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Reviews

Impact of Genetic and Environmental Factors on hsCRP Concentrations and Response to Therapeutic Agents

Jian Shen[1] and Jose M. Ordovas[1*]

BACKGROUND: Inflammation plays an instrumental role in all stages of atherosclerosis. High-sensitivity C-reactive protein (hsCRP), a systemic inflammatory marker, has been gaining recognition as an independent risk factor for cardiovascular disease (CVD). Both baseline hsCRP concentrations and drug-induced hsCRP changes are highly variable and potentially subject to genetic regulation.

CONTENT: This review summarizes the current studies examining the effect of genetic and environmental factors on baseline plasma hsCRP concentrations, with a main focus on C-reactive protein, pentraxin-related (*CRP*) genetic polymorphisms and various dietary components that affect hsCRP concentrations. We also address the association of *CRP* genetic variations with CVD risk, a relationship that may support or refute the causality of CRP in the atherosclerotic process. Moreover, we discuss the impact of *CRP* genetic polymorphisms on hsCRP changes in response to 3-week fenofibrate treatment in the genetic intervention of the Genetics of Lipid Lowering Drugs and Diet Network study.

SUMMARY: Genetic variants on the *CRP* locus and other loci and dietary and lifestyle factors are responsible for the interindividual variability of plasma hsCRP concentrations. *CRP* genetic variants further influence differing plasma hsCRP response after 3-week fenofibrate treatment in patients with metabolic syndrome. Future studies focusing on the influence and interaction of genetic variation on the hsCRP response to dietary and other behavior modification as well as drug treatment could have important implications for the development of more personalized preventive and therapeutic approaches to reduce CVD.

C-reactive protein (CRP)[2] is an acute-phase protein belonging to the family of proteins known as pentraxins. CRP is a plasma protein that is phylogenetically highly conserved across different species and participates in the systemic response to inflammation *(1)*. CRP is synthesized and released primarily by hepatocytes, although reported data suggest local CRP synthesis and secretion may occur at other sites, such as macrophages *(2)* and smooth muscle cells *(3)*.

Inflammation plays an instrumental role in all stages of atherosclerosis. A number of inflammatory markers have been investigated for use in predicting cardiovascular disease (CVD), and among these CRP has been gaining recognition as an independent risk factor for CVD events. Results of recent studies in animal models suggest that CRP also directly participates in the pathogenesis of CVD *(4)*. In addition, increased high-sensitivity CRP (hsCRP) is associated with multiple risk factors for CVD, including obesity, insulin resistance, and hypertension, and has demonstrated significant predictive value for risk of metabolic syndrome (MetS) *(5)*.

In apparently healthy individuals plasma hsCRP concentrations are widely distributed, reflecting substantial interindividual variability *(6)* driven by multiple environmental, sociodemographic, behavioral, and lifestyle factors, as well as obesity and type II diabetes *(7, 8)*. Moreover, results of twin and family studies have led to estimations that genetic factors could contribute up to 35%–50% of the phenotypic variation of plasma hsCRP concentrations *(9, 10)*.

This review summarizes results of studies that have examined the effects of genetic polymorphisms as

[1] Nutrition and Genomics Laboratory, Jean Mayer-USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA.
* Address correspondence and reprint requests to this author at: Nutrition and Genomics Laboratory, Jean Mayer USDA HNRCA at Tufts University, 711 Washington, St., Boston, MA 02111-1524. E-mail jose.ordovas@tufts.edu.
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[2] Nonstandard abbreviations: CRP, C-reactive protein; CVD, cardiovascular disease; hsCRP, high sensitivity CRP; MetS, metabolic syndrome; SNP, single-nucleotide polymorphism; NHANES, National Health and Nutritional Examination Survey; TNF-α, tumor necrosis factor α; PUFA, polyunsaturated fatty acids; ALA, α-linolenic acid.

well as environmental factors, mainly dietary components, on plasma baseline hsCRP concentrations and associations with risk of CVD events. We also discuss the influence of C-reactive protein, pentraxin-related (*CRP*)[3] genetic polymorphisms on individual differences in response to treatment with the lipid-lowering drug fenofibrate.

Association between *CRP* Polymorphisms and Plasma Baseline hsCRP Concentrations and Risk of CVD Events

Data from 3 cohorts, including the Women's Health Study, the Pravastatin Inflammation/CRP Evaluation trial, and the Physicians' Health Study, demonstrated that a set of *CRP* single-nucleotide polymorphisms (SNPs)—including 2 promoter SNPs, rs3093059 and rs3091244; intron 1 SNP, rs1417938; exon 2 SNP, rs1800947; and two 3′-UTR SNPs, rs1130864 and rs1205—was consistently associated with plasma hsCRP concentrations *(11)*. Carson et al. evaluated 7 haplotype-tagging SNPs (including rs309358, rs3091244, rs1417938, rs1800947, rs3093066, rs1205, and rs2808630) in 6.8 kb surrounding the *CRP* locus and showed that *CRP* haplotypes were strongly associated with hsCRP concentrations in a large cohort study of CVD risk in European-American and African-American young adults. Among those SNPs, a promoter triallelic SNP rs3091244 was associated with the greatest proportion of overall hsCRP variance. Functional experiments revealed that this SNP resides within the hexameric core of transcription factor–binding elements. The presence of mutations alters a transcription factor (such as upstream stimulatory factor 1) binding motif and thus markedly affects the transcriptional activity of the *CRP* gene *(12)*. Two haplotype constructs (tagged by the triallelic SNP rs3091244) displayed high interleukin (IL)-6–induced promoter activity, which was consistent with the observed strong association of those 2 haplotypes with hsCRP concentrations *(13)*. The associations between *CRP* genotypes and plasma hsCRP concentrations were also observed in other large-scale studies, including the third National Health and Nutritional Examination Survey (NHANES III) and the Framingham Heart Study *(14–17)*.

Although growing evidence from experimental studies supports the direct participation of CRP in the atherosclerotic process, its causality is still under debate. Genetic dissection of CRP may provide additional evidence determining its causal role by taking advantage of "mendelian randomization." This method is similar to a randomized clinical trial in which the random assignment is the genotype that occurs at conception *(18)*. So the observed association between a disease and functional genetic polymorphisms is not susceptible to residual confounding or reverse causation, which may potentially bias the results of observational studies *(18)*. The hypothesis is that if CRP is causally involved in disease pathogenesis, then alleles that influence CRP synthesis could mediate the onset of clinical CVD events. In this regard, multiple cohort studies have examined the effect of *CRP* SNPs associated with baseline hsCRP concentrations on atherosclerotic disease progression or occurrence of clinical CVD events (such as myocardial infarction). Results from the Cardiovascular Health Study in older American adults, with a median follow-up of 13 years, showed that SNP rs1417938 was associated with increased risk of stroke and CVD mortality in white participants and SNP rs3093058 was associated with a 4-fold increased risk of myocardial infarction in black participants, whereas 2 SNPs (rs1800947 and rs1205) were associated with decreased risk of CVD mortality in white participants *(17)*. The direction of the CVD risk estimates paralleled that of the associations with plasma hsCRP concentrations. The NHANES III investigators also reported that the triallelic SNP rs3091244 was cross-sectionally associated with the prevalence of coronary heart disease (CHD) in the non-Hispanic white population *(15)*. These results have been controversial, however, because results from other cohorts, including those of the Physicians' Health Study, the Framingham Heart Study, and the Rotterdam Study, suggested little or no association between *CRP* genotype and risk of myocardial infarction or stroke *(11, 16, 19)*. Interpretation of these results requires consideration of a number of factors. First, the *CRP* locus accounts for only a small proportion of the variability of hsCRP concentrations. Therefore, some studies may be underpowered for detection of the genetic impact on disease outcome, especially given the small sample size and relatively small relative risk of disease. Second, age may play an important role, because positive associations are more commonly seen among older than among younger individuals *(17)*. Third, the influence of *CRP* may vary in association with disease stage. The association between *CRP* genotype and clinical CVD, together with the absence of association with carotid intima-media thickness *(20)*, which measures the extent of subclinical atherosclerotic disease, suggests a

[3] Human genes: *CRP*, C-reactive protein, pentraxin-related; *IL6*, interleukin 6 (interferon, beta 2); *TNF*, tumor necrosis factor (TNF superfamily, member 2); *IL1B*, interleukin 1, beta; *TH*, tyrosine hydroxylase; *ADRB1*, adrenergic, beta-1-, receptor; *ADRB2*, adrenergic, beta-2-, receptor; *APOE*, apolipoprotein E; *LEPR*, leptin receptor; *IL6R*, interleukin 6 receptor; *GCKR*, glucokinase (hexokinase 4) regulator; *HNF1A*, HNF1 homeobox A.

greater involvement of CRP in the transition from subclinical to clinical disease than in atherosclerosis progression. This observation was in agreement with the lack of association between plasma hsCRP concentrations and carotid intima-media thickness *(21)*. Moreover, associations are more likely observed in cases of disease with fatal outcomes *(11, 17, 19)*, which is in line with the involvement of hsCRP concentrations in the increase of infarct size *(22)*, suggesting the possibility that through an effect on acute-phase response *(23)*, *CRP* genotype may be more strongly associated with more severe events. Finally, the use of genetic markers as an instrumental variable to assess causality could lead to misleading conclusions in the presence of linkage disequilibrium, genetic heterogeneity, pleiotropy, or population stratification *(24)*.

In summary, current studies have provided convincing evidence of the significant impact of *CRP* polymorphisms on baseline plasma hsCRP concentrations; however, the genetic association with risk of CVD events is equivocal despite the fact that hsCRP concentrations are a strong independent predictor of CVD. In this regard, the recently launched international consortium, the CRP CHD Genetics Collaboration, from more than 30 relevant studies of *CRP* genetic variants and CHD risk, should provide compelling evidence to elucidate the casual relationship of *CRP* genetic variants and circulating hsCRP concentrations with CHD *(25)*.

CRP Polymorphisms Affect hsCRP Response to Fenofibrate Lipid-Lowering Therapy

Fenofibrate, a PPAR (peroxisome proliferator-activated receptor) α agonist, is a member of the fibrate class of lipid-lowering drugs. Both experimental studies and clinical trials have demonstrated that fibrates may additionally reduce CVD risk through antiinflammatory effects, including attenuation of constitutive and induced *CRP* gene expression *(26, 27)*. Fibrates target both the atherogenic "lipid triad" (high triglycerides and low HDL with small and dense LDL particles) and inflammation *(28)*. Because both phenotypes are important components of diabetes and MetS and potentially link these 2 metabolic disorders to CVD *(29, 30)*, fibrates are hypothesized to be candidates for treating dyslipidemia associated with diabetes and MetS, and more effective in reducing CVD in those at high risk *(31–33)*.

It has been documented that the individual response to fibrate is highly variable, and multiple genes have been identified to be associated with the efficacy of lipid lowering *(34, 35)*. However, the genetic impact on the antiinflammatory effect of this drug is less well understood. In this regard, we examined the association of *CRP* genetic polymorphisms with hsCRP response to a 3-week fenofibrate treatment among US white participants in the Genetics of Lipid Lowering Drugs and Diet Network study, a single-arm, uncontrolled, nonrandomized intervention funded by the National Heart, Lung, and Blood Institute with the purpose of identifying genetic variants associated with interindividual variability of triglyceride responses to a high fat meal and fenofibrate *(36, 37)*. The study population consisted of 539 men and 584 women, and the majority of participants were rerecruited from the ongoing National Heart, Lung, and Blood Institute Family Heart Study conducted in 2 genetically homogeneous centers (Minneapolis and Salt Lake City) with predominantly white populations. The baseline characteristics of the study participants are provided in Supplemental Table 1, which accompanies the online version of this review at http://www.clinchem.org/content/vol55/issue2. In this study, and consistent with previous reports, SNPs m301G>A >T (rs3091244), i178T>A (rs1417938), 3u1273C>T (rs1130864), and 3u2131C>T (rs1205) were significantly associated with baseline hsCRP concentrations. Moreover, we observed effects of the m301G>A >T and the i178T>A SNPs on hsCRP response to fenofibrate intervention among participants with MetS. Specifically, G-allele carriers for the m301G>A>T SNP displayed greater reduction of hsCRP concentrations than noncarriers. Similarly, TT individuals with the i178T>A SNP had greater reductions in hsCRP concentrations than TA and AA individuals (Fig. 1). It is of interest that the alleles associated with high baseline inflammatory status appear to be more resistant to the antiinflammatory effect of fenofibrate. Conversely, in the presence of an inflammatory stimuli, these alleles, such as the minor allele of 3u1273C>T (previously reported as 1444C>T, rs1130864, in complete linkage disequilibrium with i178T>A, rs1417938), have been shown to be associated with greater hsCRP increases in patients undergoing coronary artery bypass graft or periodontal therapy *(14, 38)*. The mechanism underlying the modulation of genetic variants on hsCRP response to fenofibrate among individuals with MetS is undefined. However, because both SNPs appear to be involved in transcription factor–binding motifs, it is possible that some of the genetic effects may be attributable to the interaction of these transcription factors, in particular upstream stimulatory factor 1 with PPARα. Our findings have practical relevance because lipid-lowering drugs, such as statins and fibrates, remain critical elements in the prevention of CVD *(35)*. In addition, although a series of large-scale intervention trials using fibrates have established the role of fibrates in normalizing lipid profiles, the results regarding the efficacy of fibrates in the reduction of CVD

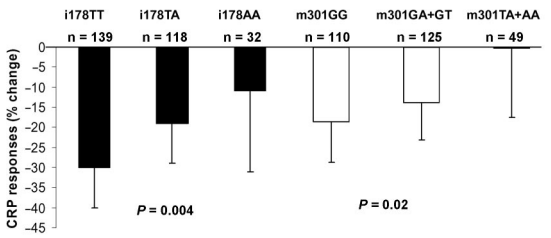

Fig. 1. Plasma hsCRP response to 3-week fenofibrate treatment among patients with MetS according to *CRP* i178T>A and m301G>A>T genotypes (geometric means ±95% CI).

P-value obtained from additive model was adjusted for baseline hsCRP concentrations, change of triglyceride, change of IL-6, age, sex, body-mass index, smoking status, alcohol intake, physical activity and use of aspirin and nonsteroidal antiinflammatory drugs; drugs for lowering cholesterol, diabetes, and hypertension; and hormone treatment in women. Patients with hsCRP >10 mg/L at the baseline or after the treatment were excluded from the analysis.

events have been inconsistent *(39)*. Further subgroup analyses revealed that features of the MetS modify the effect of fibrate on CVD such that cardiovascular benefits are largely confined to individuals with features of the MetS *(39)*. Our data provide additional insight into the heterogeneity of the treatment response, suggesting that genetic differences could further differentiate individual responses to fenofibrate and thus potentially may affect the disease outcome among individuals at high risk. Last, if the reduction of hsCRP concentrations could directly lead to decreased rates of recurrent CVD events and of coronary atherosclerosis progression reported from multiple randomized clinical trials using statins *(27, 40)*, individuals carrying certain genotypes that potentially impact hsCRP response to treatment may have a trajectory of cardiovascular outcomes differing from that of noncarriers, and therefore may require different lifestyle modifications or therapeutic regimens.

Association of Plasma hsCRP Concentrations with Other Inflammatory Markers and Genetic Determinants

CRP is considered an important downstream inflammatory marker, and its activity may reflect the action of several upstream cytokines. Experimental studies indicated that hepatic expression of CRP is regulated at the transcription level by various cytokines, including IL-6, IL-1β *(1)*, and tumor necrosis factor α (TNF-α) *(41)*. A recent study revealed that the protein kinase C pathway is also involved in the regulation of CRP, and that IL-8 acts as a potential physiological protein kinase C activator that significantly induces hepatic CRP release *(42)*. CRP may also exert proinflammatory activity through the induction of adhesion-molecule expression, activation of the complement system, and inhibition of fibrinolysis by inducing plasminogen activator inhibitor-1 *(43, 44)*. Because of the strong biological connection between CRP and those inflammatory mediators, circulating hsCRP values correlate closely with other markers of inflammation such as IL-6, TNF-α, intercellular adhesion molecule-1, and fibrinogen *(45–47)*. Some of those inflammatory markers have been shown to predict CVD; however, the association is less significant and consistent than that of hsCRP *(47)*. Nevertheless, characterizing the relationship between hsCRP and other markers of inflammation opens up a new perspective for the identification of improved predictors and additional therapeutic targets for CVD.

Understanding of the interrelation between CRP and other inflammatory mediators has laid the foundation for the search for the genetic determinants of CRP that reside outside of the *CRP* locus. To date, multiple candidate genes involving the CRP regulatory pathway have been reported to affect hsCRP concentrations. The interleukin 6 (interferon, beta 2) (*IL6*) –174G/C and –572C/G SNPs, the tumor necrosis factor (TNF superfamily, member 2) (*TNF*) G-308A SNP, and the interleukin 1, beta (*IL1B*) –511C/T and 3954C/T SNPs have all been shown to be associated with baseline hsCRP concentrations *(48–50)*. In addition to the obvious inflammation candidate genes, other loci reported to be associated with hsCRP concentrations include tyrosine hydroxylase (*TH*), a rate-limiting enzyme of catecholamine biosynthesis that has been linked to CRP production; 2 β-adrenergic receptors, adrenergic, beta-1-, receptor (*ADRB1*) and adrenergic, beta-2-, receptor (*ADRB2*) *(51)*; and the apolipoprotein E (*APOE*) locus *(52)*.

In addition, a genome-wide association study among 6345 healthy women participating in the Women's Genome Health Study, in which 336 108 SNPs were successfully genotyped, has revealed several novel loci associated with plasma hsCRP concentrations. Those new loci included leptin receptor (*LEPR*), interleukin 6 receptor (*IL6R*), glucokinase (hexokinase 4) regulator (*GCKR*), and the hepatic transcription-factor gene HNF1 homeobox A (*HNF1A*). Because these genes are directly involved in MetS, insulin resistance, β-cell function, and weight homeostasis, this new pathogenetic link opens a new field involving the regulation of plasma hsCRP and the roles of CRP in CVD

as both a useful biomarker and an active participant *(53)*.

The Association of Environmental Factors with Plasma hsCRP Concentrations

The environmental factors discussed below have been shown to contribute to the phenotypic variation in hsCRP. Dietary intake has been among the best studied *(7, 8)*.

DIETARY FAT AND hsCRP CONCENTRATIONS

Epidemiological studies have revealed that dietary fatty acid composition can modulate inflammation *(54)*. A cross-sectional study of 730 women from the Nurses' Health Study I cohort found that women in the highest quintile of trans fat intake had a 73% higher hsCRP concentration compared with those with the lowest quintile of intake *(55)*. Similarly, data from both a subsample of the Health Professionals Follow-up Study (n = 446 men) and the NHANES participants (1999–2000, n = 4900) suggested that high fat intake, particularly saturated and trans fatty acids, was associated with increased hsCRP concentrations *(56, 57)*. Intervention trials have provided further evidence in support of the relationship of increases in inflammation with the intake of saturated and trans fatty acids. Pirro et al. found that the 8-week consumption of a low cholesterol/low saturated fat diet significantly decreased hsCRP concentrations in 35 hypercholesterolemic patients *(58)*. Similar increases were reported in healthy individuals when trans fatty acid was used as a replacement fat within the context of a high-fat diet (39% fat) *(59)*.

The relationship between dietary n-3 polyunsaturated fatty acids (PUFAs) [α-linolenic acid (ALA), eicosapentaenoic acid, and docosahexaenoic acid] and chronic inflammation has also been examined. The Nurses' Health Study I cohort (n = 727 women) showed lower concentrations of markers of inflammation and endothelial activation, including hsCRP, IL-6, and E-selectin, among women in the highest quintile of n-3 PUFA compared with those in the lowest quintile *(60)*. Moreover, results from a study of 3042 Greek healthy adults showed that study participants who consumed at least 300 g of fish per week had 33% lower hsCRP compared with those who did not consume fish *(61)*. Several clinical trials also confirmed the antiinflammatory effect of ALA. Rallidis et al. found a significant reduction of hsCRP and IL-6 concentrations after ALA supplementation, whereas LA supplementation decreased cholesterol concentrations with no significant effects on inflammation in 90 male dyslipidemic patients (The ratio of n-6 to n-3 was 1.3:1 in the ALA-supplemented group and 13.2:1 in the LA-supplemented group) *(62)*. In addition, Bemelmans et al. reported a lowering of hsCRP concentrations in 103 moderately hypercholesterolemic men and women after consumption of an ALA-enriched margarine compared to those consuming an LA-enriched margarine *(63)*. Although epidemiological studies have shown an inverse correlation between consumption of dietary fish or fish oil (eicosapentaenoic acid and docosahexaenoic acid) and biomarkers of inflammation *(60, 64)*, results from clinical trials are inconclusive *(65, 66)*.

As for monounsaturated fatty acids, results of a cross-sectional study of a Japanese population consisting of 1556 men and 1461 women suggested that intake of oleic acid was inversely associated with hsCRP concentrations *(67)*. Another study of 180 patients with MetS, but free of CVD, demonstrated that patients consuming a Mediterranean-style diet high in oleic acid as well as fiber and antioxidants had lower serum concentrations of hsCRP and cytokines (IL-6, IL-7, and IL-18) compared with a control group consuming their usual diet *(68)*.

Taken together, the current evidence supports the notion that the overall quantity of fat intake; the sources and type of dietary fat, with special emphasis on saturated and trans fatty acids, ALA and oleic acid; and the ratio of n-6 to n-3 PUFA play significant roles in modulating hsCRP concentrations and other markers of inflammation.

CARBOHYDRATES, DIETARY FIBER, MICRONUTRIENTS, AND hsCRP CONCENTRATIONS

The quantity and quality of carbohydrate intake affect the risk of CVD through alteration of blood lipid concentrations and inflammation. High intake of refined carbohydrates, such as starch and sugar, results in the increase of postprandial hyperglycemia, which may lead to the increased circulating concentrations of free radicals, proinflammatory cytokines, and hsCRP *(69)*. Among 18 137 healthy women participating in the Women's Health Study, dietary glycemic index and glycemic load were significantly associated with hsCRP; the highest quintiles of glycemic index and glycemic load were associated with high hsCRP compared with the lowest quintiles *(70)*.

Regarding the relation between dietary fiber and inflammation, data from the NHANES indicated that dietary fiber intake was inversely associated with serum hsCRP concentration among 3920 adult participants *(71)*. Moreover, a longitudinal study involving 524 individuals demonstrated that the likelihood of increased hsCRP concentrations was 63% lower (odds ratio 0.37, 95% CI 0.16, 0.87) in participants in the highest quartile of total fiber intake compared to participants in the lowest quartile *(72)*. The antiinflammatory effect of

dietary fiber may be mediated through reduction of lipid oxidation, normalization of bowel flora, and inhibition of hyperglycemia *(73)*.

The antiinflammatory effects of micronutrients (i.e., vitamins and minerals) have also been explored, and several studies have demonstrated an inverse association between vitamin E, vitamin B_6, carotenoids, and magnesium and plasma hsCRP concentrations *(74)*.

FRUIT, VEGETABLE, AND NUT INTAKE AND INFLAMMATION

Esmaillzadeh et al. reported that in 486 Tehrani women, higher intakes of fruits and vegetables were associated with a lower risk of MetS and lower hsCRP concentrations, and after adjustment for age, body-mass index, and waist circumference, mean plasma hsCRP concentrations across increasing quintile categories of fruit intake were 1.94, 1.79, 1.65, 1.61, and 1.56 mg/L and of vegetable intakes were 2.03, 1.82, 1.58, 1.52, and 1.47 mg/L *(75)*. In a randomized controlled 4-week trial in 64 nonsmoking men, study participants who consumed 8 servings per day of carotenoid-rich vegetables and fruit had significantly reduced hsCRP concentrations compared with those who consumed 2 servings per day *(76)*. The antiinflammatory effect appears to be mainly attributable to the antioxidant components of fruits and vegetables *(77)*.

High consumption of nuts that are rich in monounsaturated fatty acids, PUFA, and arginine has been inversely associated with risk of CVD. The beneficial effect is partially attributable to an antiinflammatory effect *(78)*.

DIETARY PATTERNS AND hsCRP CONCENTRATIONS

In addition to focusing on individual nutrients and food items, research has also focused on dietary patterns, which may reveal more details of nutrient–nutrient synergy and interaction with respect to the modulation of inflammation.

Results of a cross-sectional study of 732 healthy women suggested that a prudent dietary pattern characterized by higher intakes of fruit, vegetables, legumes, fish, poultry, and whole grains was inversely associated with plasma hsCRP, whereas a Western-type diet characterized by high intakes of red and processed meats, sweets, desserts, french fries, and refined grains was positively associated with hsCRP. Study participants categorized as having the most prudent diet had average hsCRP of 1.3 mg/L compared with an average of 1.7 mg/L in those classified as having the most Western diet *(55)*. Interestingly, a randomized trial conducted among 180 patients with MetS found that patients who consumed the Mediterranean diet rich in fruits and vegetables, nuts (274 g/day), whole grains (103 g/day), and olive oil (8 g/day) for 2 years showed significantly reduced inflammatory markers such as hsCRP, increased insulin sensitivity, and decreased risk of MetS compared with patients following a prudent diet *(68)*.

OTHER LIFESTYLE FACTORS AND hsCRP CONCENTRATIONS

Results from a prospective study of 27 055 healthy women participating in the Women's Health Study clearly demonstrated that the beneficial effects of physical activity on a reduced risk of CVD could be mediated in part by decreases in chronic inflammation in addition to other known risk factors *(79)*. The inverse association between high levels of physical activity or exercise training and markers of chronic inflammation such as hsCRP has been consistently reported *(80–82)*. Physical activity and cardiorespiratory fitness have been estimated to reduce hsCRP concentrations by 6%–35% *(83)*. For example, data from the NHANES III, which included 13 748 participants, demonstrated that the odds ratios for increased hsCRP concentrations were 0.98 (95% CI 0.78–1.23), 0.85 (0.70–1.02), and 0.53 (0.40–0.71) for participants who engaged in light, moderate, and vigorous physical activity, respectively, compared with participants who did not engage in any leisure-time physical activity *(80)*. Moreover, physically active individuals displayed low concentrations of lipopolysaccharide-stimulated production of IL-6, IL-1β, TNF-α, TLR4, and hsCRP compared with inactive subjects *(81)*. Moreover, intervention in the form of a 12-week aerobic and resistance exercise regimen significantly reduced hsCRP concentrations among physically inactive young and old adults down to the similar values observed among physically active young and old adults *(82)*. In addition to effects observed in healthy individuals, the exercise training also significantly improved hsCRP among patients with chronic diseases, such as CHD and type II diabetes *(84, 85)*.

Increasing levels of physical activity appear to reduce plasma hsCRP by mechanisms beyond effects on body weight, as evidenced by a study showing that both low levels of physical activity and high levels of body-mass index were independently associated with increased inflammatory markers *(86)*. Physical activity has been postulated to have favorable effects on proatherogenic adipokines, insulin metabolism, and endothelial function *(87)*. Other mechanisms have also been suggested, including exercise-induced release of heat-shock protein, alteration of immune function, or reduced tissue hypoxia *(88)*.

Whereas physical inactivity as a CVD risk factor is not yet well understood, cigarette smoking is a well-established risk factor. Smoking triggers an immunologic response and vascular injury, which are associated

with increased concentrations of inflammatory markers, such as hsCRP *(89)*. Several studies have demonstrated strong links between smoking and increased concentrations of hsCRP and other markers of inflammation *(90, 91)*. For example, a study in 2920 British older men showed that compared with never smokers, current cigarette smokers had significantly higher concentrations of hsCRP (2.53 vs 1.35 mg/L). However, most inflammatory levels improved within 5 years of smoking cessation, but reversion to values of never smokers did not occur until more than 20 years of smoking cessation *(91)*. Data from the NHANES III with 15 489 participants (1988–1994) suggested that after adjustment for traditional CVD risk factors, cigarette smoking was related to increased concentrations of hsCRP and fibrinogen, with a dose-dependent and temporal relationship *(89)*.

Collectively, dietary habits and other lifestyle factors that influence hsCRP provide the tools for CVD risk prevention. Furthermore, preventive and therapeutic recommendations could be even more successful if they were tailored by using genetic information aimed at the *CRP* gene. Current knowledge is not solid enough, however, to use this approach to provide clinically relevant advice.

Conclusions

The *CRP* locus, together with other loci that are involved in its regulatory pathway, significantly influences plasma hsCRP concentrations. The reported impact of *CRP* genetic variants on CVD risk and events provides some support to the notion that CRP may play a causal role in the pathogenesis of atherosclerotic disease. The evidence for this role is not yet conclusive, however. Moreover, *CRP* genetic variants could affect hsCRP response to lipid-lowering drugs, such as fenofibrate, and thus may have a defining influence on the success of the intervention. Environmental exposures such as diet and other lifestyle factors also affect interindividual variation of hsCRP phenotypes, and there is support for the interaction of genetic and environmental factors in these complex traits. Therefore, further characterization of the influence and interaction of genetic variation on the hsCRP response to dietary and other behavior modification as well as drug treatment could have great implications for the development of more personalized preventive and therapeutic approaches to CVD.

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References

1. Black S, Kushner I, Samols D. C-reactive protein. J Biol Chem 2004;279:48487–90.
2. Dong Q, Wright JR. Expression of C-reactive protein by alveolar macrophages. J Immunol 1996;156:4815–20.
3. Kobayashi S, Inoue N, Ohashi Y, Terashima M, Matsui K, Mori T, et al. Interaction of oxidative stress and inflammatory response in coronary plaque instability: important role of C-reactive protein. Arterioscler Thromb Vasc Biol 2003;23:1398–404.
4. Paul A, Ko KW, Li L, Yechoor V, McCrory MA, Szalai AJ, Chan L. C-reactive protein accelerates the progression of atherosclerosis in apolipoprotein E-deficient mice. Circulation 2004;109:647–55.
5. Haffner SM. The metabolic syndrome: inflammation, diabetes mellitus, and cardiovascular disease. Am J Cardiol 2006;97:3A–11A.
6. Ridker PM. High-sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation 2001;103:1813–8.
7. de Maat MP, Kluft C. Determinants of C-reactive protein concentration in blood. Ital Heart J 2001;2:189–95.
8. Ford ES, Giles WH, Mokdad AH, Myers GL. Distribution and correlates of C-reactive protein concentrations among adult US women. Clin Chem 2004;50:574–81.
9. MacGregor AJ, Gallimore JR, Spector TD, Pepys MB. Genetic effects on baseline values of C-reactive protein and serum amyloid a protein: a comparison of monozygotic and dizygotic twins. Clin Chem 2004;50:130–4.
10. Pankow JS, Folsom AR, Cushman M, Borecki IB, Hopkins PN, Eckfeldt JH, Tracy RP. Familial and genetic determinants of systemic markers of inflammation: the NHLBI family heart study. Atherosclerosis 2001;154:681–9.
11. Miller DT, Zee RY, Suk Danik J, Kozlowski P, Chasman DI, Lazarus R, et al. Association of common CRP gene variants with CRP levels and cardiovascular events. Ann Hum Genet 2005;69:623–38.
12. Szalai AJ, Wu J, Lange EM, McCrory MA, Langefeld CD, Williams A, et al. Single-nucleotide polymorphisms in the C-reactive protein (CRP) gene promoter that affect transcription factor binding, alter transcriptional activity, and associate with differences in baseline serum CRP level. J Mol Med 2005;83:440–7.
13. Carlson CS, Aldred SF, Lee PK, Tracy RP, Schwartz SM, Rieder M, et al. Polymorphisms within the

C-reactive protein (CRP) promoter region are associated with plasma CRP levels. Am J Hum Genet 2005;77:64–77.

14. Brull DJ, Serrano N, Zito F, Jones L, Montgomery HE, Rumley A, et al. Human CRP gene polymorphism influences CRP levels: implications for the prediction and pathogenesis of coronary heart disease. Arterioscler Thromb Vasc Biol 2003;23: 2063–9.
15. Crawford DC, Sanders CL, Qin X, Smith JD, Shephard C, Wong M, et al. Genetic variation is associated with C-reactive protein levels in the Third National Health and Nutrition Examination Survey. Circulation 2006;114:2458–65.
16. Kathiresan S, Larson MG, Vasan RS, Guo CY, Gona P, Keaney JF Jr, et al. Contribution of clinical correlates and 13 C-reactive protein gene polymorphisms to interindividual variability in serum C-reactive protein level. Circulation 2006; 113:1415–23.
17. Lange LA, Carlson CS, Hindorff LA, Lange EM, Walston J, Durda JP, et al. Association of polymorphisms in the CRP gene with circulating C-reactive protein levels and cardiovascular events. JAMA 2006;296:2703–11.
18. Davey Smith G, Lawlor DA, Harbord R, Timpson N, Rumley A, Lowe GD, et al. Association of C-reactive protein with blood pressure and hypertension: life course confounding and mendelian randomization tests of causality. Arterioscler Thromb Vasc Biol 2005;25:1051–6.
19. Kardys I, de Maat MP, Uitterlinden AG, Hofman A, Witteman JC. C-reactive protein gene haplotypes and risk of coronary heart disease: the Rotterdam Study. Eur Heart J 2006;27:1331–7.
20. Wang Q, Hunt SC, Xu Q, Chen YE, Province MA, Eckfeldt JH, et al. Association study of CRP gene polymorphisms with serum CRP level and cardiovascular risk in the NHLBI Family Heart Study. Am J Physiol Heart Circ Physiol 2006;291: H2752–7.
21. Juonala M, Viikari JS, Ronnemaa T, Taittonen L, Marniemi J, Raitakari OT. Childhood C-reactive protein in predicting CRP and carotid intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. Arterioscler Thromb Vasc Biol 2006;26:1883–8.
22. Pepys MB, Hirschfield GM, Tennent GA, Gallimore JR, Kahan MC, Bellotti V, et al. Targeting C-reactive protein for the treatment of cardiovascular disease. Nature (Lond) 2006;440:1217–21.
23. Suk Danik J, Chasman DI, Cannon CP, Miller DT, Zee RY, Kozlowski P, et al. Influence of genetic variation in the C-reactive protein gene on the inflammatory response during and after acute coronary ischemia. Ann Hum Genet 2006;70: 705–16.
24. Davey Smith G, Ebrahim S. "Mendelian randomization": can genetic epidemiology contribute to understanding environmental determinants of disease? Int J Epidemiol 2003;32:1–22.
25. CRP CHD Genetics Collaboration. Collaborative pooled analysis of data on C-reactive protein gene variants and coronary disease: judging causality by Mendelian randomisation. Eur J Epidemiol 2008;23:531–40.
26. Kleemann R, Verschuren L, de Rooij BJ, Lindeman J, de Maat MM, Szalai AJ, et al. Evidence for anti-inflammatory activity of statins and PPARalpha activators in human C-reactive protein transgenic mice in vivo and in cultured human hepatocytes in vitro. Blood 2004;103:4188–94.
27. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, et al. C-reactive protein levels and outcomes after statin therapy. N Engl J Med 2005;352:20–8.
28. Libby P, Plutzky J. Inflammation in diabetes mellitus: role of peroxisome proliferator-activated receptor-alpha and peroxisome proliferator-activated receptor-gamma agonists. Am J Cardiol 2007;99:27B–40B.
29. Roberts AW, Evans M. The metabolic syndrome, inflammation and cardiovascular disease in type 2 diabetes. Curr Opin Lipidol 2004;15:89–91.
30. Turner RC, Millns H, Neil HA, Stratton IM, Manley SE, Matthews DR, Holman RR. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). BMJ 1998;316: 823–8.
31. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005; 366:1849–61.
32. Rubins HB, Robins SJ, Collins D, Nelson DB, Elam MB, Schaefer EJ, et al. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). Arch Intern Med 2002;162:2597–604.
33. Tenenbaum A, Motro M, Fisman EZ, Tanne D, Boyko V, Behar S. Bezafibrate for the secondary prevention of myocardial infarction in patients with metabolic syndrome. Arch Intern Med 2005; 165:1154–60.
34. Brisson D, Ledoux K, Bosse Y, St-Pierre J, Julien P, Perron P, et al. Effect of apolipoprotein E, peroxisome proliferator-activated receptor alpha and lipoprotein lipase gene mutations on the ability of fenofibrate to improve lipid profiles and reach clinical guideline targets among hypertriglyceridemic patients. Pharmacogenetics 2002;12:313–20.
35. Schmitz G, Schmitz-Madry A, Ugocsai P. Pharmacogenetics and pharmacogenomics of cholesterol-lowering therapy. Curr Opin Lipidol 2007;18: 164–73.
36. Corella D, Arnett DK, Tsai MY, Kabagambe EK, Peacock JM, Hixson JE, et al. The -256T>C polymorphism in the apolipoprotein A-II gene promoter is associated with body mass index and food intake in the Genetics of Lipid Lowering Drugs and Diet Network Study. Clin Chem 2007; 53:1144–52.
37. Shen J, Arnett DK, Parnell LD, Peacock JM, Lai CQ, Hixson JE, et al. Association of common C-reactive protein (CRP) gene polymorphisms with baseline plasma CRP levels and fenofibrate response: the GOLDN study. Diabetes Care 2008; 31:910–5.
38. D'Aiuto F, Casas JP, Shah T, Humphries SE, Hingorani AD, Tonetti MS. C-reactive protein (+1444C>T) polymorphism influences CRP response following a moderate inflammatory stimulus. Atherosclerosis 2005;179:413–7.
39. Barter PJ, Rye KA. Is there a role for fibrates in the management of dyslipidemia in the metabolic syndrome? Arterioscler Thromb Vasc Biol 2008; 28:39–46.
40. Nissen SE, Tuzcu EM, Schoenhagen P, Crowe T, Sasiela WJ, Tsai J, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med 2005;352:29–38.
41. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest 2003;111:1805–12.
42. Ivashchenko Y, Kramer F, Schafer S, Bucher A, Veit K, Hombach V, et al. Protein kinase C pathway is involved in transcriptional regulation of C-reactive protein synthesis in human hepatocytes. Arterioscler Thromb Vasc Biol 2005;25: 186–92.
43. Devaraj S, Xu DY, Jialal I. C-reactive protein increases plasminogen activator inhibitor-1 expression and activity in human aortic endothelial cells: implications for the metabolic syndrome and atherothrombosis. Circulation 2003;107: 398–404.
44. Szmitko PE, Wang CH, Weisel RD, de Almeida JR, Anderson TJ, Verma S. New markers of inflammation and endothelial cell activation; part I: circulation 2003;108:1917–23.
45. Berrahmoune H, Herbeth B, Lamont JV, Lambert D, Blankenberg S, Tiret L, et al. Association of classical and related inflammatory markers with high-sensitivity C-reactive protein in healthy individuals: results from the Stanislas cohort. Clin Chem Lab Med 2007;45:1339–46.
46. Piche ME, Lemieux S, Weisnagel SJ, Corneau L, Nadeau A, Bergeron J. Relation of high-sensitivity C-reactive protein, interleukin-6, tumor necrosis factor-alpha, and fibrinogen to abdominal adipose tissue, blood pressure, and cholesterol and triglyceride levels in healthy postmenopausal women. Am J Cardiol 2005;96:92–7.
47. Ridker PM, Brown NJ, Vaughan DE, Harrison DG, Mehta JL. Established and emerging plasma biomarkers in the prediction of first atherothrombotic events. Circulation 2004;109:IV6–19.
48. Eklund C, Jahan F, Pessi T, Lehtimaki T, Hurme M. Interleukin 1B gene polymorphism is associated with baseline C-reactive protein levels in healthy individuals. Eur Cytokine Netw 2003;14:168–71.
49. Lakka HM, Lakka TA, Rankinen T, Rice T, Rao DC, Leon AS, et al. The TNF-alpha G-308A polymorphism is associated with C-reactive protein levels: the HERITAGE Family Study. Vascul Pharmacol 2006;44:377–83.
50. Vickers MA, Green FR, Terry C, Mayosi BM, Julier C, Lathrop M, et al. Genotype at a promoter polymorphism of the interleukin-6 gene is associated with baseline levels of plasma C-reactive protein. Cardiovasc Res 2002;53:1029–34.
51. Wessel J, Moratorio G, Rao F, Mahata M, Zhang L, Greene W, et al. C-reactive protein, an "intermediate phenotype" for inflammation: human twin studies reveal heritability, association with blood pressure and the metabolic syndrome, and the influence of common polymorphism at catecholaminergic/beta-adrenergic pathway loci. J Hypertens 2007;25:329–43.
52. Marz W, Scharnagl H, Hoffmann MM, Boehm BO, Winkelmann BR. The apolipoprotein E polymorphism is associated with circulating C-reactive protein (the Ludwigshafen risk and cardiovascular health study). Eur Heart J 2004;25:2109–19.
53. Ridker PM, Pare G, Parker A, Zee RY, Danik JS, Buring JE, et al. Loci related to metabolic-syndrome pathways including LEPR,HNF1A, IL6R,

and GCKR associate with plasma C-reactive protein: the Women's Genome Health Study. Am J Hum Genet 2008;82:1185–92.
54. Phinney SD. Fatty acids, inflammation, and the metabolic syndrome. Am J Clin Nutr 2005;82: 1151–2.
55. Lopez-Garcia E, Schulze MB, Fung TT, Meigs JB, Rifai N, Manson JE, Hu FB. Major dietary patterns are related to plasma concentrations of markers of inflammation and endothelial dysfunction. Am J Clin Nutr 2004;80:1029–35.
56. Fung TT, Rimm EB, Spiegelman D, Rifai N, Tofler GH, Willett WC, Hu FB. Association between dietary patterns and plasma biomarkers of obesity and cardiovascular disease risk. Am J Clin Nutr 2001;73:61–7.
57. King DE, Egan BM, Geesey ME. Relation of dietary fat and fiber to elevation of C-reactive protein. Am J Cardiol 2003;92:1335–9.
58. Pirro M, Schillaci G, Savarese G, Gemelli F, Mannarino MR, Siepi D, et al. Attenuation of inflammation with short-term dietary intervention is associated with a reduction of arterial stiffness in subjects with hypercholesterolaemia. Eur J Cardiovasc Prev Rehabil 2004;11:497–502.
59. Baer DJ, Judd JT, Clevidence BA, Tracy RP. Dietary fatty acids affect plasma markers of inflammation in healthy men fed controlled diets: a randomized crossover study. Am J Clin Nutr 2004;79:969–73.
60. Lopez-Garcia E, Schulze MB, Manson JE, Meigs JB, Albert CM, Rifai N, et al. Consumption of (n-3) fatty acids is related to plasma biomarkers of inflammation and endothelial activation in women. J Nutr 2004;134:1806–11.
61. Zampelas A, Panagiotakos DB, Pitsavos C, Das UN, Chrysohoou C, Skoumas Y, Stefanadis C. Fish consumption among healthy adults is associated with decreased levels of inflammatory markers related to cardiovascular disease: the ATTICA study. J Am Coll Cardiol 2005;46:120–4.
62. Rallidis LS, Paschos G, Papaioannou ML, Liakos GK, Panagiotakos DB, Anastasiadis G, Zampelas A. The effect of diet enriched with alpha-linolenic acid on soluble cellular adhesion molecules in dyslipidaemic patients. Atherosclerosis 2004;174: 127–32.
63. Bemelmans WJ, Lefrandt JD, Feskens EJ, van Haelst PL, Broer J, Meyboom-de Jong B, et al. Increased alpha-linolenic acid intake lowers C-reactive protein, but has no effect on markers of atherosclerosis. Eur J Clin Nutr 2004;58:1083–9.
64. Madsen T, Skou HA, Hansen VE, Fog L, Christensen JH, Toft E, Schmidt EB. C-reactive protein, dietary n-3 fatty acids, and the extent of coronary artery disease. Am J Cardiol 2001;88:1139–42.
65. Geelen A, Brouwer IA, Schouten EG, Kluft C, Katan MB, Zock PL. Intake of n-3 fatty acids from fish does not lower serum concentrations of C-reactive protein in healthy subjects. Eur J Clin Nutr 2004;58:1440–2.
66. Vega-Lopez S, Kaul N, Devaraj S, Cai RY, German B, Jialal I. Supplementation with omega3 polyunsaturated fatty acids and all-rac alpha-tocopherol alone and in combination failed to exert an anti-inflammatory effect in human volunteers. Metabolism 2004;53:236–40.
67. Yoneyama S, Miura K, Sasaki S, Yoshita K, Morikawa Y, Ishizaki M, et al. Dietary intake of fatty acids and serum C-reactive protein in Japanese. J Epidemiol 2007;17:86–92.
68. Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, et al. Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. JAMA 2004; 292:1440–6.
69. Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M, et al. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. Circulation 2002;106:2067–72.
70. Levitan EB, Cook NR, Stampfer MJ, Ridker PM, Rexrode KM, Buring JE, et al. Dietary glycemic index, dietary glycemic load, blood lipids, and C-reactive protein. Metabolism 2008;57:437–43.
71. Ajani UA, Ford ES, Mokdad AH. Dietary fiber and C-reactive protein: findings from National Health and Nutrition Examination Survey data. J Nutr 2004;134:1181–5.
72. Ma Y, Griffith JA, Chasan-Taber L, Olendzki BC, Jackson E, Stanek EJ 3rd, et al. Association between dietary fiber and serum C-reactive protein. Am J Clin Nutr 2006;83:760–6.
73. King DE. Dietary fiber, inflammation, and cardiovascular disease. Mol Nutr Food Res 2005;49: 594–600.
74. Basu A, Devaraj S, Jialal I. Dietary factors that promote or retard inflammation. Arterioscler Thromb Vasc Biol 2006;26:995–1001.
75. Esmaillzadeh A, Kimiagar M, Mehrabi Y, Azadbakht L, Hu FB, Willett WC. Fruit and vegetable intakes, C-reactive protein, and the metabolic syndrome. Am J Clin Nutr 2006;84:1489–97.
76. Watzl B, Kulling SE, Moseneder J, Barth SW, Bub A. A 4-wk intervention with high intake of carotenoid-rich vegetables and fruit reduces plasma C-reactive protein in healthy, nonsmoking men. Am J Clin Nutr 2005;82:1052–8.
77. Maron DJ. Flavonoids for reduction of atherosclerotic risk. Curr Atheroscler Rep 2004;6:73–8.
78. Giugliano D, Ceriello A, Esposito K. The effects of diet on inflammation: emphasis on the metabolic syndrome. J Am Coll Cardiol 2006;48:677–85.
79. Mora S, Cook N, Buring JE, Ridker PM, Lee IM. Physical activity and reduced risk of cardiovascular events: potential mediating mechanisms. Circulation 2007;116:2110–8.
80. Ford ES. Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. Epidemiology 2002;13:561–8.
81. McFarlin BK, Flynn MG, Campbell WW, Craig BA, Robinson JP, Stewart LK, et al. Physical activity status, but not age, influences inflammatory biomarkers and toll-like receptor 4. J Gerontol A Biol Sci Med Sci 2006;61:388–93.
82. Stewart LK, Flynn MG, Campbell WW, Craig BA, Robinson JP, Timmerman KL, et al. The influence of exercise training on inflammatory cytokines and C-reactive protein. Med Sci Sports Exerc 2007;39:1714–9.
83. Tchernof A, Nolan A, Sites CK, Ades PA, Poehlman ET. Weight loss reduces C-reactive protein levels in obese postmenopausal women. Circulation 2002;105:564–9.
84. Milani RV, Lavie CJ, Mehra MR. Reduction in C-reactive protein through cardiac rehabilitation and exercise training. J Am Coll Cardiol 2004;43: 1056–61.
85. Oberbach A, Tonjes A, Kloting N, Fasshauer M, Kratzsch J, Busse MW, et al. Effect of a 4 week physical training program on plasma concentrations of inflammatory markers in patients with abnormal glucose tolerance. Eur J Endocrinol 2006;154:577–85.
86. Mora S, Lee IM, Buring JE, Ridker PM. Association of physical activity and body mass index with novel and traditional cardiovascular biomarkers in women. JAMA 2006;295:1412–9.
87. Kasapis C, Thompson PD. The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review. J Am Coll Cardiol 2005;45:1563–9.
88. Flynn MG. The anti-inflammatory actions of exercise training. Am J Lifestyle Med 2007;1:220–35.
89. Bakhru A, Erlinger TP. Smoking cessation and cardiovascular disease risk factors: results from the Third National Health and Nutrition Examination Survey. PLoS Med 2005;2:e160.
90. Bazzano LA, He J, Muntner P, Vupputuri S, Whelton PK. Relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States. Ann Intern Med 2003;138: 891–7.
91. Wannamethee SG, Lowe GD, Shaper AG, Rumley A, Lennon L, Whincup PH. Associations between cigarette smoking, pipe/cigar smoking, and smoking cessation, and haemostatic and inflammatory markers for cardiovascular disease. Eur Heart J 2005;26:1765–73.