International Journal of Obesity (2009) 33, 267–272
 0307-0565/09 $32.00
www.nature.com/ijo

ORIGINAL ARTICLE

The interaction of adiposity with the *CRP* gene affects CRP levels: Age, Gene/Environment Susceptibilty-Reykjavik Study

G Eiriksdottir[1,5], AV Smith[1,5], T Aspelund[1,2], SH Hafsteinsdottir[1], E Olafsdottir[1], LJ Launer[4], TB Harris[4] and V Gudnason[1,3]

[1]*Icelandic Heart Association, Kopavogur, Iceland;* [2]*Department of Mathematics, University of Iceland, Reykjavik, Iceland;* [3]*Department of Medicine, Landspitali University Hospital, Reykjavik, Iceland and* [4]*Laboratory of Epidemiology, Demography and Biometry, Intramural Research Program, National Institute on Aging, Bethesda, MD, USA*

Objective: Common diseases often have an inflammatory component reflected by associated markers such as serum C-reactive protein (CRP) levels. Circulating CRP levels have also been associated with adipose tissue as well as with specific *CRP* genotypes. We examined the interaction between measures of body mass index (BMI), waist circumference and fat percent (total fat measured by bioimpedance) with genotypes of the *CRP* gene in the determination of CRP levels.
Methods: The first 2296 participants (mean age 76 ± 6 years, 42% men) in the Age, Gene/Environment Susceptibility-Reykjavik Study, a multidisciplinary epidemiological study to determine risk factors in aging, were genotyped for 10 single nucleotide polymorphisms (SNPs) in the *CRP* gene. General linear models with age and terms for interaction of *CRP* genotypes with BMI, waist circumference and percent fat were used to evaluate the association of genotypes to CRP levels (high-sensitivity method, range 0–10 mg l^{-1}) in men and women separately.
Results: We focused on the SNP rs1205 that represents the allele that captures the strongest effects of the gene on CRP levels. Carriers of the rs1205 G allele had significantly higher CRP levels than noncarriers in a dose-dependent manner. Compared to the AA genotype, the slope of the increase in CRP with increasing BMI ($P = 0.045$) and waist circumference ($P = 0.014$) was different for the G allele carriers and of similar magnitude in both men and women. The rs1205 interactions were not significant for fat mass percent, suggesting a possible association with fat localization.
Conclusions: This study further illuminates the known association between measures of adiposity and CRP levels and is shown to be dependent on variation in the rs1205 SNP of the *CRP* gene. The correlated increase in CRP levels with adiposity is accentuated by presence of the G allele.
International Journal of Obesity (2009) **33,** 267–272; doi:10.1038/ijo.2008.274; published online 13 January 2009

Keywords: *CRP* gene; CRP levels; adiposity; gene/environment interaction; AGES-Reykjavik Study

Introduction

C-reactive protein (CRP) has been implicated as a marker of systemic low-grade inflammation. Elevated circulating CRP levels have been found in Alzheimer's disease[1,2] as well as in common diseases such as cardiovascular disease (CVD)[3–7] and type 2 diabetes mellitus (T2DM),[8–10] suggesting that these common diseases could have an inflammatory connection.

CRP is primarily produced in the liver and synthesis is regulated by other inflammatory cytokines such as interleukin 6 (IL-6).[11–13] However, in obese individuals an important part of the circulating CRP is produced in adipose tissue.[14] Circulating CRP levels have been shown to be associated with adipose tissue, and total body fat has been shown to be a predictor of CRP levels. There is evidence for a different degree of participation of the different adipose tissue compartments.[15] Visceral adipose tissue has been shown to be a promoter of low-grade CRP inflammation[16,17] and can produce higher levels of Il-6 than subcutaneous fat.[18]

Circulating CRP levels have been associated to some extent with common variation in several genes[19] but primarily *CRP*

Correspondence: Dr G Eiriksdottir, Hjartavernd/Icelandic Heart Association, Holtasmari 1, 201 Kopavogur, Iceland.
E-mail: gudny@hjarta.is
[5]These authors contributed equally to this work.
Received 27 August 2008; revised 25 October 2008; accepted 3 December 2008; published online 13 January 2009

gene variation.[19–21] This is reviewed in detail in an article by Hage *et al*.,[6] Kathiresan *et al*.[22] constructed a linkage disequilibrium (LD) map and found associations between individual single nucleotide polymorphisms (SNPs) and CRP levels, and one common triallelic *CRP* SNP that is modestly associated with serum CRP levels. In addition, genetic variation associated with CRP levels has been associated with coronary heart disease[21] or acute myocardial infarction.[23] Lange *et al*.[4] found genetic association with CRP levels as well as CVD risk in the elderly. However, there are a number of other studies that have not been able to identify an association between *CRP* genotype and the risk of CVD.[24–26]

The two major factors consistently influencing circulating CRP levels are adipose tissue[14–17] and the *CRP* gene itself.[4,20–22] The aim of this study was to analyze the effects of *CRP* gene polymorphisms on CRP levels in a cohort of older Icelanders and determine if there is interaction between various measures of adiposity and genotypes of the *CRP* gene in the determination of CRP levels.

Materials and methods

Study population

This sample is drawn from the first 2296 participants who were enrolled in the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study (mean age 76 ± 6 years, 42% men). The AGES-Reykjavik Study is a follow-up of the original Reykjavik Study,[27] started in 1967 by the Icelandic Heart Association where all inhabitants in the Reykjavik area, born between 1907 and 1935, were invited to participate, consisting of approximately 30 000 individuals. AGES-Reykjavik is an epidemiological study that focuses on four biological systems: vascular, neurocognitive, musculoskeletal and body composition, which was initiated in 2002 to investigate the contribution of genetic and environmental risk factors and their interactions to disorders of importance in old age. All participants signed an informed consent form and the AGES-Reykjavik Study was approved by the Icelandic National Bioethics Committee (VSN: 00-063), the Data Protection Authority and the institutional review board of the National Institute on Aging. A more detailed description of the AGES-Reykjavik study and collection of data can be found elsewhere.[28]

Measurements

Blood pressure and anthropometric data including body mass index (BMI) and waist circumference were collected using standardized protocols.[28] Individuals missing either BMI or waist circumference measurements were excluded. A Xitron HYDRA ECF/ICF, Model 4200, was used to measure body composition with the bioelectrical impedance analysis (BIA) to assess the composition of the total body. From these BIA data, and additional variables such as age, gender and body weight, the fat-free mass (FFM, in kg) of the body can be estimated using prediction equations. Fat mass (FM, in kg) can subsequently be calculated as body weight minus FFM.

High-sensitivity CRP was measured on a Hitachi 912, using reagents from Roche Diagnostics and following the manufacturer's instructions. Both within- and between-assay quality control procedures were used and the coefficient of variation of the method was 1.3–3.4%, respectively, through the period of data collection. The assay could detect a minimal CRP concentration of $0.1\,mg\,l^{-1}$ and values below this level were classified as undetectable. All participants in this study had detectable CRP levels. A total of 145 persons with CRP levels greater than $10\,mg\,l^{-1}$ were excluded, as this high level of CRP was considered to be due to the acute-phase response.

Fasting blood glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were also measured on a Hitachi 912 using reagents from Roche Diagnostics and following the manufacturer's instructions. Insulin was measured by an electrochemiluminescence immunoassay on a Roche Elecsys 2010 instrument, using two monoclonal antibodies and a sandwich principle. The method was standardized using the first IRP WHO Reference Standard 66/304 (NIBSC). Trained interviewers administered a health history questionnaire to obtain smoking history information (ever smokers).

The 10 SNPs in the *CRP* gene, rs2808630, rs2808631, rs1205, rs1130864, rs1800947, rs1417938, rs3093062, rs2027471, rs1341665 and rs2808634, were analyzed using an Illumina GoldenGate assay (Illumina, San Diego, USA). These SNPs were chosen as candidate SNPs to cover the *CRP* gene including 10 kb surrounding the gene, in a larger group of candidate genes as part of a cardiovascular panel. SNPs were chosen as those that effectively tag the region based on HapMap CEU genotypes, as well as being compatible with Illumina GoldenGate technology. The SNPs were overlapping with SNPs that have been used in other studies.[21,22] Two SNPs (rs2808631 and rs3093062) were nonpolymorphic in the samples examined and DNA samples from seven individuals failed to be genotyped.

Statistical analyses

C-reactive protein was log-transformed and analyzed with general linear regression models by sex and adjusted for age. rs1205 was entered as a categorical variable with genotype AA as the reference. Association with body fat measurements was estimated by genotype-specific slopes by introducing interaction terms. The significance of the interaction was found by testing the hypothesis of equal slopes between genotypes based on an F-test from the general linear model. The level of significance was set at 0.05. We analyzed the data using SAS/STAT software, version 9.1.

Results

Table 1 shows the general characteristics of the study cohort and the difference between sexes. Women have higher fat

Table 1 General characteristics

Characteristics	*Men*		*Women*		*Difference of effect between sexes*	
	n	*Mean, s.d. (95% CI)*	n	*Mean, s.d. (95% CI)*	*% (95% CI)*	P[a]
Age (years)	904	76.3 (5.6)	1226	76.2 (5.8)		
SBP (mm Hg)	904	142.4 (20.4)	1226	141.6 (21.2)	None	
Anthropometric measures						
BMI (kg m^{-2})	904	26.6 (3.6)	1226	26.9 (4.8)	None	
Waist circumference (cm)	904	101.8 (10.3)	1226	99.7 (12.9)	2.5 (1.5, 3.6)	<0.0001
Fat (%)	757	32.8 (6.5)	923	42.4 (5.6)	31.1 (28.9, 33.3)	<0.0001
Blood measurements						
CRP (mg l^{-1})[b]	904	1.73 (0.75, 3.98)	1226	1.86 (0.80, 4.29)	6.8 (−0.6, 14.8)	0.0713
Glucose (mM)	904	6.0 (1.2)	1226	5.7 (1.0)	2.8 (1.8, 3.8)	<0.0001[c]
Cholesterol (mM)	904	5.3 (1.0)	1226	6.1 (1.1)	16.2 (14.3, 8.1)	<0.0001
HDL (mM)	904	1.4 (0.4)	1226	1.7 (0.4)	22.7 (20.0, 25.5)	<0.0001
Triglycerides (mM)[b]	904	1.07 (0.68, 1.69)	1226	1.14 (0.73, 1.78)	6.2 (2.2, 10.4)	0.0022
Insulin (mU l^{-1})[b]	904	8.7 (8.4, 9.1)	1226	7.8 (7.6, 8.1)	7.6 (1.9, 13.5)	0.0283[c]

Abbreviations: BMI, body mass index; CRP, C-reactive protein; HDL, high-density lipoprotein; SBP, systolic blood pressure. The difference between sexes is shown by the percent difference in effect size. [a]Age adjusted. [b]Geometric means. [c]Adjusted for T2DM (type 2 diabetes mellitus).

Table 2 *(a) LD of SNPs (3′-5′ order) tested in the CRP gene. (b) Correlation of genotypes of individual SNPs in the CRP gene with CRP levels*

LD(r^2)	*rs2808630*	*rs1205*	*rs1130864*	*rs1800947*	*rs1417938*	*rs2027471*	*rs1341665*	*rs2808634*
(a)								
rs2808630	1	0.197995	0.187928	0.028194	0.191442	0.205566	0.205915	0.975775
rs1205		1	0.222652	0.143046	0.223100	0.967392	0.965347	0.191156
rs1130864			1	0.031875	0.994888	0.228120	0.226536	0.202133
rs1800947				1	0.032499	0.141475	0.141725	0.027718
rs1417938					1	0.228684	0.227288	0.204529
rs2027471						1	0.998964	0.198381
rs1341665							1	0.198719
rs2808634								1

SNP	*MAF*	β[a]	P-*value*
(b)			
rs2808630	0.31	−0.037	0.19
rs1205	0.31	−0.116	3.1×10^{-5}
rs1130864	0.32	0.110	7.7×10^{-5}
rs1800947	0.06	−0.235	5.2×10^{-6}
rs1417938	0.32	0.115	3.7×10^{-5}
rs2027471	0.32	−0.103	1.9×10^{-4}
rs1341665	0.32	−0.101	2.8×10^{-4}
rs2808634	0.30	−0.044	0.12

Abbreviations: CRP, C-reactive protein; LD, linkage disequilibrium; SNP, single nucleotide polymorphism. [a]β values are relative to the major allele.

mass percent, cholesterol, HDL and triglycerides than men. Men have higher waist circumference, glucose and insulin levels than women. There is an increase in serum CRP levels with increasing BMI ($r=0.26$, $r^2=0.07$, $P<0.0001$), waist circumference ($r=0.21$, $r^2=0.05$, $P<0.0001$) and fat mass percent ($r=0.21$, $r^2=0.05$, $P<0.0001$) in both sexes. These factors account for 5–7% of the variance of CRP levels, shown by r^2.

The observed allele frequencies for all SNPs were consistent with expectation under Hardy–Weinberg equilibrium ($P>0.01$). LD values (r^2) are shown in Table 2a. The following individual SNPs, rs1205, rs1130864, rs1800947, rs1417938, rs2027471 and rs1341665, were significantly associated with CRP levels, when tested individually after adjusting for age and sex (Table 2b). There was a dose-dependent decrease in CRP levels with the minor allele of rs1205 in men (Table 3). Looking at the LD values in Table 2a, there are three distinct groups of tagging SNPs that can be observed: (1) rs1800947 does not capture the effect of other SNPs, (2) rs1205 captures the effects of rs2027471 and rs1341665 and (3) rs1130864 captures the effect of rs1417938 on CRP levels. Haplotypes derived from these SNPs were tested and no clear evidence for stronger association to CRP levels with any one haplotype as compared to individual SNPs was observed.

All SNPs were tested to see if the effects of anthropometric factors on CRP levels vary across genotypes. A statistically

Table 3 CRP levels according to rs1205 genotypes

	CRP mg l^{-1} (95% CI)[a]	P-*value*
Men rs1205		
AA ($n=77$)	1.33 (1.11, 1.60)	
AG ($n=411$)	1.69 (1.54, 1.80)	0.0313[b]
GG ($n=421$)	1.89 (1.75, 2.04)	0.0007
Women rs1205		
AA ($n=119$)	1.54 (1.33, 1.80)	
AG ($n=562$)	1.86 (1.74, 2.00)	0.0261
GG ($n=554$)	1.94 (1.80, 2.08)	0.0077

Adjusted for age and excluding CRP >10 mg l^{-1}. [a]Geometric means. [b]Between AG and GG, $P=0.0256$.

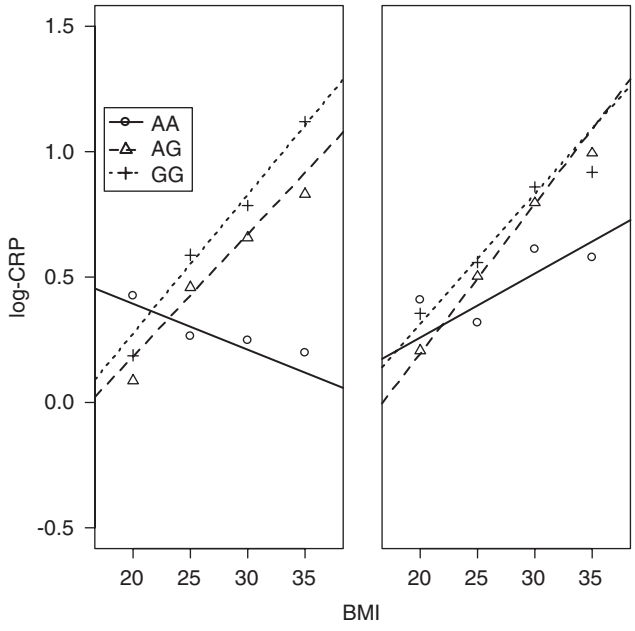

Figure 1 The association of body mass index (BMI) with log-CRP in rs1205 genotypes. The increase in C-reactive protein (CRP) levels with BMI is different for the AA genotype than for the GA and GG genotypes in both men (left) and women (right). The marks (dot, triangle and cross) represent mean log-CRP values by genotypes around BMI values of 20, 25, 30 and 35 using bins of width 5.

significant effect was found with SNPs rs1205, rs2027471 and rs1341665. As discussed above the two latter SNPs, rs2027471 and rs1341665, are in complete LD with rs1205 and do not capture any signal independent of and beyond that observed between rs1205 and CRP levels, adjusted for sex and age. Therefore, we focused on the SNP rs1205, which represents the allele that captures the strongest effects of the gene on CRP levels. The SNP rs1800947 is also strongly associated with CRP levels, but the MAF of rs1800947 is so low that it is difficult to analyze this SNP fully in the context of interaction with BMI.

The association for BMI and CRP levels is shown in Figure 1. For both men and women there is a clear relationship between increasing BMI and CRP levels for individuals with a G allele. This relationship is of the magnitude of 5.7% (95% CI: 4.8; 6.6) for an increase of one BMI unit in both sexes but is different for the AA homozygote. In Table 4 , the interaction of BMI, waist circumference and fat mass percent with genotypes of rs1205 on CRP levels is shown by genotype-specific β coefficients for the association (representing effect of one unit change) and test for equivalence. Results for men and women were tested separately. There is a statistically significant interaction between BMI and r1205 ($P=0.045$) and also between waist circumference and rs1205 in men ($P=0.014$). Although the direction of the effect for the G allele is the same in women the interaction does not reach significance. However, this is not the case for fat mass percent in either sex. BMI and waist circumference are highly correlated factors ($r=0.85$), though BMI and fat mass percent are only moderately correlated ($r=0.32$).

Discussion

Measuring of inflammatory markers has been used to try to improve the prediction of common diseases. CRP is one such inflammatory marker that has been associated with common disease including coronary heart disease and diabetes and therefore it is important to know what factors can influence CRP levels. The results reported here are consistent with

Table 4 The interaction of anthropometric measurements with genotypes of rs1205 on circulating CRP levels shown by genotype-specific β coefficients for the association, representing effect of one unit change

rs1205 genotype	*BMI*	N = *904*	*WC*	N = *904*	F%	N = *754*
Men	β *coefficient*	*s.e.*	β *coefficient*	*s.e.*	β *coefficient*	*s.e.*
AA	−0.003	0.022	−0.006	0.008	0.030	0.018
AG	0.049	0.011	0.015	0.004	0.021	0.007
GG	0.060	0.011	0.020	0.004	0.032	0.007
P for interactionfor	0.045		0.014		0.563	
Women	*BMI*	N = *1226*	*WC*	N = *1226*	F%	N = *923*
AA	0.031	0.017	0.012	0.006	0.025	0.017
AG	0.065	0.007	0.017	0.003	0.028	0.007
GG	0.048	0.007	0.015	0.003	0.050	0.007
P for interactionfor	0.088		0.780		0.054	

Abbreviations: BMI, body mass index; F%, fat mass %; WC, waist circumference.

many studies where polymorphisms in the *CRP* gene are associated with CRP levels. In addition, the results presented here confirm the effect of measures of adipose tissue on circulating CRP levels found in other studies.[12,16] The novel finding in this study is the interaction of adiposity with *CRP* genotypes to influence CRP levels where the relationship of increasing CRP with adiposity is carried by selected genotypes.

Total body fat has been shown to be a predictor of circulating CRP levels but it is also important to understand the possible influence of fat distribution in the production of low-grade inflammatory markers. Visceral fat has been shown to be important as a promoter of moderately increased CRP levels in both sexes.[29–31] BMI, fat mass percent and waist circumference, which is thought to be a surrogate for visceral fat, are shown here to be positively associated with CRP levels, in both men and women. BMI and waist circumference have a different effect on CRP levels in individuals with the AA genotype of the rs1205 SNP than carriers of the G allele. The difference is more pronounced in men than women. The association of the adiposity measurements with CRP levels is carried by the GG and GA genotypes and the effect is of the same magnitude for both sexes. The size of the effect is larger for BMI than for waist circumference. This difference in effect between the AA genotype and G carriers was not seen for the fat mass percent and could thus suggest that fat localization might be involved in CRP production as shown in other studies.[15,29–31]

Considerable work has been done in determining the mechanism of expression of the *CRP* gene. The regulatory effect of the adipocyte-produced IL-6 on the transcription of the *CRP* gene has been carefully studied[11–13] and binding sites for liver transcription factors have been identified in the *CRP* promoter.[32] Carlson *et al*.[20] made a number of promoter constructs of the *CRP* gene demonstrating an effect of IL-6 on CRP production by a variation in the promoter region. Another possibility for regulation is through the stability of the mRNA and could be important because of the known short half-life of *CRP* mRNA.[33] Brull *et al*.[34] suggested that the SNP rs1130864 in the 3′UTR is related to *CRP* mRNA levels, an effect that was not influenced by cytokines. In this study, the interaction of adiposity is shown specifically with genotypes of the rs1205 SNP, which is in the 3′ flanking region of the gene. This effect could possibly be explained in that obesity stimulates through the G allele a more stable mRNA. Because of the strong LD over the *CRP* gene, both mechanisms could explain the consistently lower CRP levels associated with the rs1205 AA genotype,[4,35] which has weak if any association with CRP levels and increasing obesity.

Many studies have put emphasis on determining haplotype effect on disease. Risk haplotypes in the *CRP* gene have been reported for CVD[22] and diabetes[8,36] and CRP level has been shown to be an independent risk factor for both these common diseases although not over and above other known risk factors.[3] In our data, these haplotypes did not add to the effect on CRP levels beyond the effect of the single SNP, rs1205. This is most likely reflected in the fact that there is extremely strong LD over and upstream of the *CRP* gene as identified with our panel of SNPs and has been discussed in a recent review paper.[6] This calls out for further genetic studies using more detailed fat measures as well as more detailed measures of proinflammatory molecules produced in fat tissue, for example, IL-6, which are necessary to determine whether the genetic interaction is mediated through these types of stimulants of CRP production.

The AA genotype of the rs1205 SNP has consistently been shown to be associated with low CRP[4,35] and has also been found to be associated with lower cardiovascular mortality.[4] Genetic effects in common diseases are generally small[26,36] but gene/environment interaction could be important in modulating risk for common diseases. Such a gene/environment interaction is reported here where the effect of BMI and waist circumference on the levels of circulating CRP may be mediated by an adipose-tissue-related factor acting in an allele-specific way through the *CRP* gene.

Acknowledgements

This study was funded by National Institutes of Health contract N01-AG-12100, the National Institute on Aging Intramural Research Program, Hjartavernd (the Icelandic Heart Association) and the Althingi (the Icelandic Parliament).

References

1 Finch CE, Morgan T. Systemic inflammation, infection, ApoE alleles, and Alzheimer disease: a position paper. *Curr Alzheimer Res* 2007; **4**: 185–189.
2 Zaciragic A, Lepara O, Valjevac A, Arslanagic S, Fajkic A, Hadzovic-Dzuvo A *et al*. Elevated serum C-reactive protein concentration in Bosnian patients with probable Alzheimer's disease. *J Alzheimers Dis* 2007; **12**: 151–156.
3 Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A *et al*. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med* 2004; **350**: 1387–1397.
4 Lange LA, Carlsson 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**: 2703–2711.
5 Kolz M, Koenig W, Müller M, Andreani M, Greven S, Illig T *et al*. DNA variants, plasma levels and variability of C-reactive protein in myocardial infarction survivors: results from the AIRGENE study. *Eur Heart J* 2008; **29**: 1250–1258.
6 Hage FG, Szalai AJ. C-reactive protein gene polymorphisms, C-reactive protein blood levels, and cardiovascular disease risk. *J Am Coll Cardiol* 2007; **50**: 1115–1122.
7 Sattar N, Murray HM, McConnachie A, Blauw GJ, Bollen EL, Buckley BM *et al*. C-reactive protein and prediction of coronary heart disease and global vascular events in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). *Circulation* 2007; **115**: 981–999.

8 Dehghan A, Kardys I, de Maat MP, Uitterlinden AG, Sijbrands EJ, Bootsma AH *et al*. Genetic variation, C-reactive protein levels, and incidence of diabetes. *Diabetes* 2007; **56**: 872–878.
9 Freeman DJ, Nome J, Caslake MJ, Gaw A, Ford I, Lowe GD *et al*. C-reactive protein is an independent predictor of risk for the development of diabetes in the West of Scotland Coronary Prevention Study. *Diabetes* 2002; **51**: 1596–1600.
10 Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 2001; **286**: 327–334.
11 Kushner I, Jiang SL, Zhang D, Lozanski G, Samols D. Do post-transcriptional mechanisms participate in induction of C-reactive protein and serum amyloid A by IL-6 and IL-1? *Ann NY Acad Sci* 1995; **762**: 102–107.
12 Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol* 1999; **19**: 972–978.
13 Bastard JP, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H *et al*. Recent advances in the relationship between obesity, inflammation, and insulin resistance. *Eur Cytokine Netw* 2006; **17**: 4–12.
14 Anty R, Bekri S, Luciani N, Saint-Paul MC, Dahman M, Iannelli A *et al*. The inflammatory C-reactive protein is increased in both liver and adipose tissue in severely obese patients independently from metabolic syndrome, type 2 diabetes, and NASH. *Am J Gastroenterol* 2006; **101**: 1824–1833.
15 Memoli B, Procino A, Calabrò P, Esposito P, Grandaliano G, Pertosa G *et al*. Inflammation may modulate IL-6 and C-reactive protein gene expression in the adipose tissue: the role of IL-6 cell membrane receptor. *Am J Physiol Endocrinol Metab* 2007; **293**: E1030–E1035.
16 Forouhi NG, Sattar N, McKeigue PM. Relation of C-reactive protein to body fat distribution and features of the metabolic syndrome in Europeans and South Asians. *Int J Obes Relat Metab Disord* 2001; **9**: 1327–1331.
17 Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. *JAMA* 1999; **282**: 2131–2135.
18 Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. *J Clin Endocrinol Metab* 1998; **83**: 847–850.
19 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**: 1185–1192.
20 Carlson CS, Lee PK, Tracy RP, Stephen M, Schwartz SM, Liu K *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.
21 Crawford DC, Qin X, Smith JD, Shephard C, Wong M, Witrak L *et al*. Genetic variation is associated with C-reactive protein levels in the Third National Health and Nutrition Examination Survey. *Circulation* 2006; **114**: 2458–2465.
22 Kathiresan S, Larson MG, Vasan RS, Guo CY, Gona P, Keaney Jr JF *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**: 1415–1423.
23 Balistreri CR, Vasto S, Listì F, Grimaldi MP, Lio D, Colonna-Romano G *et al*. Association between+1059G/C CRP polymorphism and acute myocardial infarction in a cohort of patients from Sicily: a pilot study. *Ann NY Acad Sci* 2006; **1067**: 276–281.
24 Pai JK, Mukamal KJ, Rexrode KM, Rimm EB. C-reactive protein (CRP) gene polymorphisms, CRP levels, and risk of incident coronary heart disease in two nested case–control studies. *PLoS ONE* 2008; **3**: e1395.
25 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–H2757.
26 Kardys I, Knetsch AM, Bleumink GS, Deckers JW, Hofman A, Stricker BH *et al*. C-reactive protein and risk of heart failure. The Rotterdam Study. *Am Heart J* 2006; **152**: 514–520.
27 Jónsdóttir LS, Sigfusson N, Sigvaldason H, Thorgeirsson G. Incidence and prevalence of recognised and unrecognised myocardial infarction in women. The Reykjavik Study. *Eur Heart J* 1998; **19**: 1011–1018.
28 Harris TB, Launer LJ, Eiriksdottir G, Kjartansson O, Jonsson PV, Sigurdsson G *et al*. Age, Gene/Environment Susceptibility-Reykjavik Study: multidisciplinary applied phenomics. *Am J Epidemiol* 2007; **165**: 1076–1087.
29 Lemieux I, Pascot A, Prud'homme D, Alméras N, Bogaty P, Nadeau A *et al*. Elevated C-reactive protein another component of the atherothrombotic profile of abdominal obesity . *Arterioscler Thromb Vasc Biol* 2001; **21**: 961–967.
30 Piché ME, Lapointe A, Weisnagel SJ, Corneau L, Nadeau A, Bergeron J *et al*. Regional body fat distribution and metabolic profile in postmenopausal women. *Metabolism* 2008; **57**: 1101–1107.
31 Piché 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**: 92–97.
32 Toniatti C, Demartis A, Monaci P, Nicosia A, Ciliberto G. Synergistic trans-activation of the human C-reactive protein promoter by transcription factor HNF-1 binding at two distinct sites. *EMBO J* 1990; **9**: 4467–4475.
33 Lozanski G, Jiang SL, Samols D, Kushner I. C-reactive protein and serum amyloid A mRNA stability following induction by cytokines. *Cytokine* 1996; **8**: 534–540.
34 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**: 2063–2069.
35 Danik JS, Ridker PM. Genetic determinants of C-reactive protein. *Curr Atheroscler Rep* 2007; **9**: 195–203.
36 Zee RY, Germer S, Thomas A, Raji A, Rhees B, Ridker PM *et al*. C-reactive protein gene variation and type 2 diabetes mellitus: a case–control study. *Atherosclerosis* 2008; **197**: 931–936.