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Circulating HMW adiponectin isoform is heritable and shares a common genetic background with insulin resistance in non diabetic White Caucasians from Italy: evidence from a family-based study

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Abstract

Objective—Reduced circulating adiponectin levels contribute to the etiology of insulin-resistance. Adiponectin circulates in three different isoforms: high (HMW), medium (MMW), and low (LMW) molecular weight. The genetics of adiponectin isoforms is mostly unknown. Our aim was to investigate whether and to which extent circulating adiponectin isoforms are heritable and whether they share common genetic backgrounds with insulin resistance-related traits.

Methods—In a family based sample of 640 non diabetic White Caucasians from Italy, serum adiponectin isoforms concentrations were measured by ELISA. Three SNPs in the *ADIPOQ* gene previously reported to affect total adiponectin levels (rs17300539, rs1501299 and rs677395) were genotyped. The heritability of adiponectin isoform levels was assessed by variance component analysis. A linear mixed effects model was used to test association between SNPs and adiponectin isoforms. Bivariate analyses were conducted to study genetic correlations between adiponectin isoforms levels and other insulin resistance-related traits.

Results—All isoforms were highly heritable (h^2=0.60−0.80, $p=1\times10^{-13}$–1×10^{-23}). SNPs rs17300539, rs1501299 and rs6773957 explained a significant proportion of HMW variance (2–9%, $p=1\times10^{-3}$–1×10^{-5}). In a multiple-SNP model, only rs17300539 and rs1501299 remained associated with HMW adiponectin ($p=3\times10^{-4}$ and 2.0×10^{-2}). Significant genetic correlations ($p=1\times10^{-2}$–1×10^{-5}) were observed between HMW adiponectin and fasting insulin, $HOMA_{IR}$, HDL-cholesterol and the metabolic syndrome score. Only rs1501299 partly accounted for these genetic correlations.

Conclusion—Circulating levels of adiponectin isoforms are highly heritable. The genetic control of HMW adiponectin is shared in part with insulin resistance-related traits and involves, but is not limited to the *ADIPOQ* locus.

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Conflict of interest statement
No conflicts of interest to declare.

Keywords

ADIPOQ gene; Adiponectin isoforms; insulin resistance

Introduction

Adiponectin, a hormone exclusively secreted from adipose tissue, has insulin enhancing and anti-inflammatory actions and may therefore be involved in the etiology of insulin-resistance and related abnormalities [1–3]. Circulating adiponectin levels and insulin resistance traits have been reported to be both heritable and to share, at least in part, a common genetic background [4]. Recent evidences have shown that adiponectin circulates in three different higher order complexes: high (HMW), medium (MMW), and low (LMW) molecular weight isoforms [5,6]. Whether and to which extent circulating adiponectin isoforms are heritable and, if so, whether they share a common genetic background with insulin resistance-related traits has not been thus far investigated.

We addressed these questions in a family based sample of 640 non-diabetic White Caucasians from Italy. In addition, we investigated whether SNPs rs17300539, rs1501299 and rs6773957 in the *ADIPOQ* gene play a role in the genetic regulation of adiponectin isoforms. These SNPs were selected because of their previously reported association with total adiponectin levels [7–9].

Material and Methods

Subjects

A total of 640 non-diabetic individuals from 235 families were recruited in the Gargano area (an homogeneous geographical area in Center-East Italy [10]) and examined as previously described [11,12]. All study subjects were not treated with medications known to interfere with glucose homeostasis, lipid profile and blood pressure. The study and the informed consent procedures were approved by the local research committee.

Serum total adiponectin, HMW and MMW+HMW adiponectin concentrations were measured by enzyme-linked immunosorbant assay ELISA (ALPCO, NH) [13]. MMW values were obtained by subtracting the concentrations of HMW from the combined concentrations of MMW+HMW. LMW adiponectin fractions were obtained by subtracting the combined concentrations of MMW+HMW from the total adiponectin concentrations.

The intra-assay coefficient of variation (CV), calculated by measuring 4 samples in 6 replicates in a single assay and the inter-assay CV, calculated by measuring replicates of the same samples in 20 consecutive assays, were 5.4% and 5.0%, 5.2% and 4.9%, 5.0% and 4.8% for total adiponectin, MMW+HMW adiponectin and HMW adiponectin, respectively.

The metabolic syndrome score was calculated for each study subject summing the number of individual components of the syndrome, according to ATP III criteria, as follows: waist circumference >102 cm for men and >88 cm for women; systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg; serum HDL-cholesterol <40 mg/dl for men and <50 mg/dl for women; serum TG levels ≥150 mg/dl; and venous plasma glucose ≥110 mg/dl [12]. Smoking habit was recorded as smoker (i.e. an individual who had regularly smoked one or more cigarette a day for >1 year) or never smoker. Physical exercise was assessed as follows: no physical activity = equal or less than 2 hr weekly exercise, including walking; physical activity = more than 2 hours weekly exercise.

SNP genotyping

SNPs rs17300539, rs1501299, and rs6773957 in the *ADIPOQ* gene were genotyped by Taqman SNP allelic discrimination technique, by means of an ABI 7000 (Applied Biosystems, CA). Call rate and concordance rate were ≥96% (average 98%) and >99% respectively. Out of 640 study individuals, genotypes were available for 623 study subjects for rs17300539, for 625 study subject for rs1501299 and for 612 study subjects for rs6773957. All the SNPs were in Hardy-Weinberg Equilibrium (HWE) (P>0.05).

Data Analysis

Data are summarized as means ± SD. If the data were not normally distributed (kurtosis >1.9), a log transformation was performed before further analyses. Some residual kurtosis, slightly above the threshold (i.e. 2.0), was present only for the HMW. A χ^2 test was used to assess whether genotypes prevalence were in HWE.

To determine the contribution of genetic factors to serum adiponectin isoforms, the SOLAR software package (Version 4.1.7) was utilized [14]. SOLAR performs a variance components analysis of family data that decomposes the total variance of the phenotypes (adiponectin isoforms) into components that are due to genetic effects (i.e. polygenic, additive genetic variance), measured covariates, and random environmental effects (i.e. measured environmental factors and random unmeasured factors). The relative contribution of genetic factors to serum adiponectin isoforms is then estimated by heritability (h^2), defined as the ratio of the genetic variance component to the residual (after removal of covariates) phenotypic variance. Heritability estimates, so obtained, also include any environmental contributions to similarities in adjusted values between relatives. To assess phenotypic correlations between adiponectin isoforms and insulin resistance related traits we used a mixed effects model by SOLAR that includes fixed covariate effects. This method could account for the dependence of the family data and provide a more stringent p value. To evaluate the contribution of the *ADIPOQ* genotypes to adiponectin isoforms variance, and test the associations between each trait and each SNP, a linear mixed effects model implemented in SOLAR, to account for within-family correlations, was performed. Each SNP was included in a model as a fixed effect with additive coding. All analyses were performed first with sex, age, age^2, smoking habits, and physical exercise and then with sex, age, age^2 smoking habits, physical exercise and BMI as covariates in the model, to examine the strength of the SNP associations after accounting for the portion of variance due to BMI. Bivariate analyses were conducted to partition the phenotypic correlation between two traits (ρp) into genetic (ρg) and environmental (ρe) correlations [14]. Evidence of pleiotropy (i.e. a common set of genes influencing more than one trait) is indicated by a genetic correlation significantly different from zero.

Results

The clinical characteristics of study participants are shown in Table 1. This study comprises 140 nuclear families, 75 sibships and 20 extended sibships (ranging 3–5 individuals).

Among the 640 individuals, mean HMW, MMW and LMW adiponectin levels were 4.3 ± 2.9 μg/ml (median 3.6, range 0.02 – 24.1), 1.6 ± 1.5 μg/ml (median 1.2, range 0.01–11.6) and 2.1 ± 1.8 μg/ml (median 1.7, range (0.01 – 13.5), respectively (Table 1).

HMW adiponectin was inversely associated with several traits related to insulin resistance, including BMI, waist circumference, fasting glucose, insulin and $HOMA_{IR}$ levels (Table 2). Correlations were also evident with triglycerides, HDL-cholesterol and the metabolic syndrome score (Table 2). MMW and LMW isoforms were associated, in a much weaker manner, only with HDL-cholesterol and the metabolic syndrome score and with HDL-

cholesterol, respectively (Table 2). No association was found between any adiponectin isoform and C-reactive protein (CRP) (Table 2).

The overall effect of genetic factors on serum adiponectin isoforms was investigated by variance component analysis. After adjusting for age, age^2, gender, smoking habits, and physical exercise, all the different isoforms were found to be highly heritable, with HMW showing a somewhat higher heritability (0.79 ± 0.06, $p = 1.0\times10^{-13}$) than MMW and LMW (0.58 ± 0.06, $p = 2.4\times10^{-23}$ and 0.58 ± 0.09, $p = 6.5\times10^{-13}$, respectively) (Table 3). *ADIPOQ* SNPs rs17300539, rs1501299 and rs6773957 explained a highly significant proportion of HMW, but not MMW and LMW adiponectin variance (Table 3). Further adjustment for BMI did not significantly change the observed associations (Table 3). Adjustment for CRP also did not affect the observed associations (data not shown). When the two SNPs in the 3' UTR block (which are in moderate LD, $r^2 = 0.64$) were simultaneously considered into the model, rs1501299 ($p = 2.0\times10^{-2}$), but not rs6773957 ($p = 0.51$) remained significantly associated with HMW isoform levels. When all the three SNPs were included into the same model only the promoter rs17300539 and rs1501299 remained significantly associated with HMW adiponectin ($p = 3\times10^{-4}$ and 2.0×10^{-2}, respectively).

Table 4 shows the genetic (ρ_g) correlations between serum adiponectin isoforms levels and insulin resistance-related traits. Significant genetic correlations were observed between HMW isoform and fasting insulin ($\rho_g = -0.37$, $p = 1.1\times10^{-5}$), $HOMA_{IR}$ ($\rho_g = -0.32$, $p = 4.9\times10^{-3}$), HDL-cholesterol ($\rho_g = 0.22$, $p = 1.6\times10^{-2}$) and the metabolic syndrome score ($\rho_g = -0.32$, $p = 4.2\times10^{-2}$). In contrast, no genetic correlations were observed between MMW and LMW isoforms and any trait (Table 4). After the inclusion into the model of SNP rs1501299, genetic correlations of HMW adiponectin with insulin (p=0.06), $HOMA_{IR}$ (p=0.12) and metabolic syndrome score (p=0.11) were no longer significant. No effect of the promoter rs17300539 and the 3' UTR rs6773957 was observed on these genetic correlations (data not shown).

Environmental, and phenotypic correlations between serum adiponectin isoforms levels and insulin resistance-related traits are summarized in Supplemental Table 1. Significant environmental correlations (ρ_e) were observed only between LMW and waist circumference, insulin and $HOMA_{IR}$ (Supplemental Table 1).

Discussion

Several studies have clearly established the important role of adiponectin in the pathogenesis of insulin resistance-related disorders [2,3,15,16]. More recently, it has been shown that adiponectin is secreted, and then circulates, in several multimeric forms [5,6,17,18], of which the HMW isoform is the most biologically active in peripheral target tissues [19,20].

In the present study, we investigated for the first time several aspects of the genetics of adiponectin isoforms. Our findings show that these isoforms are highly heritable and are therefore likely to be under a strong genetic control. Heritability estimates observed in our population are consistent with those of total adiponectin levels previously reported in studies with similar family structures [9,21], although we acknowledge that under these circumstances (i.e. family structures prevalently composed by nuclear families and sib pairs rather than extended pedigrees) heritability is usually overestimated and different from that estimated by twin studies [22,23]. In addition, HMW, but not MMW or LMW adiponectin levels are genetically correlated with fasting insulin, $HOMA_{IR}$, HDL-cholesterol and the metabolic syndrome score. This implies that a common set of genes that controls some of the insulin-resistance traits also controls HMW adiponectin. *ADIPOQ* SNPs rs17300539 and

rs1501299 were strongly and independently associated with HMW adiponectin levels and explained a proportion of its variance. In addition, *ADIPOQ* rs1501299 partly accounted for the common genetic background shared by HMW and insulin resistance traits. Taken together, these data indicate an impact of *ADIPOQ* gene variability on HMW, but not on MMW and LMW isoforms. The presentation of circulating adiponectin under each different isoform is entirely due to a post-translational modification process [5]. However, the production of HMW isoform is more likely to be affected by reduced gene expression, as compared to that of MMW and LMW [18]. This makes possible that the observed associations between *ADIPOQ* SNPs and HMW, but not MMW and LMW, is a consequence of an impact of these SNPs on gene expression. In this context it is of note that, while rare gene variants harbored in the *ADIPOQ* coding region (i.e. G84R and G90S) may influence the ability to form HMW oligomer and consequently adiponectin isoforms levels [17], no common variants in the coding sequence have been so far described with the potential to influence circulating adiponectin at a post transcriptional level.

A recent comprehensive analysis of the evidence published thus far on the role of *ADIPOQ* gene common variants on adiponectin circulating levels and insulin resistance traits has clearly indicated the existence of two distinct signals, corresponding to the two linkage disequilibrium blocks in the *ADIPOQ* gene [7]. SNP rs17300539 in the promoter region and SNPs rs1501299 in the 3'UTR block are the variants that best capture these associations [7]. More recently rs6773957 in the 3'UTR has been associated to total adiponectin levels [8,9]. Our present data on adiponectin isoforms confirm the association of rs17300539 and rs1501299 with adiponectin levels and indicate that this is due exclusively to an effect on the HMW fraction. On the other hand, a clear functional role has been shown for rs17300539 [24], but not for rs1501299 [24]. Thus, additional fine-mapping and functional studies are needed to pin point the causal variant(s) responsible for this association. Given the lack of association between *ADIPOQ* SNPs and MMW and LMW levels, as well as the large proportion of unexplained variability of HMW levels, after taking into account *ADIPOQ* SNPs, other yet unidentified genetic determinants are certainly playing a role in modulating adiponectin isoforms levels.

Although not a primary aim of this study, we also confirmed previous observations [25,26] indicating that, of the three adiponectin isoforms, HMW is the one showing the best correlation with insulin resistance traits.

The main strength of our findings relates to the novelty of studying all circulating adiponectin isoforms in a family based cohort. In addition, our sample of non-diabetic White Caucasians comes from a genetically homogeneous population [10], further minimizing the risk of false results due to population stratification. Nonetheless, our study has some limitations. Our genotyping was limited to the three SNPs reported to be associated with total adiponectin levels in previous studies and we cannot exclude that other *ADIPOQ* SNPs play also a role on the genetics of adiponectin isoforms. In addition, whether our data can be generalized to other populations with different study design (i.e. sample with extended pedigrees where genetic heritability can be more accurately estimated), and with different environmental and/or genetic background is not known and deserves further investigation.

In conclusion, our data indicate that circulating levels of adiponectin isoforms are under a strong additive genetic control which, as far as HMW is concerned, is shared with other traits related to insulin resistance. Our results also point to a role of the *ADIPOQ* locus in influencing both HMW adiponectin and insulin resistance. Taken together, these data reinforce the hypothesis that differences in HMW isoform levels play a pathogenic role in the development of insulin resistance-related abnormalities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Clinical characteristics of 640 non-diabetic individuals from 235 nuclear families

	Mean±SD	Median	Range
M/F	246/394		
Age (yrs)	40.3±14.5	40.0	16–82
BMI (Kg/m^2)	26.3±4.7	25.5	17.1–48.2
Waist circumference (cm)	84.7±12.6	84.0	50–126.0
SBP (mmHg)	116.8±14.9	115.0	80–180
DBP (mmHg)	77.1±9.0	80.0	50–112
FBG (mg/dl)	90.1±10.3	88.2	57.7–125.2
Insulin (μU/ml)	8.0±4.6	7.1	1.8–48.0
$HOMA_{IR}$	1.8±1.1	1.54	0.36–10.0
Triglycerides (mg/dl)	100.3±66.1	81.0	28.0–520.0
HDL cholesterol (mg/dl)	52.9±13.3	52.0	21–119.0
MS (% affected)	8.4		
CRP (mg/L)	**0.43±0.35**	**0.35**	**0.3–5.0**
HMW Adiponectin (μg/ml)	4.3±2.9	3.6	0.02–24.1
MMW Adiponectin (μg/ml)	1.6±1.5	1.2	0.01–11.6
LMW Adiponectin (μg/ml)	2.1±1.8	1.7	0.01–13.5
Smokers (%)	**16.5**		
Physical exercise >2 hours/week (%)	**15.3**		

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; FBG: Fasting Blood Glucose; $HOMA_{IR}$ homeostasis model assessment of insulin-resistance; HDL-Cholesterol: high-density lipoprotein cholesterol; MS: Metabolic Syndrome; CRP: C-reactive protein; HMW: High Molecular Weight; MMW: Medium Molecular Weight; LMW: Low Molecular Weight.

Table 2

Association of serum adiponectin isoforms levels and insulin resistance-related traits in 640 non-diabetic individuals from 235 nuclear families

	HMW Adiponectin (μg/ml)		MMW Adiponectin (μg/ml)		LMW Adiponectin (μg/ml)	
	β±SE	P value	β±SE	P value	β±SE	P value
BMI (Kg/m^2)	−0.12±0.02	**3.3×10^{-7}**	−0.0043±0.013	0.75	−0.012±0.017	0.48
Waist circumference (cm)	−0.05±0.0099	**6.5×10^{-8}**	−0.0069±0.0055	0.21	−0.012±0.007	0.08
SBP (mmHg)	−0.0076±0.0083	0.36	−0.0028±0.0044	0.53	−0.00042±0.0055	0.94
DBP (mmHg)	−0.014±0.013	0.27	−0.0011±0.0068	0.87	−0.0067±0.0083	0.42
FBG (mg/dl)	−0.04±0.01	**8.7×10^{-5}**	−0.0076±0.0059	0.20	−0.015±0.0073	0.05
Insulin (μU/ml)	−2.8±0.49	**2.9×10^{-9}**	−0.23±0.25	0.35	−0.19±0.31	0.54
$HOMA_{IR}$	−2.7±0.43	**5.4×10^{-10}**	−0.26±0.24	0.27	−0.27±0.29	0.35
Triglycerides (mg/dl)	−2.2±0.47	**3.2×10^{-6}**	−0.40±0.26	0.13	−0.0044±0.032	0.99
HDL cholesterol (mg/dl)	0.068±0.0079	**6.3×10^{-17}**	0.015±0.004	**1.1×10^{-3}**	0.012±0.005	**2.9×10^{-2}**
MS score	−0.56±0.11	**1.2×10^{-7}**	−0.13±0.056	**1.7×10^{-2}**	−0.06±0.07	0.36
CRP (mg/L)	**−1.5±1.4**	**0.29**	**0.25±0.85**	**0.77**	**0.49±1.06**	**0.64**
Smoking habit	**−0.13±0.2**	**0.59**	**−0.04±0.1**	**0.69**	**−0.02±0.16**	**0.90**
Physical exercise	**0.25±0.25**	**0.32**	**0.2±0.13**	**0.12**	**0.03±0.16**	**0.19**

The β coefficients represent the change in adiponectin levels for 1 unit increase in the predictor. HMW: High Molecular Weight; MMW: Medium Molecular Weight; LMW: Low Molecular Weight; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; FBG: Fasting Blood Glucose; $HOMA_{IR}$ homeostasis model assessment of insulin-resistance; HDL-Cholesterol: high-density lipoprotein cholesterol; MS score: Metabolic Syndrome score; CRP: C-reactive protein. Analyses are adjusted for age, age^2, gender, smoking habit and physical exercise.

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Table 3

Serum adiponectin isoforms levels according to *ADIPOQ* SNPs in nuclear families

Overall Heritability		**H^2±SE**		**P value***		
HMW Adiponectin (μg/ml)		0.79±0.06		**1.01×10^{-13}**		
MMW Adiponectin (μg/ml)		0.58±0.06		**2.4×10^{-23}**		
LMW Adiponectin (μg/ml)		0.58±0.09		**6.5×10^{-13}**		
				P value*	P value†	Variance explained (%)
rs17300539						
N (623 subjects from 235 Families)	GG (498)	GA (119)	AA (7)			
HMW Adiponectin (μg/ml)	4.1±2.8	4.9±2.9	7.2±2.8	**5.5×10^{-5}**	**4.4×10^{-5}**	9
MMW Adiponectin (μg/ml)	1.5±1.4	1.7±1.6	2.3±3.3	0.51	0.51	
LMW Adiponectin (μg/ml)	2.0±1.7	2.4±2.1	3.2±2.3	0.038	0.039	0.5
rs1501299						
N (625 subjects from 235 Families)	GG (301)	GT (259)	TT (65)			
HMW Adiponectin (μg/ml)	4.1±2.9	4.3±2.8	5.1±3.1	**6.0×10^{-3}**	**4.4×10^{-3}**	5
MMW Adiponectin (μg/ml)	1.6±1.5	1.6±1.4	1.6±1.3	0.9	0.9	
LMW Adiponectin (μg/ml)	2.1±1.7	2.1±1.9	1.9±1.8	0.26	0.26	
rs6773957						
N (612 subjects from 231 Families)	GG (156)	GA (306)	AA (150)			
HMW Adiponectin (μg/ml)	3.9±2.7	4.3±3.0	4.6±2.7	**2.4×10^{-2}**	**1.8×10^{-5}**	2
MMW Adiponectin (μg/ml)	1.6±1.5	1.5±1.5	1.6±1.4	0.80	0.80	
LMW Adiponectin (μg/ml)	1.9±1.7	2.3±1.9	1.9±1.6	0.83	0.83	

Values are reported as means±SD.

*Analyses are adjusted for age, age^2, gender, smoking habit and physical exercise.

†Analyses are adjusted for age, age^2, gender, smoking habits, physical exercise and BMI; H^2 heritability HMW: High Molecular Weight; MMW: Medium Molecular Weight; LMW: Low Molecular Weight; P values for additive model.

Table 4

Genetic (ρ_g) correlations between adiponectin isoforms levels and insulin resistance-related traits in 640 non-diabetic individuals from 235 nuclear families

	HMW Adiponectin		MMW Adiponectin		LMW Adiponectin	
	$\rho_g \pm SE$	P value	$\rho_g \pm SE$	P value	$\rho_g \pm SE$	P value
BMI	−0.21±0.11	0.08	−0.03±0.11	0.78	−0.03±0.11	0.78
Waist circumference	−0.23±0.12	0.08	−0.05±0.12	0.70	−0.05±0.12	0.70
SBP	−0.006±0.14	0.97	−0.21±0.13	0.11	−0.21±0.13	0.11
DBP	−0.24±0.14	0.09	−0.02±0.13	0.85	−0.02±0.13	0.85
FBG	−0.15±0.14	0.28	−0.10±0.14	0.45	−0.10±0.14	0.45
Insulin	−0.37±0.14	**1.1×10^{-5}**	−0.07±0.14	0.66	−0.07±0.14	0.66
$HOMA_{IR}$	−0.32±0.14	**4.9×10^{-3}**	−0.08±0.14	0.62	−0.08±0.14	0.62
Triglycerides	−0.17±0.12	0.14	−0.02±0.12	0.88	−0.02±0.12	0.88
HDL cholesterol	0.22±0.11	**1.6×10^{-2}**	0.14±0.11	0.21	0.14±0.11	0.21
MS score	−0.32±0.14	**4.2×10^{-2}**	−0.13±0.14	0.39	−0.13±0.14	0.39
CRP	**−0.24±0.55**	**0.65**	**−0.17±0.51**	**0.72**	**−0.69±0.57**	**0.19**

HMW: High Molecular Weight; MMW: Medium Molecular Weight; LMW: Low Molecular Weight; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; FBG: Fasting Blood Glucose; $HOMA_{IR}$ homeostasis model assessment of insulin-resistance; HDL-Cholesterol: high-density lipoprotein cholesterol; MS score: Metabolic Syndrome score; CRP: C-reactive protein.

Analyses are adjusted for age, age^2, gender, smoking habit and physical exercise.