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Very low C-reactive protein in apparently healthy individuals: physiological status or just a reflection of an improved health profile

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Abstract

The objective of our study was to determine whether the very low concentrations of C-reactive protein (CRP) detected by high-sensitivity CRP (hs-CRP) assays that one encounters from time to time in apparently healthy individual represent a physiological status or are just a reflection of an improved general health profile. The concentration of hs-CRP was determined by using the Behring BN II nephelometer**.** The arbitrary cut-off point of hs-CRP ($\leq 0.16\ mg\ l^{-1}$) was determined at the lower detection level of the assay. A total of 6588 apparently healthy individuals were screened following exclusion of recent infection/inflammation by using a detailed questionnaire. One hundred and sixty (2.4%) individuals out of the above-mentioned cohort presented hs-CRP concentrations of $\leq 0.16\ mg\ l^{-1}$. They were found to be significantly younger and lean, had an improved lipid profile and an attenuated acute-phase response in terms of lower erythrocyte sedimentation rate and fibrinogen concentration as well as white blood cell count. In addition, these individuals had less atherothrombotic risk factors, except for smoking habits which were as frequent as in those of individuals with a higher hs-CRP concentration. After calculating the concentration of this biomarker following multiple adjustments, the individuals with very low CRP remained with a very low value despite the multiplicity of the adjustments. We raise the possibility that this particular low concentration might represent a physiological status and is not necessarily a result of the improved general health profile per se.

Keywords: *C-reactive protein, health profile, apparently healthy*

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Introduction

It has been repeatedly shown that high-sensitivity C-reactive protein (hs-CRP) is a useful biomarker for eventual future cardiovascular events (Libby et al. 2002, Ridker

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2002, Ridker et al. 2002, 2003, Hackman & Anand 2003, Sesso et al. 2003). In addition, it has been suggested that apparently healthy individuals be categorized into three groups of risk where those having concentrations of $<1\ mg\ l^{-1}$ are at low risk while those who present concentrations of 1–3 and $>3\ mg\ l^{-1}$ are, respectively, at a moderate and high risk for future vascular events (Ridker 2003).

We have raised the question of whether or not the presence of very low CRP concentrations is solely a result of an improved heath profile or if the possibility exists that this is also a reflection of a particular physiological status. By physiological status we include the whole biological, humoral and cellular machinery of protein production, beginning with cytokine sensing and signal transduction and ending in the release of CRP from the hepatocytes into the blood stream. In fact, it has been already shown in the past, that there is an individual variability, partly explained by polymorphism differences, in individuals' responses regarding CRP production (Ben-Assayag et al. 2007). In order to test this hypothesis we evaluated individuals who participated in the Tel Aviv Medical Center Inflammation Survey (TAMCIS) and in whom very low CRP concentrations were detected. The results of this study support the notion that very low CRP concentrations might indeed reflect a physiological status rather than being a result of an improved general health profile solely.

Materials and methods

Study population

Patients attending the Tel Aviv Sourasky Medical Center for a routine health examination between September 2002 and July 2006 were asked to participate in the TAMCIS. A total of 9289 subjects agreed (5821 male, 3468 female). Systematic examination of the reasons for participation yielded no effect of sociodemographic or biomedical variables. An additional 1725 subjects were later excluded from the analysis because of malignancy or any known inflammatory disease (arthritis, inflammatory bowel disease, psoriasis, etc.), pregnancy, steroidal or non-steroidal treatment (except for aspirin at a dose of $\leq 325\ mg\ day^{-1}$), acute infection or invasive procedures (surgery, catheterization, etc.) during the previous 6 months. An additional 297 subjects were excluded from the analysis because of hs-CRP concentrations above $10\ mg\ l^{-1}$, 159 subjects due to missing hs-CRP concentrations and 520 women taking hormonal replacement therapy or oral contraceptives. The study was approved by the local ethics committee. A written informed consent was obtained from all participants.

Definition of risk factors

Diabetes mellitus was defined as blood glucose of $\geq 126\ mg\ dl^{-1}$ fasting or $>200\ mg\ dl^{-1}$ random on two separate occasions or the use of insulin or oral hypoglycaemic medications. Hypertension was defined as a blood pressure of $\geq 140/90$ mmHg or the use of any antihypertensive medications, while hyperlipidaemia was defined as low-density lipoprotein (LDL) cholesterol concentration or non-high-density lipoprotein (HDL) cholesterol concentrations, for individuals with triglyceride concentrations of $\geq 200\ mg\ dl^{-1}$, above the recommended goal according to the risk profile defined by the updated ATP III recommendations (National Cholesterol

Education Program 2001) or the use of lipid-lowering medications. Smokers were defined as those who smoke at least five cigarettes daily while past smokers were those who quit smoking at least 30 days prior to examination.

Analytical methods

All blood samples were obtained only once between 08.00 and 10.00 in the morning, following a night fast. The white blood cell count (WBCC) and differential were performed by using the Coulter STKS (Beckman Coulter, Nyon, Switzerland) automatic cell analyzer, the erythrocyte sedimentation rate (ESR) by the method of Westergren (International Committee for Standardization in Hematology 1965), fibrinogen concentration by the method of Clauss (Clauss 1957) and a Sysmex 600 (Sysmex Corporation, Hyaga, Japan) autoanalyzer, while the hs-CRP assay was performed by using the Behring BN II (DADE Behring, Marburg, Germany) nephelometer according to Rifai et al. (1999). Cholesterol and triglycerides levels were measured by an enzymatic method.

High-sensitivity CRP categories

We have presently defined three groups of risk according to Ridker (2003), namely individuals with hs-CRP of $\leq 1\ \mathrm{mg\,l^{-1}}$, those with 1–3 and others with ≥ 3–$10\ \mathrm{mg\,l^{-1}}$. To this we added a fourth group of individuals in whom hs-CRP concentrations were below the detection limit of the assay ($\leq 0.16\ \mathrm{mg\,l^{-1}}$). This group was arbitrarily defined as very low hs-CRP concentration.

Statistical analysis

The statistical analysis was performed separately for men and women, due to significant differences in CRP concentrations and different variables that affect the variability of CRP between the genders (Rogowski et al. 2004). All data were summarized and displayed as mean $\pm$ SD for the continuous variables (age, all the inflammation-sensitive biomarkers, etc.), and as number of patients plus the percentage in each group for categorical variables (gender, smoking and other cardiovascular risk factors, medications, etc.). The crosstabs and descriptive procedures were used to produce frequencies of categorical variables and means $\pm$ SD of continuous variables. Participants were divided into four groups according to the concentrations of hs-CRP based on the proposed cut-offs of 1, 3 and 10 $\mathrm{mg\,l^{-1}}$, and a fourth group was divided from the low hs-CRP group with very low hs-CRP concentration ($\leq 0.16\ \mathrm{mg\,l^{-1}}$), and for all calculations and statistical analyses, the hs-CRP values of this group were defined as hs-CRP $= 0.16\ \mathrm{mg\,l^{-1}}$. This is a conservative approach, due to the fact that some of the individuals in this group have concentrations below $0.16\ \mathrm{mg\,l^{-1}}$. The hs-CRP and the triglyceride concentration have non-normal distribution, thus we used a logarithmic transformation which converts it to a normal distribution for all statistical procedures like ANOVA and ANCOVA, and all the results expressed as hs-CRP and triglyceride concentrations are a back-transformed geometrical mean and standard deviation. The one-sample Kolmogorov–Smirnov test was used to test for normal distribution. For all continuous variables, a one-way ANOVA analysis was performed to compare the various parameters between the different groups and to calculate the p for trend. For all

categorical variables the chi-square phi & Cramer's V statistics was used for assessing the overall significance across the four groups. In order to minimize the influence of the differences in cardiovascular risk factors, medication used, age, body mass index (BMI) and lipid profile between the CRP groups we calculated the estimated marginal means of hs-CRP after adjustment for age, BMI, history of any vascular event, hypertension, hyperlipidaemia, diabetes mellitus, smoking status, family history of coronary heart disease, alcohol consumption and sport intensity. Complete lipid profile included HDL, LDL and triglycerides and medications including aspirin, beta blockers, calcium channel blockers, ACE inhibitors, statins, fibrates and oral hypoglycaemics, using ANCOVA, under a general linear model. The level of significance used for all of the above analyses was two tailed, $p < 0.05$. The SPSS statistical package was used to perform all statistical evaluation (SSPS Inc, Chicago, IL, USA).

Results

We have presently analyzed data from a total of 6588 individuals who underwent a routine health screening programme, 4633 men and 1955 women at a mean $\pm$ SD age of 45.3 $\pm$ 10.7 years. They were divided into three groups of risk categories according to whether they had hs-CRP concentrations of ≤ 1 mg l^{-1}, 1–3 and 3–10 mg l^{-1} (Ridker 2003). In addition, the first group was further divided into individuals who had very low (≤ 0.16 mg l^{-1}) hs-CRP concentrations. The mean $\pm$ SD age, as well as BMI, in these four groups is reported in Table I. It is clear that both women and men with very low hs-CRP concentrations are significantly younger and have a clearly reduced BMI.

Medication intake in the four hs-CRP groups is reported in Table II for both men and women. It is clear that the finding of very low hs-CRP concentrations cannot be ascribed to the intake of medications with a potential anti-inflammatory activity. In Table III we report the number of individuals with atherothrombotic risk factors, as well as a past history of vascular diseases including cerebrovascular accident, ischaemic heart disease, prior myocardial infraction and peripheral artery occlusive disease. Only three individuals in the group of very low CRP had a history of a vascular disease. In this group, fewer individuals had atherothrombotic risk factors but smoking habits were similar to those observed in the other groups.

Table I. Age and body mass index (BMI) in the four groups of high-sensitivity C-reactive protein (hs-CRP) levels (mg l^{-1}) in men (upper part) and women (lower part), plus the one-way ANOVA and the *p* for trend between the groups.

	hs-CRP ≤ 0.16	0.16 < hs-CRP ≤ 1	1 < hs-CRP ≤ 3	3 < hs-CRP ≤ 10	ANOVA	
					p Value	*p* for trend
Men ($n = 4633$)	$n = 89$	$n = 1668$	$n = 1869$	$n = 1007$		
Age (years)	36.2 $\pm$ 12.5	43.4 $\pm$ 11.7	45.8 $\pm$ 10.9	46.2 $\pm$ 10.3	<0.001	<0.001
BMI (kg m^{-2})	23.6 $\pm$ 3.0	25.5 $\pm$ 3.0	27.3 $\pm$ 3.5	28.8 $\pm$ 4.1	<0.001	<0.001
Women ($n = 1955$)	$n = 71$	$n = 736$	$n = 670$	$n = 478$		
Age (years)	38.6 $\pm$ 9.8	45.6 $\pm$ 9.4	47.3 $\pm$ 9.0	48.1 $\pm$ 8.6	<0.001	<0.001
BMI (kg m^{-2})	21.3 $\pm$ 2.4	23.4 $\pm$ 3.1	25.9 $\pm$ 4.3	29.2 $\pm$ 4.9	<0.001	<0.001

Table II. Medications used in the four groups of high-sensitivity C-reactive protein (hs-CRP) levels (mg l^{-1}) in men (upper part) and women (lower part).

	hs-CRP ≤0.16		0.16 <hs-CRP ≤1		1 <hs-CRP ≤3		3 <hs-CRP ≤10		
	n	%	*n*	%	*n*	%	*n*	%	*p* Value
Men (*n* =4628)	*n* =89		*n* =1668		*n* =1869		*n* =1007		
Aspirin	4	4.5	136	8.2	154	8.2	103	10.2	0.109
Alpha blockers	1	1.1	29	1.7	40	2.1	17	1.7	0.718
Beta blockers	0	0	74	4.4	95	5.1	56	5.6	0.091
Calcium channel blockers	0	0	33	2.0	50	2.7	51	5.1	<0.001
ACE inhibitors	0	0	50	3.0	85	4.5	51	5.1	0.006
Angiotensin II receptor blockers	1	1.1	10	0.6	19	1.0	8	0.8	0.574
HMG-CoA reductase inhibitors	6	6.7	169	10.1	190	10.2	92	9.1	0.593
Fibrates	0	0	8	0.5	27	1.4	17	1.7	0.008
Diuretics	1	1.1	29	1.7	53	2.8	37	3.7	0.014
Insulin	0	0	6	0.4	3	0.2	3	0.3	0.649
Oral hypoglycaemics	2	2.2	21	1.3	36	1.9	32	3.2	0.007
Women (*n* =1955)	*n* =71		*n* =736		*n* =670		*n* =478		
Aspirin	0	0	14	1.9	26	3.9	24	5.0	0.007
Alpha blockers	0	0	1	0.1	1	0.1	4	0.8	0.119
Beta blockers	1	1.4	19	2.6	29	4.3	39	8.2	<0.001
Calcium channel blockers	0	0	8	1.1	14	2.1	16	3.3	0.026
ACE inhibitors	1	1.4	7	1.0	18	2.7	21	4.4	0.002
Angiotensin II receptor blockers	1	1.4	4	0.5	2	0.3	4	0.8	0.495
HMG-CoA reductase inhibitors	1	1.4	37	5.0	44	6.6	39	8.2	0.049
Fibrates	0	0	0	0	2	0.3	3	0.6	0.194
Diuretics	0	0	11	1.5	13	1.9	16	3.3	0.083
Insulin	0	0	2	0.3	0	0	3	0.6	0.212
Oral hypoglycaemics	0	0	4	0.5	6	0.9	17	3.6	<0.001

Table III. Cardiovascular risk factors and history of vascular events in the four groups of high-sensitivity C-reactive protein (hs-CRP) levels (mg l^{-1}) in men (upper part) and women (lower part).

	hs-CRP ≤0.16		0.16 <hs-CRP ≤1		1 <hs-CRP ≤3		3 <hs-CRP ≤10		
	n	%	*n*	%	*n*	%	*n*	%	*p* Value
Men (*n* = 4633)	*n* = 89		*n* = 1668		*n* = 1869		*n* = 1007		
Present smoker	14	15.9	242	14.9	290	15.8	211	21.4	<0.001
Past smoker	18	20.5	420	25.9	536	29.2	280	28.4	
Hypertension	11	12.4	317	19.0	508	27.2	328	32.6	<0.001
Hyperlipidaemia	10	11.2	461	27.6	732	39.2	466	46.3	<0.001
Diabetes mellitus	2	2.2	60	3.6	87	4.7	89	8.8	<0.001
Family history of CHD	10	11.2	236	14.1	303	16.2	182	18.1	0.030
Prior CVA	0	0	7	0.4	8	0.4	4	0.4	0.942
IHD	2	2.2	67	4.0	72	3.9	36	3.6	0.815
Prior MI	0	0	32	1.9	35	1.9	19	1.9	0.631
PAOD	1	1.1	13	0.8	15	0.8	8	0.8	0.988
Women (*n* = 1955)	*n* = 71		*n* = 736		*n* = 670		*n* = 478		
Present smoker	14	20.0	143	19.9	132	20.2	101	21.7	0.988
Past smoker	16	22.9	147	20.4	136	20.8	94	20.2	
Hypertension	5	7.0	84	11.4	112	16.7	126	26.4	<0.001
Hyperlipidaemia	3	4.2	124	16.8	204	30.4	193	40.4	<0.001
Diabetes mellitus	0	0	10	1.4	15	2.2	42	8.8	<0.001
Family history of CHD	11	15.5	133	18.1	131	19.6	111	23.2	0.123
Prior CVA	0	0	2	0.3	5	0.7	8	1.7	0.044
IHD	0	0	13	1.8	12	1.8	10	2.1	0.672
Prior MI	0	0	3	0.4	0	0	3	0.6	0.248
PAOD	0	0	6	0.8	4	0.6	8	1.7	0.213

CHD, coronary heart disease; CVA, cerebrovascular accident; IHD, ischaemic heart disease; MI, myocardial infarction; PAOD, peripheral arterial obstructive disease.

Table IV. Lipid profile in the four groups of high-sensitivity C-reactive protein (hs-CRP) levels (mg l^{-1}) in men (upper part) and women (lower part), plus the one-way ANOVA and the p for trend between the groups.

	hs-CRP ≤0.16	0.16 <hs-CRP ≤1	1 <hs-CRP ≤3	3 <hs-CRP ≤10	ANOVA p Value	ANOVA p for trend
Men (n = 4633)	n = 89	n = 1668	n = 1869	n = 1007		
Total cholesterol (mg dl^{-1})	181 ± 39	196 ± 35	204 ± 38	207 ± 41	<0.001	<0.001
Triglycerides (mg dl^{-1})	84	100	123	135	<0.001	<0.001
HDL cholesterol (mg dl^{-1})	55 ± 13	52 ± 11	50 ± 10	48 ± 9	<0.001	<0.001
LDL cholesterol (mg dl^{-1})	107 ± 32	120 ± 30	126 ± 32	128 ± 35	<0.001	<0.001
Women (n = 1955)	n = 71	n = 736	n = 670	n = 478		
Total cholesterol (mg dl^{-1})	190 ± 31	200 ± 36	211 ± 40	215 ± 41	<0.001	<0.001
Triglycerides (mg dl^{-1})	63	75	93	116	<0.001	<0.001
HDL cholesterol (mg dl^{-1})	69 ± 14	66 ± 13	63 ± 14	58 ± 13	<0.001	<0.001
LDL cholesterol (mg dl^{-1})	107 ± 26	118 ± 31	128 ± 34	130 ± 34	<0.001	<0.001

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

The results of the lipid profile in the above-mentioned four hs-CRP groups are reported in Table IV. Individuals with very low CRP concentrations had lower concentrations of total and LDL cholesterol, lower triglycerides and higher HDL cholesterol values. We have further analyzed the involvement of our participants in sports activities and obtained information about the intake of alcohol (Table V). The results demonstrate higher sports activity and alcohol intake in the group of very low hs-CRP, especially in men, with less prominent differences in women. We also report

Table V. Sport/work activity as well as alcohol intake in the four groups of high-sensitivity C-reactive protein (hs-CRP) levels (mg l^{-1}) in men (upper part) and women (lower part).

	hs-CRP ≤0.16	0.16 <hs-CRP ≤1	1 <hs-CRP ≤3	3 <hs-CRP ≤10	ANOVA p Value	ANOVA p for Trend
Men (n = 4633)	n = 89	n = 1668	n = 1869	n = 1007		
Sport intensity (hours per week)	3.8 ± 4.6	2.8 ± 3.4	2.4 ± 2.9	1.9 ± 2.6	<0.001	<0.001
Alcohol (glasses per week)	1.7 ± 2.6	1.4 ± 2.4	1.3 ± 2.3	1.2 ± 2.9	0.042	0.050
Women (n = 1955)	n = 71	n = 736	n = 670	n = 478		
Sport intensity (hours per week)	1.9 ± 2.6	2.2 ± 2.9	2.0 ± 2.7	1.6 ± 3.0	0.002	0.299
Alcohol (glasses per week)	0.5 ± 1.0	0.7 ± 1.5	0.5 ± 1.3	0.3 ± 1.0	<0.001	0.088

the results of other inflammation-sensitive biomarkers including ESR and fibrinogen concentrations, as well as the WBCC and differential. The group of individuals with very low CRP concentrations presented reduced levels of all these biomarkers for both genders (Table VI). In order to minimize the influence of the differences in all above-mentioned potential confounders on hs-CRP concentration between the groups, we calculated the hs-CRP concentration after adjustment for age, BMI, history of any vascular event, hypertension, hyperlipidaemia, diabetes mellitus, smoking status, family history of coronary heart disease (CHD), alcohol consumption and sports intensity, complete lipid profile including HDL, LDL and triglycerides, and medications including aspirin, beta blockers, calcium channel blockers, ACE inhibitors, statins, fibrates and oral hypoglycaemics (Table VII). It is evident that individuals with very low CRP levels remained with very low CRP despite all the above-mentioned adjustments.

Finally, we had the opportunity to repeat the hs-CRP measurements in some of the individuals with very low hs-CRP as several of them returned for a routine annual

Table VI. Inflammation-sensitive biomarkers in the four groups of high-sensitivity C-reactive protein (hs-CRP) ($mg\,l^{-1}$) in men (upper part) and women (lower part) plus the one-way ANOVA and the p for trend between the groups.

					ANOVA	
	hs-CRP ≤ 0.16	0.16 $<$hs-CRP ≤ 1	1 $<$hs-CRP ≤ 3	3 $<$hs-CRP ≤ 10	p Value	p for trend
Men ($n=4633$)	$n=89$	$n=1668$	$n=1869$	$n=1007$		
ESR ($mm\,h^{-1}$)	6.3 ± 6.3	7.7 ± 5.7	9.9 ± 6.7	12.9 ± 7.9	<0.001	<0.001
Fibrinogen ($mg\,dl^{-1}$)	217 ± 46	250 ± 45	279 ± 48	317 ± 54	<0.001	<0.001
WBC ($cells\times10^3\,mm^{-3}$)	5.9 ± 1.4	6.4 ± 1.4	6.8 ± 1.6	7.4 ± 1.9	<0.001	<0.001
PMN ($cells\times10^3\,mm^{-3}$)	3.4 ± 1.1	3.7 ± 1.1	4.0 ± 1.3	4.5 ± 1.4	<0.001	<0.001
Mon ($cells\times10^3\,mm^{-3}$)	0.5 ± 0.1	0.5 ± 0.2	0.5 ± 0.2	$0.6\pm.02$	<0.001	<0.001
Lymp ($cells\times10^3\,mm^{-3}$)	1.9 ± 0.4	2.0 ± 0.6	2.0 ± 0.6	2.1 ± 0.7	<0.001	<0.001
Plt ($cells\times10^3\,mm^{-3}$)	226 ± 55	231 ± 50	241 ± 55	250 ± 57	<0.001	<0.001
Women ($n=1955$)	$n=71$	$n=736$	$n=670$	$n=478$		
ESR ($mm\,h^{-1}$)	11.7 ± 7.2	15.3 ± 8.6	18.4 ± 8.6	22.7 ± 9.9	<0.001	<0.001
Fibrinogen ($mg\,dl^{-1}$)	246 ± 43	280 ± 48	307 ± 49	335 ± 54	<0.001	<0.001
WBC ($cells\times10^3\,mm^{-3}$)	6.2 ± 1.7	6.3 ± 1.6	6.6 ± 1.5	7.2 ± 1.8	<0.001	<0.001
PMN ($cells\times10^3\,mm^{-3}$)	3.6 ± 1.2	3.8 ± 1.2	3.9 ± 1.2	4.3 ± 1.3	<0.001	<0.001
Mon ($cells\times10^3\,mm^{-3}$)	0.5 ± 0.2	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.012	0.199
Lymp ($cells\times10^3\,mm^{-3}$)	1.9 ± 0.6	2.0 ± 0.5	2.0 ± 0.5	2.1 ± 0.6	<0.001	0.002
Plt ($cells\times10^3\,mm^{-3}$)	236 ± 54	247 ± 53	259 ± 57	273 ± 60	<0.001	<0.001

ESR, erythrocyte sedimentation rate; WBC, white blood cells; PMN, polymorphonuclear cells; Mon, monocytes; Lymp, lymphocytes; Plt, platelets.

Table VII. Multivariate adjusted* estimated marginal mean ± SE of mean high-sensitivity C-reactive protein (hs-CRP) in the four groups of hs-CRP levels (mg l^{-1}) in men (upper part) and women (lower part).

	hs-CRP ≤0.16	0.16 <hs-CRP ≤1	1 <hs-CRP ≤3	3 <hs-CRP ≤10
Men (n = 4633)	n = 89	n = 1668	n = 1869	n = 1007
hs-CRP (mg l^{-1})	0.16 ± 1.1	0.55 ± 1.0	1.61 ± 1.0	4.52 ± 1.0
Women (n = 1955)	n = 71	n = 736	n = 670	n = 478
hs-CRP (mg l^{-1})	0.17 ± 1.1	0.54 ± 1.1	1.67 ± 1.1	4.66 ± 1.1

*Estimated marginal means were adjusted for age, body mass index, history of any vascular event, hypertension, hyperlipidaemia, diabetes mellitus, smoking status, family history of coronary heart disease, alcohol consumption and sport intensity, complete lipid profile includes high-density lipoprotein, low-density lipoprotein and triglycerides and medications including aspirin, beta blockers, calcium channel blockers, ACE inhibitors, statins, fibrates and oral hypoglycaemics.

check-up at time intervals of 1 year apart. In fact, 22 men and 12 women were examined at time 2 (1 year following their baseline examination), seven men and six women were examined at time 3 (2 years following baseline), while three men and one woman were examined at time 4 (3 years following baseline). The individual values obtained at these three time points are reported in Table VIII and demonstrate that 20 (39%) of the repeated measurements maintained the very low hs-CRP concentrations, 10 (20%) had minor elevations (up to 0.2 mg l^{-1}) and only three repeated measurements (6%) moved to the medium risk category of >1 mg l^{-1}.

Table VIII. High-sensitivity C-reactive protein (hs-CRP) concentrations (mg l^{-1}) at intervals of 1 year apart in individuals who were available for follow-up following their baseline examination (time 1, not shown) during which they all had a hs-CRP of ≤0.16 mg l^{-1}.

Men (n = 22)			Women (n = 12)		
Time 2	Time 3	Time 4	Time 2	Time 3	Time 4
0.2	≤0.16	≤0.16	0.46		
≤0.16			≤0.16		
≤0.16			0.42	0.17	
0.44			≤0.16		
0.18	≤0.16		≤0.16		
1.06	0.49	0.32	0.21	0.24	0.51
≤0.16	0.19		0.15	≤0.16	
≤0.16			0.29	0.23	
0.2			≤0.16		
0.39			0.25	≤0.16	
0.19			0.26		
0.17			0.64	0.52	
≤0.16					
0.16					
≤0.16					
0.17					
≤0.16	≤0.16	≤0.16			
0.35					
1.26					
0.18	0.22				
≤0.16	0.54				
1.03					

Discussion

This is the first study to suggest that the presence of very low CRP concentrations in apparently healthy individuals is not necessarily only a result of an improved health profile but might represent a physiological status. In fact, adjustments for a relatively large number of confounders that have been shown to affect the serum concentrations of this particular biomarker (Kushner et al. 2006) did not change the observation.

The subject of low CRP concentrations has been previously discussed. For example, Tomaszewski et al. (2003) reported strikingly low circulating CRP concentrations in ultramarathon runners. The authors examined 67 ultramarathon male runners as well as 63 sedentary age- and BMI-matched controls and found that the median CRP concentrations in the lean marathon runners was as low as 0.4 (0.2–0.9) $mg\,l^{-1}$. They ascribed this low concentration to the intense regular physical exercise of these athletes. In addition, it has been clearly shown that low CRP is associated with less cardiovascular risk factors (reviewed by Tsimikas et al. 2006).

There is evidence that genetic variations could have a role in the determination of CRP concentrations (Kathiresan et al. 2006). The main finding of the present study is therefore that even following multiple adjustments for various known variables that can affect the concentration, the CRP retained its low level in this particular group of individuals. This finding suggests, although in an indirect way, that the particularly low CRP concentrations in our cohort might reflect a physiological status and is not necessarily a simple expression of the particularly favourable biology of these individuals. Of interest is our finding that the prevalence of smokers in the group of very low CRP was similar to that of other groups with higher CRP concentrations. This is another hint to our assumption, that even a proven aetiology for elevated serum CRP concentrations (Gan et al. 2005) did not affect hs-CRP concentrations in this particular group. However, increased consumption of alcohol, although of borderline significance, has been noted in men with very low hs-CRP. One cannot exclude the possibility that this is a contributory factor for reduced hs-CRP concentrations in this particular group, as was previously described (Imhof et al. 2001).

The main limitation of our study is the lack of follow-up for this particular group of individuals with very low CRP concentrations. Such a follow-up was reported by Ridker & Cook (2004) and showed an excellent vascular prognosis for individuals with a hs-CRP level of $<0.5\,mg\,l^{-1}$. The contribution of the present study is in the fact that the multiplicity of adjustments for most confounders did not change the results suggesting that the very low CRP concentrations of this particular group is probably related to their particular physiological status (perhaps genetic) rather than a mere refection of environmental and background risk factors.

We conclude that individuals with particularly low hs-CRP concentrations have a good general health profile, except for smoking habits which were as frequent as those observed in groups with higher hs-CRP concentrations. Following multiple adjustments for various confounders we could suggest that this might be related to the physiological status of these individuals.

Patients with very low hs-CRP concentrations might be of special interest due to the evolving role of this biomarker both as a diagnostic tool (Yeh & Khan 2006), an effector of the disease (Fuji et al. 2006, Singh et al. 2006) and a candidate for therapeutic manipulation (Pepys et al. 2006).

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