic: P=0.09
Cubic: P=0.31
Individual slopes significant at P<0.0001
C. Full-sib-parent quantile regression plot
Linear: P=0.0008
Quadratic: P=0.045
Cubic: P=0.151
Individual slopes significant at P≤0.001
Robust estimate of quantile-specific h^2
Offspring-parent or full-sib quantile regression slope
Percentiles of the offspring's or full sibs' CRP distribution

Figure 2

Quantile-specific offspring-parent (β_{OP}) and full-sib regression slopes (β_{FS}) for the offspring's logarithmically transformed CRP concentrations

Quantile-specific offspring-parent (β_{OP}) and full-sib regression slopes (β_{FS}) for the offspring's logarithmically transformed CRP concentrations with corresponding estimates of heritability [26], where the correlation between spouses was r_{spouse}=0.0482. (A) Offspring-parent; (B) Full-siblings


Offspring-parent quantile regression
Robust estimate of quantile-specific h^2
Offspring-parent quantile regression slope
Linear: P=0.33
Quadratic: P=0.001
Cubic: P=0.52
0.0
0.2
0.4
0.6
0.8
0.1
0.3
0
10
20
30
40
50
60
70
80
90
100
Percentiles of the offspring's log CRP distribution

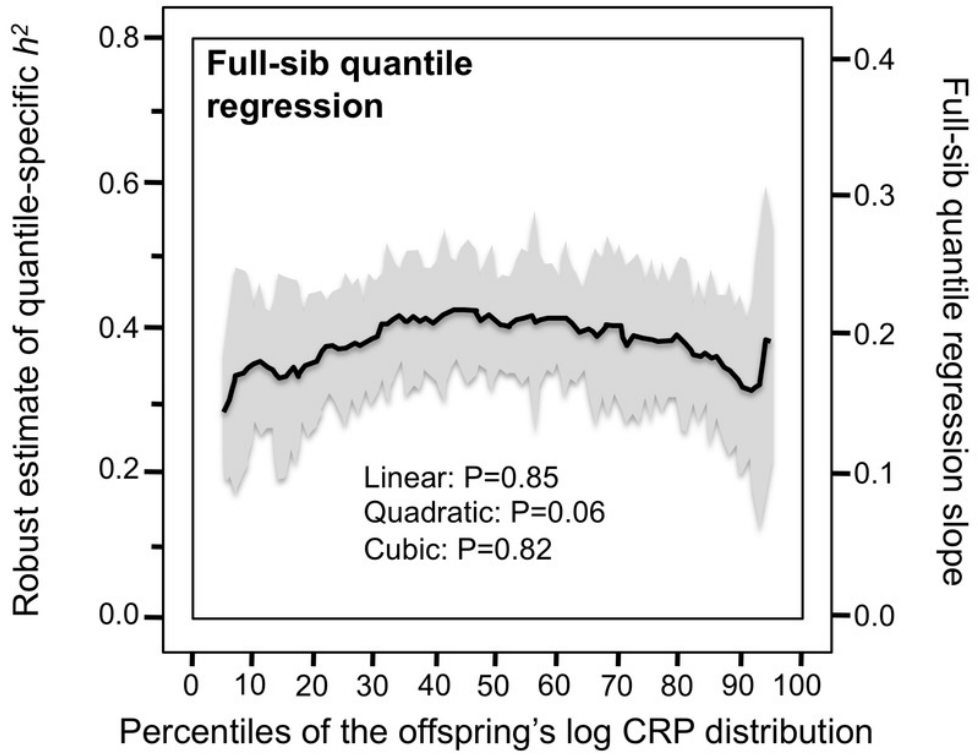

Full-sib quantile regression
Robust estimate of quantile-specific h^2
Full-sib quantile regression slope
Linear: P=0.85
Quadratic: P=0.06
Cubic: P=0.82
0.0
0.2
0.4
0.6
0.8
0.1
0.3
0
10
20
30
40
50
60
70
80
90
100
Percentiles of the offspring's log CRP distribution

Figure 3

Simple regression analysis of showing larger genotype differences associated with higher estimated average CRP response

Simple regression analysis of showing larger genotype differences associated with higher estimated average CRP response for: (A) Farup et al.'s [54] 2020 report on the *APOE* CRP differences (non-carriers minus carriers of ε4-allele) in morbidly obese patients losing weight; (B) Perry et al.'s [84] 2009 report on the rs3091244 CRP difference (T-allele carrier minus noncarrier) post CABG surgery (P_{linear}=0.08); (C) Perry et al.'s [84] 2009 report on the rs1800947 CRP difference (GG homozygotes minus C-allele carrier) post CABG surgery (P_{linear}=0.11); (D) Brull et al.'s [64] 2003 report on the rs1130864 CRP difference (TT homozygotes minus C-allele carriers) pre- and post CABG surgery (P_{linear}=0.02); (E) D'Aiuto et al.'s [35] 2005 report on the rs1130864 CRP difference (TT homozygotes minus C-allele carriers) following periodontal intensive therapy (P_{linear}=0.002); (F) Motoyama et al.'s [86] 2009 report on the rs1800947 CRP difference (GG homozygotes minus C-allele carriers) following esophagectomy surgery (P_{linear}=0.07).

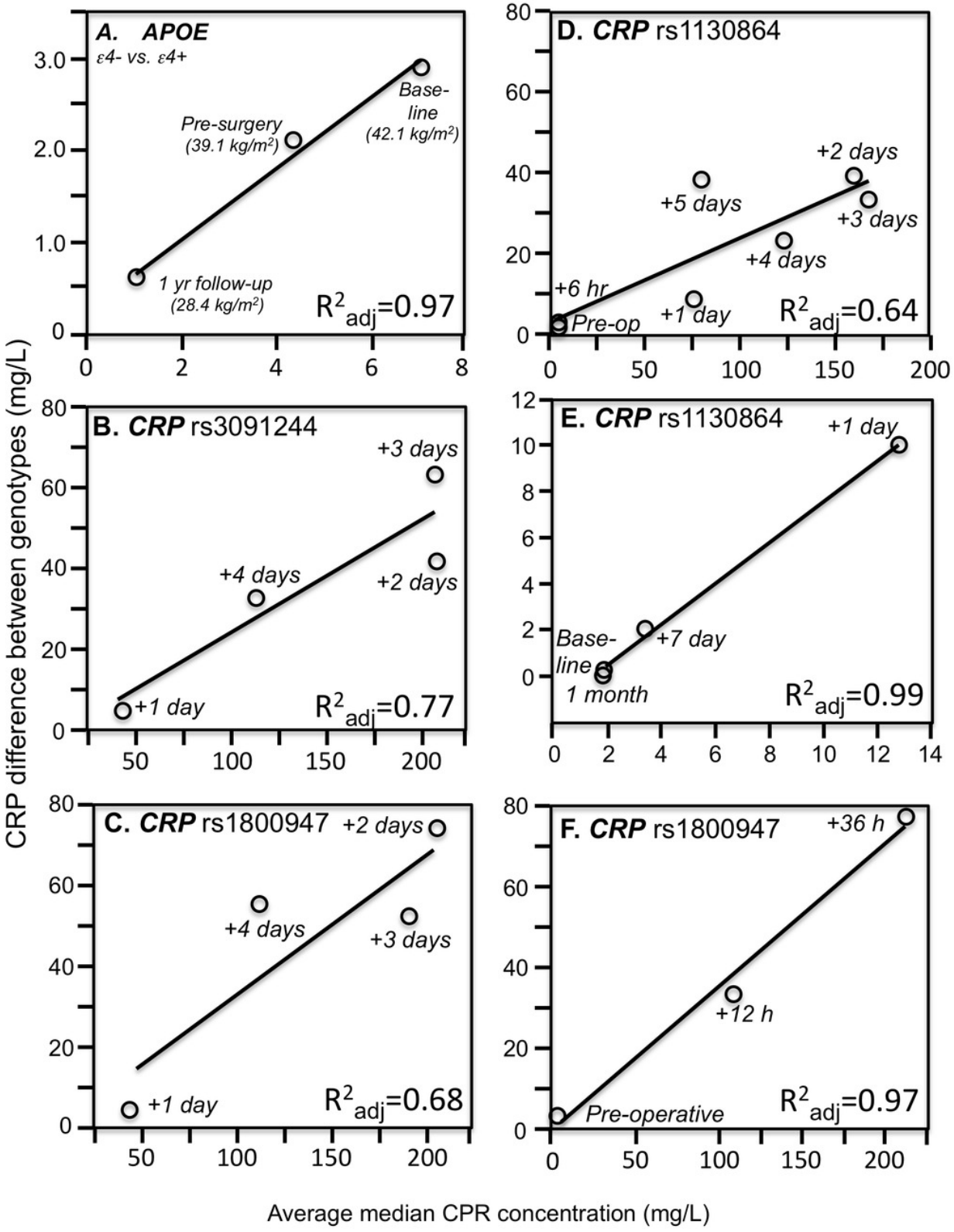

A. APOE
ε4- vs. ε4+
Base-line (42.1 kg/m²)
Pre-surgery (39.1 kg/m²)
1 yr follow-up (28.4 kg/m²)
R²adj=0.97
B. CRP rs3091244
+3 days
+4 days
+2 days
+1 day
R²adj=0.77
C. CRP rs1800947
+2 days
+4 days
+3 days
+1 day
R²adj=0.68
D. CRP rs1130864
+2 days
+5 days
+3 days
+4 days
+6 hr
Pre-op
+1 day
R²adj=0.64
E. CRP rs1130864
+1 day
+7 day
Base-line
1 month
R²adj=0.99
F. CRP rs1800947
+36 h
+12 h
Pre-operative
R²adj=0.97
CRP difference between genotypes (mg/L)
Average median CPR concentration (mg/L)

Figure 4

Precision medicine perspective of genotype-specific CRP differences (histogram inserts) vs. quantile-dependent expressivity perspective (line graphs).

Precision medicine perspective of genotype-specific CRP differences (histogram inserts) vs. quantile-dependent expressivity perspective (line graphs showing larger genetic effect size when average fibrinogen concentrations were high) for: (A) Pramudji et al. [55] of the CRP difference between obese and non-obese subjects by the -174 G>C *IL-6* polymorphism; (B) Teng et al.'s [56] 2009 report on the CRP difference between obese and non-obese subjects by the rs2794521 genotypes ($P_{interaction}$=0.034); (C) Teng et al.'s [56] 2009 report on the CRP difference between obese and non-obese subjects by the rs1800947 genotypes ($P_{interaction}$=0.02); (D) Teng et al.'s [56] 2009 report on the CRP difference between obese and non-obese subjects by the rs1205 genotypes ($P_{interaction}$=0.02); (E) Luetragoon et al.'s [61] 2017 report on the CRP difference between smokers and nonsmokers by *CRP* 1800947 genotypes; (F) Shin et al.'s [62] 2007 report on the CRP difference between smokers and nonsmokers by *CRP* rs1800796 genotypes.

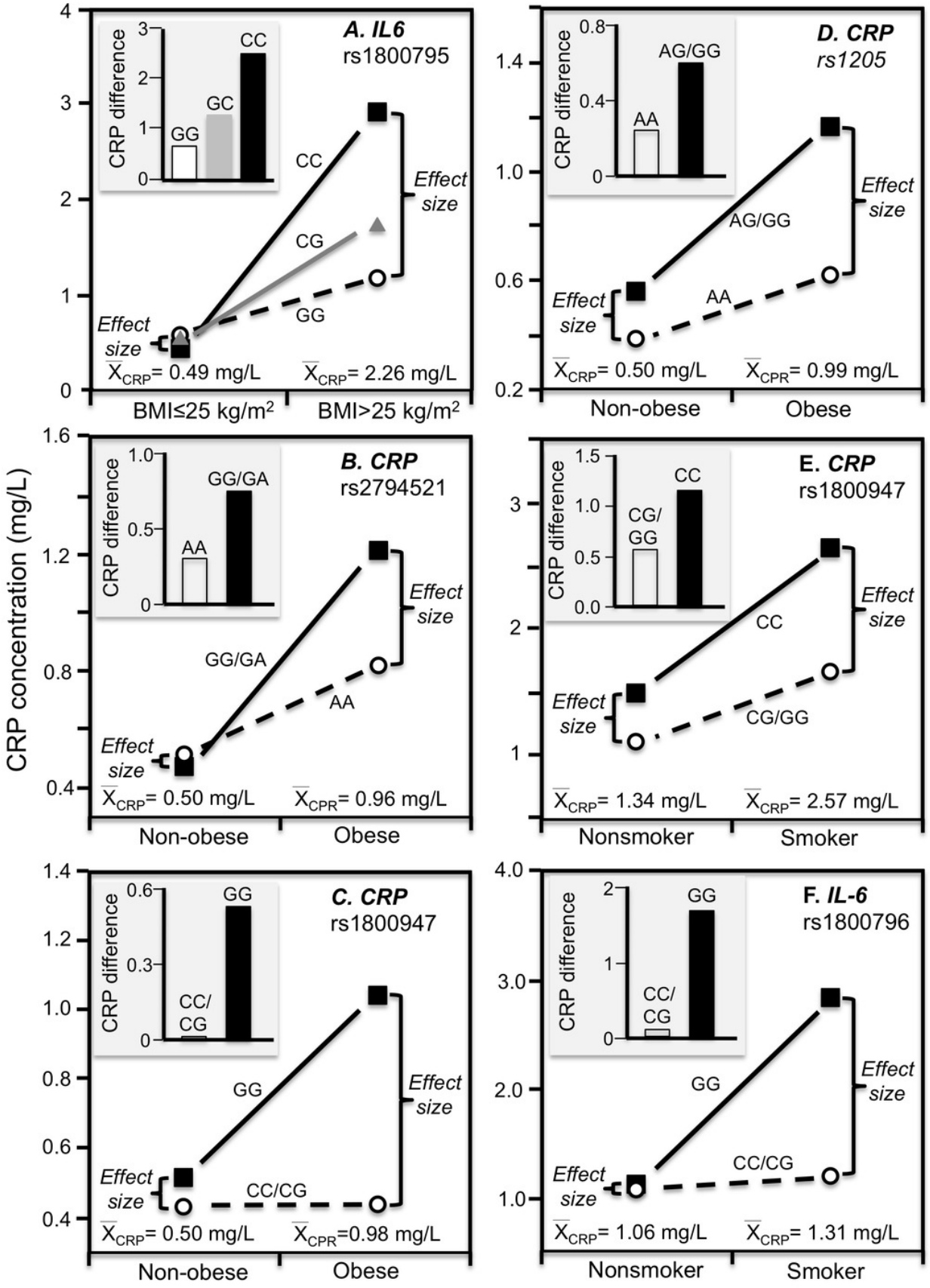

A. IL6
rs1800795
CRP difference
GG
GC
CC
CC
CG
GG
Effect size
Effect size
$\overline{X}_{CRP}$= 0.49 mg/L
$\overline{X}_{CRP}$= 2.26 mg/L
BMI≤25 kg/m²
BMI>25 kg/m²
D. CRP
rs1205
CRP difference
AA
AG/GG
AG/GG
AA
Effect size
Effect size
$\overline{X}_{CRP}$= 0.50 mg/L
$\overline{X}_{CPR}$= 0.99 mg/L
Non-obese
Obese
CRP concentration (mg/L)
B. CRP
rs2794521
CRP difference
AA
GG/GA
GG/GA
AA
Effect size
Effect size
$\overline{X}_{CRP}$= 0.50 mg/L
$\overline{X}_{CPR}$= 0.96 mg/L
Non-obese
Obese
E. CRP
rs1800947
CRP difference
CG/GG
CC
CC
CG/GG
Effect size
Effect size
$\overline{X}_{CRP}$= 1.34 mg/L
$\overline{X}_{CRP}$= 2.57 mg/L
Nonsmoker
Smoker
C. CRP
rs1800947
CRP difference
CC/CG
GG
GG
CC/CG
Effect size
Effect size
$\overline{X}_{CRP}$= 0.50 mg/L
$\overline{X}_{CPR}$=0.98 mg/L
Non-obese
Obese
F. IL-6
rs1800796
CRP difference
CC/CG
GG
GG
CC/CG
Effect size
Effect size
$\overline{X}_{CRP}$= 1.06 mg/L
$\overline{X}_{CRP}$= 1.31 mg/L
Nonsmoker
Smoker

Figure 5

Precision medicine perspective of genotype-specific CRP differences (histogram inserts) vs. quantile-dependent expressivity perspective (line graphs).

Precision medicine perspective of genotype-specific CRP differences (histogram inserts) vs. quantile-dependent expressivity perspective (line graphs showing larger genetic effect size when average CRP concentrations were high) for: (A) Gander et al.'s [63] 2004 report on the CRP difference between smokers and nonsmokers by *CRP* rs1800629; (B) Brull et al.'s [64] 2003 reported on the effect of 48-hour military endurance exercise on CRP concentrations by rs1130864 genotypes; (C) Keramet et al.'s [66] 2017 report on the affect of monounsaturated fat intake on CRP concentrations by *APOA2* rs5082 genotypes; (D) Carvalho-Wells et al.'s [67] 2012 report on the effect of a high fat diet by *APOE* isoform; (E) Gomez-Delgado et al.'s [68] 2015 report on the affect of a lowfat diet by *CLOCK* rs4580704 genotypes; (F) Zee and Ridker's [69] report on the CRP difference between men experiencing vs. not experiencing their first arterial thrombosis during 8.6 year follow-up by *CRP* rs1800947 genotypes.

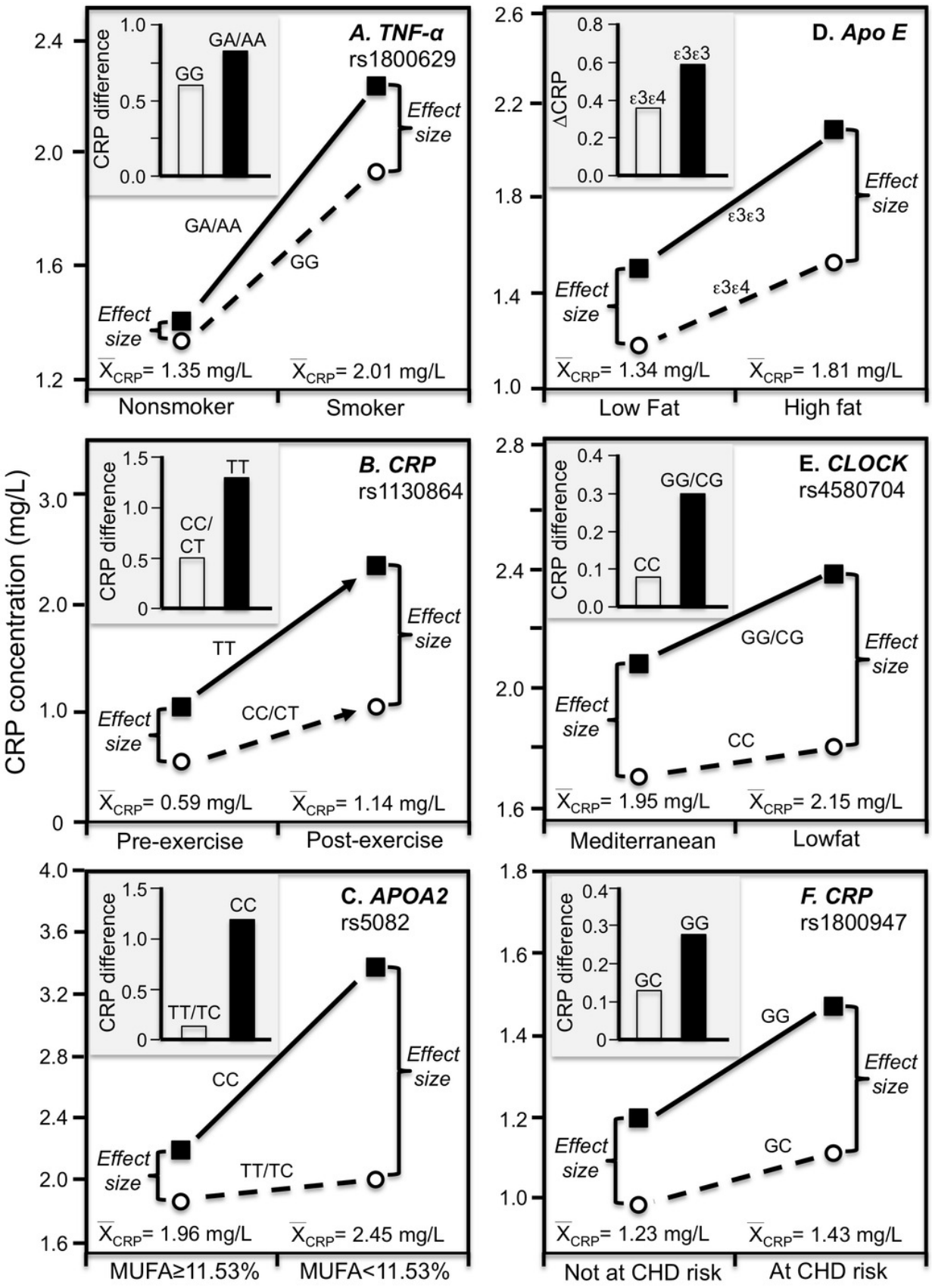

A. TNF-α
rs1800629
CRP difference
GG
GA/AA
Effect size
GA/AA
GG
Effect size
$\overline{X}_{CRP}$= 1.35 mg/L
$\overline{X}_{CRP}$= 2.01 mg/L
Nonsmoker
Smoker
D. Apo E
ΔCRP
ε3ε4
ε3ε3
Effect size
ε3ε3
ε3ε4
Effect size
$\overline{X}_{CRP}$= 1.34 mg/L
$\overline{X}_{CRP}$= 1.81 mg/L
Low Fat
High fat
CRP concentration (mg/L)
B. CRP
rs1130864
CRP difference
CC/CT
TT
Effect size
TT
CC/CT
Effect size
$\overline{X}_{CRP}$= 0.59 mg/L
$\overline{X}_{CRP}$= 1.14 mg/L
Pre-exercise
Post-exercise
E. CLOCK
rs4580704
CRP difference
CC
GG/CG
Effect size
GG/CG
CC
Effect size
$\overline{X}_{CRP}$= 1.95 mg/L
$\overline{X}_{CRP}$= 2.15 mg/L
Mediterranean
Lowfat
C. APOA2
rs5082
CRP difference
TT/TC
CC
Effect size
CC
TT/TC
Effect size
$\overline{X}_{CRP}$= 1.96 mg/L
$\overline{X}_{CRP}$= 2.45 mg/L
MUFA≥11.53%
MUFA<11.53%
F. CRP
rs1800947
CRP difference
GC
GG
Effect size
GG
GC
Effect size
$\overline{X}_{CRP}$= 1.23 mg/L
$\overline{X}_{CRP}$= 1.43 mg/L
Not at CHD risk
At CHD risk

Figure 6

Precision medicine perspective of genotype-specific CRP differences (histogram inserts) vs. quantile-dependent expressivity perspective (line graphs).

Figure 6. Precision medicine perspective of genotype-specific CRP differences (histogram inserts) vs. quantile-dependent expressivity perspective (line graphs showing larger genetic effect size when average fibrinogen concentrations were high) for: (A) Kovacs et al. [70] 2005 reported on the effect of myocardial infarction by *CRP* rs3091244 genotypes cross-sectionally; (B) Qi et al.'s [74] 2007 report on the effect of T2DM by interleukin-6 receptor (*IL6R*) rs8192284 genotypes ($P_{interaction}$=0.03); (C) Libra et al.'s [75] 2006 report on the CRP difference between T2DM with (PAD+) and without (PAD-) peripheral arterial disease by *IL-6* G(-174)C rs1800795 genotypes; (D) Wypasek et al. [81] 2012 reported on the effects of coronary artery bypass grafting (CABG) surgery on CRP by fibrinogen beta-chain (*FGB*) -148C>T genotypes (rs1800787); (E) Wypasek et al. [82] 2010 reported on the effects of CABG surgery on CRP by -174G>C *IL-6* (rs1800795) genotypes; (F) Mathew et al. [83] 2007 report on the effects of CABG with cardiopulmonary bypass by *CRP* +1059G>C (rs1800947) genotypes.

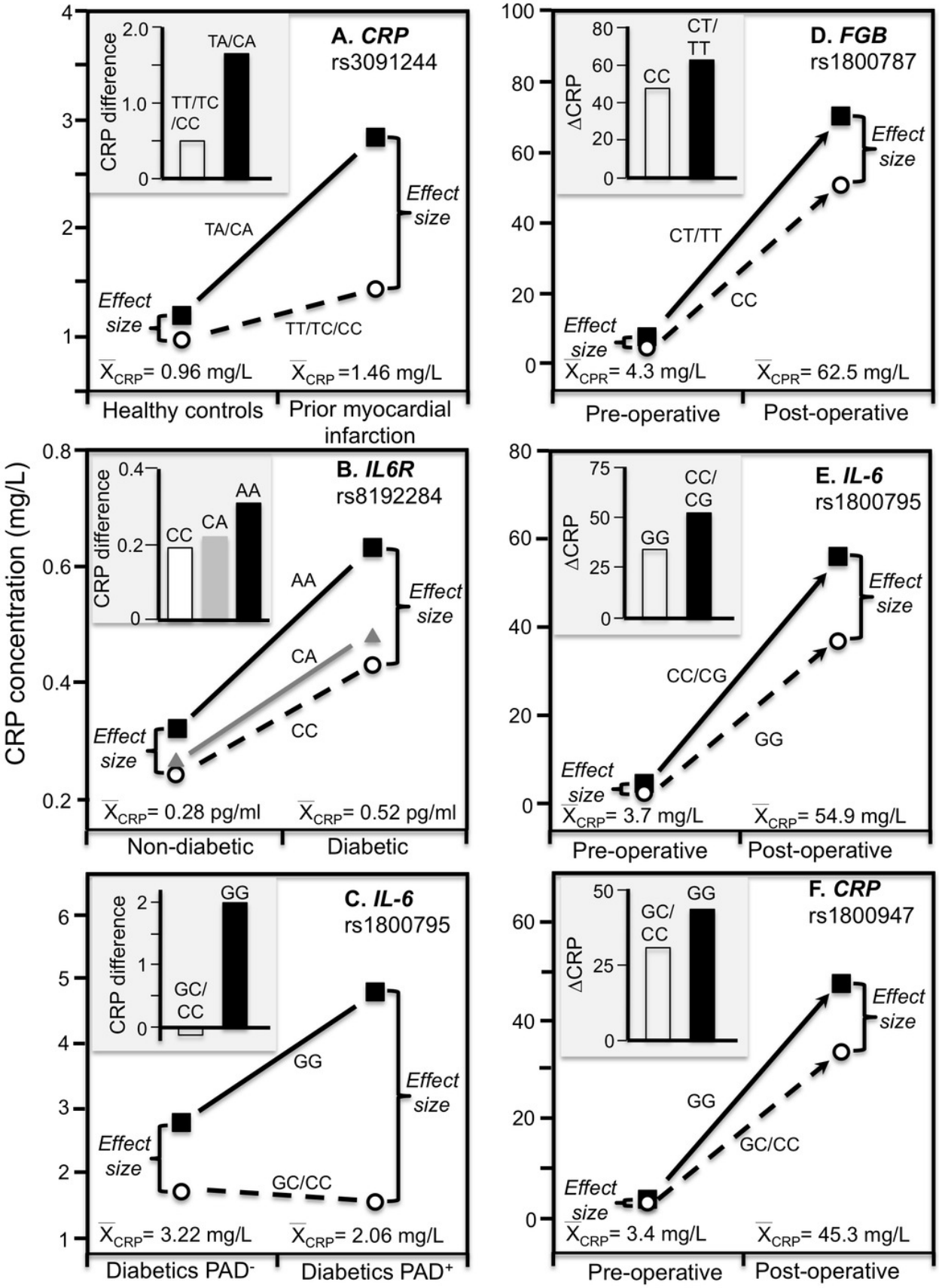

A. CRP
rs3091244
CRP difference
TA/CA
TT/TC /CC
TA/CA
TT/TC/CC
Effect size
Effect size
$\overline{X}_{CRP}$= 0.96 mg/L
$\overline{X}_{CRP}$ =1.46 mg/L
Healthy controls
Prior myocardial infarction
B. IL6R
rs8192284
CRP difference
CC
CA
AA
AA
CA
CC
Effect size
Effect size
$\overline{X}_{CRP}$= 0.28 pg/ml
$\overline{X}_{CRP}$= 0.52 pg/ml
Non-diabetic
Diabetic
C. IL-6
rs1800795
CRP difference
GC/ CC
GG
GG
GC/CC
Effect size
Effect size
$\overline{X}_{CRP}$= 3.22 mg/L
$\overline{X}_{CRP}$= 2.06 mg/L
Diabetics PAD-
Diabetics PAD+
CRP concentration (mg/L)
D. FGB
rs1800787
ΔCRP
CC
CT/ TT
CT/TT
CC
Effect size
Effect size
$\overline{X}_{CPR}$= 4.3 mg/L
$\overline{X}_{CPR}$= 62.5 mg/L
Pre-operative
Post-operative
E. IL-6
rs1800795
ΔCRP
GG
CC/ CG
CC/CG
GG
Effect size
Effect size
$\overline{X}_{CRP}$= 3.7 mg/L
$\overline{X}_{CRP}$= 54.9 mg/L
Pre-operative
Post-operative
F. CRP
rs1800947
ΔCRP
GC/ CC
GG
GG
GC/CC
Effect size
Effect size
$\overline{X}_{CRP}$= 3.4 mg/L
$\overline{X}_{CRP}$= 45.3 mg/L
Pre-operative
Post-operative

Figure 7

Precision medicine perspective of genotype-specific CRP differences (histogram inserts) vs. quantile-dependent expressivity perspective (line graphs).

Precision medicine perspective of genotype-specific CRP differences (histogram inserts) vs. quantile-dependent expressivity perspective (line graphs showing larger genetic effect size when average fibrinogen concentrations were high) for: (A) Suk Danil et al. [36] 2006 report on the effect of acute coronary syndrome by *CRP* rs3091244 genotypes; (B) Suk Danil et al. [36] 2006 report on the effect of acute coronary syndrome by *CRP* rs1800947 genotypes; and (C) Suk Danil et al. [36] 2006 report on the effect of acute coronary syndrome by *CRP* rs1800947 genotypes; (D) Kovacs et al's [70] 2005 report on the effect of myocardial infarction by *CRP* rs3091244 genotypes longitudinally; (E) Mölkänen et al. [87] 2010 reported on the effect of *Staphylococcus aureus* bacteremia by rs3091244 genotypes; F) Ammitzboll et al. [7] 2014 report on the effect of early chronic rheumatoid arthritis by *CRP* rs1205; (F) Qi et al's [74] 2007 report on the effect of T2DM by *IL6R* rs8192284 genotypes.

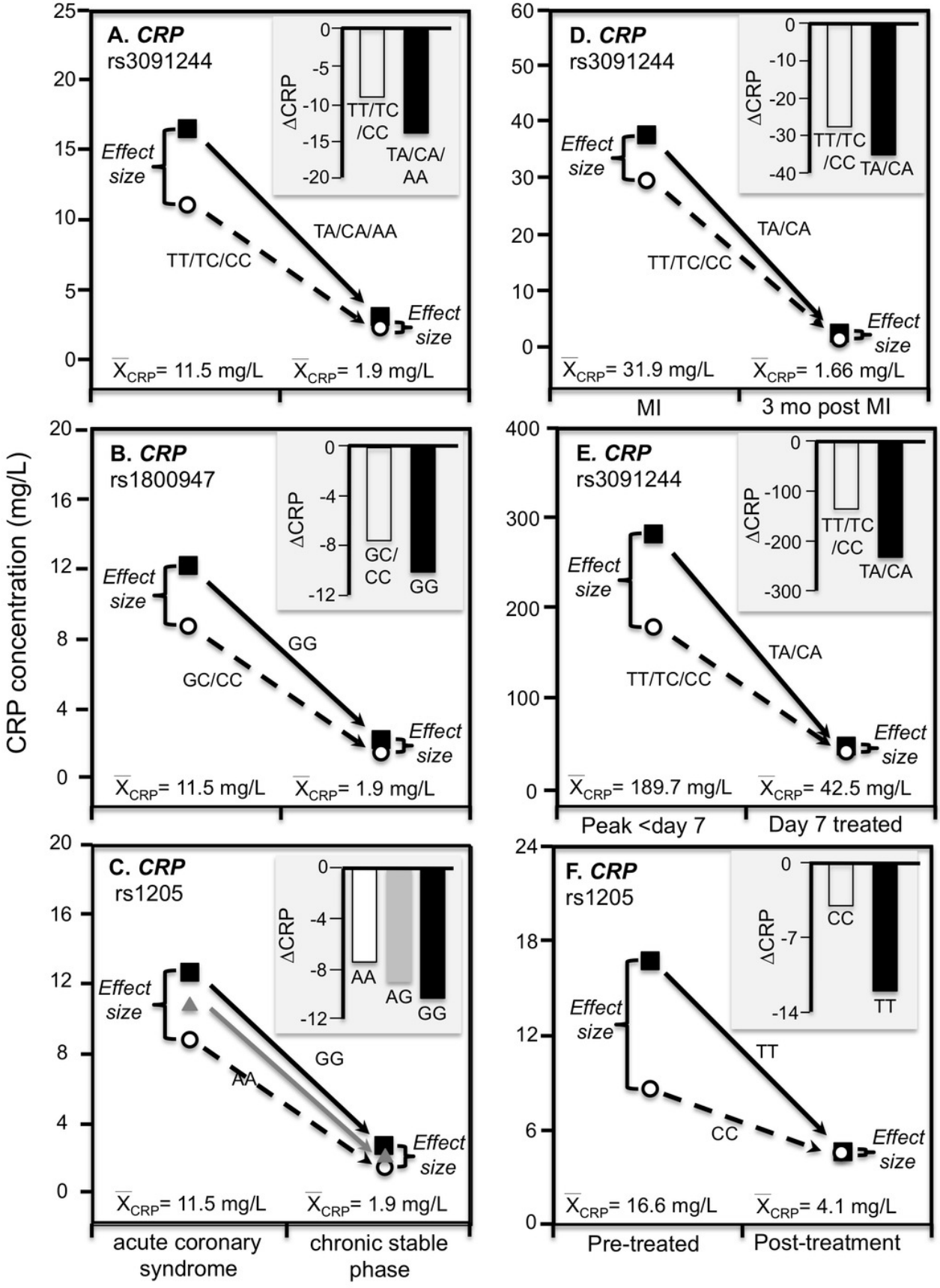

A. CRP
rs3091244
Effect size
TA/CA/AA
TT/TC/CC
Effect size
$\overline{X}_{CRP}$= 11.5 mg/L
$\overline{X}_{CRP}$= 1.9 mg/L
ΔCRP
TT/TC /CC
TA/CA/ AA
B. CRP
rs1800947
GG
GC/CC
GC/ CC
GG
C. CRP
rs1205
AA
AG
GG
acute coronary syndrome
chronic stable phase
D. CRP
rs3091244
TA/CA
TT/TC/CC
$\overline{X}_{CRP}$= 31.9 mg/L
$\overline{X}_{CRP}$= 1.66 mg/L
TT/TC /CC
TA/CA
MI
3 mo post MI
E. CRP
rs3091244
$\overline{X}_{CRP}$= 189.7 mg/L
$\overline{X}_{CRP}$= 42.5 mg/L
Peak <day 7
Day 7 treated
F. CRP
rs1205
CC
TT
$\overline{X}_{CRP}$= 16.6 mg/L
$\overline{X}_{CRP}$= 4.1 mg/L
Pre-treated
Post-treatment
CRP concentration (mg/L)

Figure 8

Precision medicine perspective of genotype-specific CRP differences (histogram inserts) vs. quantile-dependent expressivity perspective (line graphs).

Figure 8. Precision medicine perspective of genotype-specific CRP differences (histogram inserts) vs. quantile-dependent expressivity perspective (line graphs showing larger genetic effect size when average fibrinogen concentrations were high) for: (A) Wielińska et al. [8] 2020 report on the effect of anti-TNF treatment by *RANK* rs8086340 genotypes; (B) Wielińska et al.'s [8] 2020 report on the effect of anti-TNF treatment by *RANKL* rs7325635 genotypes; (C) Vatay et al's [10] 2003 report on the CRP difference between active phase inflammatory bowel disease and healthy controls by tumor necrosis factor alpha (*TNF-α*) G-308A (rs1800629) promoter polymorphism; (D) Xu et al.'s [9] 2020 report on the effect of etanercept treatment in Ankylosing spondylitis patients by *CRP* rs3091244 genotypes; (E) Liaquat et al. [89] on the effect of idiopathic dilated cardiomyopathy by *TNF-α* (rs1800629) -308G>A genotypes; (F) Liaquat et al. [89] on the effect of idiopathic dilated cardiomyopathy by *IL-6* rs1800795 (–174 G>C) genotypes.

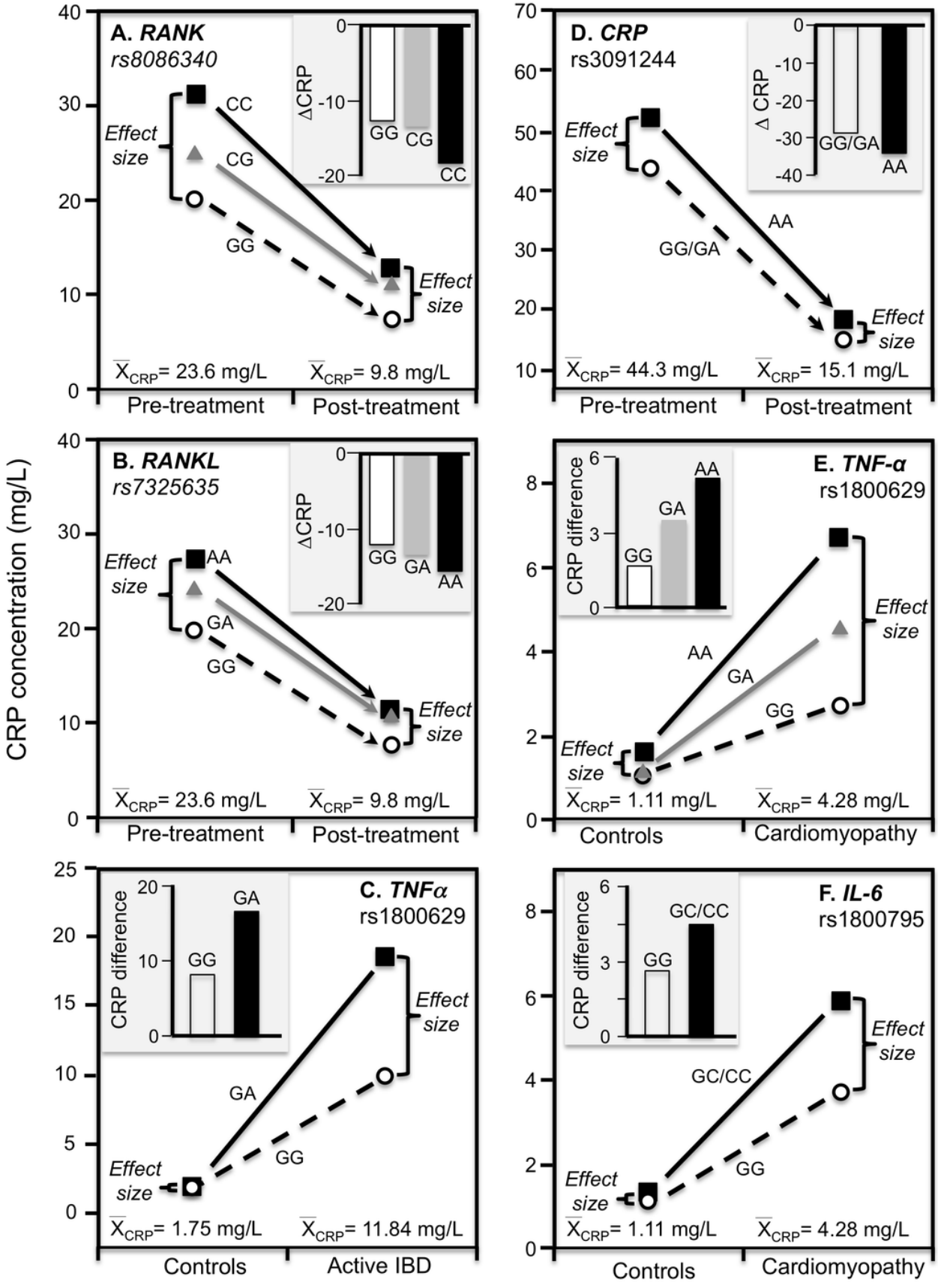
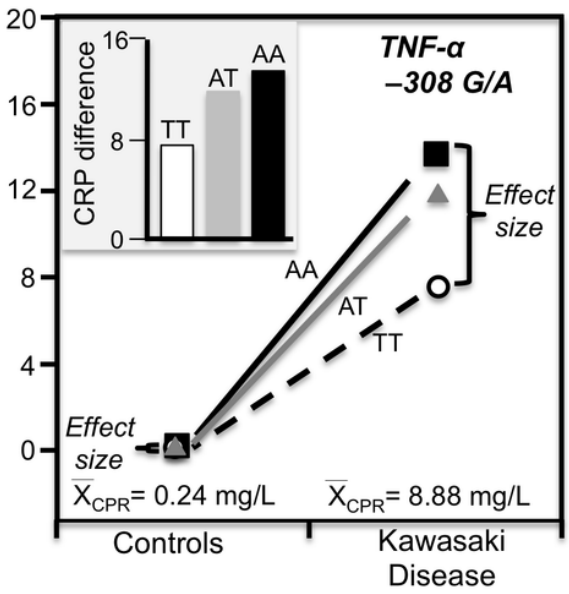

A. RANK
rs8086340
CC
CG
GG
Effect size
ΔCRP
GG
CG
CC
$\overline{X}_{CRP}$= 23.6 mg/L
$\overline{X}_{CRP}$= 9.8 mg/L
Pre-treatment
Post-treatment
B. RANKL
rs7325635
AA
GA
GG
$\overline{X}_{CRP}$= 23.6 mg/L
$\overline{X}_{CRP}$= 9.8 mg/L
Pre-treatment
Post-treatment
C. TNFα
rs1800629
GA
GG
CRP difference
$\overline{X}_{CRP}$= 1.75 mg/L
$\overline{X}_{CRP}$= 11.84 mg/L
Controls
Active IBD
D. CRP
rs3091244
AA
GG/GA
Δ CRP
$\overline{X}_{CRP}$= 44.3 mg/L
$\overline{X}_{CRP}$= 15.1 mg/L
Pre-treatment
Post-treatment
E. TNF-α
rs1800629
AA
GA
GG
CRP difference
$\overline{X}_{CRP}$= 1.11 mg/L
$\overline{X}_{CRP}$= 4.28 mg/L
Controls
Cardiomyopathy
F. IL-6
rs1800795
GC/CC
GG
CRP difference
$\overline{X}_{CRP}$= 1.11 mg/L
$\overline{X}_{CRP}$= 4.28 mg/L
Controls
Cardiomyopathy
CRP concentration (mg/L)

Figure 9

Precision medicine perspective of genotype-specific CRP differences (histogram inserts) vs. quantile-dependent expressivity perspective (line graph)

Precision medicine perspective of genotype-specific CRP differences (histogram inserts) vs. quantile-dependent expressivity perspective (line graphs showing larger genetic effect size when average fibrinogen concentrations were high) for Kim et al. [90] 2014 report on the effect of Kawasaki disease by *CRP* promoter rs12068753 genotypes.


20
16
12
8
4
0
CRP difference
16
8
0
TT
AT
AA
TNF-α
–308 G/A
Effect
size
AA
AT
TT
Effect
size
$\overline{X}_{CPR}$= 0.24 mg/L
$\overline{X}_{CPR}$= 8.88 mg/L
Controls
Kawasaki
Disease