Biomarkers, May 2008; 13(3): 296–306

informa
healthcare

Ethnic groups and high sensitivity C-reactive protein in Israel

OFIR WOLACH[1], YARON ARBEL[2], MICHAEL COHEN[2], URI GOLDBOURT[3], UZI REBHUN[4], ITZHAK SHAPIRA[2], SHLOMO BERLINER[2], & ORI ROGOWSKI[2]

[1]*Department of Internal Medicine 'A', Rabin Medical Center, Beilinson Campus, Petach Tikva, affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Israel,* [2]*Department of Internal Medicine 'D', Tel Aviv Sourasky Medical Center, affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Israel,* [3]*Division of Epidemiology and Preventive Medicine, Sackler Faculty of Medicine, Tel Aviv University, Israel and* [4]*Division of Jewish Demography & Statistics, The A Harman Institute of Contemporary Jewry, The Hebrew University of Jerusalem, Israel*

Abstract

High-sensitivity C-reactive protein (hs-CRP) is a biomarker that correlates with atherothrombotic risk and outcome. hs-CRP is influenced by various modifiable and non-modifiable factors. We studied the relationship between ethnic background and hs-CRP level, among the Jewish population in Israel. A total of 3659 men and 2180 women were divided into two ethnic groups (Ashkenazi and Sephardic Jews), based on the knowledge of Jewish immigration patterns throughout the centuries. Mean hs-CRP levels were calculated for each group and were adjusted for various factors known to influence hs-CRP. Sephardic Jews were found to have higher adjusted mean hs-CRP levels (2.0 mg l^{-1} for men and 3.9 mg l^{-1} for women) compared with Ashkenazi Jews (1.5 mg l^{-1} for men and 2.9 mg l^{-1} for women). Ethnic background emerged as an independent significant predictor of hs-CRP levels. We demonstrated that ethnicity is an important factor when considering hs-CRP as a marker of atherothrombotic risk.

Keywords: *High-sensitivity C-reactive protein, gender, ethnicity, Jewish*

(Received 24 August 2007; accepted 9 November 2007)

Introduction

Atherothrombosis is a leading cause of morbidity and mortality in Western communities. It is accompanied by a low-grade subclinical and smouldering inflammatory process (Libby et al. 2002) that probably reflects the presence of multiple factors including gender (Zeltser et al. 2004), age (Larbi et al. 2004), morbid biological factors including obesity (Frohlich et al. 2000, Rexrode et al. 2003, Ridker et al. 2003, Santos et al. 2005, Warnberg et al. 2006), diabetes (Frohlich et al. 2000, Ridker et al. 2003, Kerner et al. 2005), hypertension (Ridker et al. 2003, Tsioufis et al. 2006), dyslipidaemia (Frohlich et al. 2000, Ridker et al. 2003, Pirro et al. 2004),

Correspondence: Dr Ori Rogowski, Tel Aviv Sourasky Medical Center, Internal Medicine 'D', 6 Weizman St., Tel-Aviv 64239, Israel. Tel: + 972-3-6973776. Fax: + 972-3-6973885. E-mail: orir@tasmc.health.gov.il

ISSN 1354-750X print/ISSN 1366-5804 online
DOI: 10.1080/13547500701800023

use of hormones (Ridker et al. 1999, Kushner et al. 2006), smoking (Yasue et al. 2006), exercise (Petersen & Pedersen 2005), alcohol consumption (Imhof et al. 2001) and various other factors (Kushner et al. 2006).

Several biomarkers have been used to detect and quantify the above-mentioned microinflammatory process, the most widely used being high-sensitivity C-reactive protein (hs-CRP). This biomarker has been shown to have both prognostic and therapeutic implications (Ridker et al. 2002, 2003, Best et al. 2005, Laaksonen et al. 2005, Ridker et al. 2005, Khera et al. 2006, Kuller et al. 2006). It has not been excluded as to whether it also has a pathogenetic role in the development of the atherothrombotic process itself (Paffen & DeMaat 2006).

In addition to the above-mentioned reasons for the elevation of hs-CRP in the population, genetic factors could be operating as well. In fact, several studies have implicated ethnicity as a potential reason for the presence of increased hs-CRP concentrations (Albert et al. 2004, Anand et al. 2004) and several polymorphisms that contribute to increased hs-CRP concentrations have also been reported (Pankow et al. 2001, Crawford et al. 2006, Friedlander et al. 2006). Thus, further documentation of a potential ethnic role in the presence of enhanced hs-CRP concentrations might be of relevance.

We have taken advantage of the fact that Israel is an immigrant society. It therefore presents an opportunity to research a potential ethnic influence on the concentrations of hs-CRP. This analysis might have special relevance for the application of the biomarker in daily practice.

Methods

Population

The present survey utilizes data from 11 274 individuals included in the Tel Aviv Medical Center Inflammation Survey (TAMCIS) (Rogowski et al. 2004, 2005). TAMCIS is a relatively large sample of apparently healthy individuals attending the Tel Aviv Sourasky Medical Center for routine health examinations. Most individuals were referred from work places throughout the country which have agreements with the Center for conducting their employees' annual health check-ups. This clinic is in no way connected with referrals to the hospital. All individuals included in the present survey provided written consent according to the instructions of the Institutional Ethics Committee.

After excluding individuals with underlying inflammatory disease (arthritis, inflammatory bowel disease, etc.), as well as those with any infections or other inflammatory conditions such as infarction, surgery or angiography during the 6 months preceding study enrolment, along with cancer patients and individuals whose hs-CRP measurement was not found to be recorded, we generated a sample of 8989 individuals.

The sample is further restricted to patients whose parents were both born in the same country. Traditionally, ethnicity is defined according to the paternal birthplace but we decided to include subjects whose parents were both born in the same country with the aim of increasing the value of our findings. Applying this criterion, patients were found to be from some 40 different origin backgrounds with group sizes ranging from a handful (e.g. Spain, Croatia, Lebanon, the Netherlands) to samples as large as a few hundred (e.g. Poland, Iraq). Such a distribution of the major explanatory

variable required the merger of individual groups into wider categories of origin. Preliminary analyses of individual groups with a large enough number of cases originating in a given region, revealed significant similarities in the outcome parameters. For example, patients with a Romanian background had results which were similar to those of patients with a Polish background and each of these groups had outcomes very similar to those of an aggregate of the rest of Europe. We also witnessed a similarity between subjects of Yemenite and Iraqi backgrounds with both groups being similar to the rest of Asia. These findings largely coincide with knowledge of Jewish immigration patterns throughout the centuries (DellaPergola & Even 2001). The Arab–Israeli ethnic group was not sufficiently large in TAMCIS to form a statistically comparable group in the study and was not included in the analysis.

Accordingly, we reconstructed our survey population into two major ethnic groups. One consisted of Ashkenazi Jews originating from Europe, America and Oceania. The second consisted of Sephardic Jews originating from the Near-East and North-Africa (including France whose Jewish population largely originates from North Africa). One thousand three hundred and ninety-four individuals were excluded from the analysis as their origins according to the categories were not ascertained. In addition, 1756 individuals whose parents were from two different ethnic groups were excluded. Thus, the final sample comprised 5839 individuals of whom 3659 were men and 2180 were women.

Definition of atherothrombotic risk factors

Diabetes mellitus was defined as a fasting blood glucose of ≥ 7.0 mmol l^{-1} (126 mg dl^{-1}) or the use of insulin or oral hypoglycaemic medications. Hypertension was defined as a blood pressure of $\geq 140/90$ mmHg on two separate measurements or the use of antihypertensive medications. Dyslipidaemia was defined as low-density lipoprotein (LDL) cholesterol or non-high-density lipoprotein (non-HDL) cholesterol concentrations for individuals with triglyceride concentrations of ≥ 2.26 mmol l^{-1} (200 mg dl^{-1}) above the recommended figure 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 individuals who smoked at least five cigarettes per day while past smokers had quit smoking for at least 30 days prior to examination.

Laboratory methods

hs-CRP concentrations were measured using the Behring BN II Nephelometer (DADE Behring, Marburg, Germany) (Rifai et al. 1999).

Statistical analysis

All the analyses were performed separately for men and women due to the significant differences in hs-CRP and the different contributing factors influencing the variability in hs-CRP between the genders. All data were summarized and displayed as mean $\pm$ standard deviation (SD) for the continuous variables [age, body mass index (BMI), hs-CRP, etc.], and as number of patients plus the percentage in each group for categorical variables (medication, cardiovascular risk factors, etc.). The crosstabs and descriptive procedures were used to produce frequencies of categorical variables and

means ± SD of continuous variables. The hs-CRP and the triglyceride concentration do not have normal distributions. Thus we used a logarithmic transformation which converted them into normal distributions for all statistical procedures such as correlations, ANCOVA, etc. All of the hs-CRP or triglyceride concentrations are back-transformed geometrical means and standard deviation. The one-sample Kolmogorov–Smirnov test and the Q-Q plots were used to test for the normality of distributions.

For continuous variables, the independent Student's *t*-test was performed to compare the various parameters between the different ethnic groups. The age-adjusted comparison of the continuous variables between the ethnic groups was performed using ANCOVA under a general linear model. For all categorical variables the χ^2 test was used to assess the significance between the ethnic groups. The age standardization of the rate of risk factors and medication used by the ethnic groups was performed using the direct method with the standard population being the average population of Jewish men and women in Israel in 2004 (Central Bureau of Statistics 2005).

Estimated marginal means of hs-CRP for the different ethnic groups were adjusted for waist circumference, age, systolic and diastolic blood pressures, glucose concentration, BMI and complete lipid profile including LDL, HDL and triglyceride concentrations. Further adjustments were made for alcohol consumption, exercise intensity, the use of medications including aspirin, beta-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), statins and fibrates. The use of oral contraceptives and hormone replacement therapy was adjusted for women. Smoking status, hypertension, diabetes mellitus, history of atherothrombotic event (ischaemic heart disease, cerebrovascular event or peripheral arterial disease) and family history of coronary heart disease (CHD) were also all adjusted using ANCOVA under a general linear model. We further assessed the pairwise statistical significance between the different ethnic groups.

In order to assess which variables from the aforementioned list contribute to the variability of the inflammatory marker, hs-CRP, we used the linear regression model, with hs-CRP as the dependent variable and all other variables mentioned in addition to the ethnic group as the independent variables using the stepwise method.

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 analysed two different populations in our study: Ashkenazi Jews (originating from Europe, America and Oceania) and Sephardic Jews (originating from the Near-East and North-Africa, including France whose Jewish population is largely from North Africa).

Table I demonstrates the demographic characteristics of men according to their respective ethnic origins. The volunteers of Ashkenazi ancestry were older compared with the Sephardic volunteers and had higher values for various metabolic parameters such as age-adjusted blood pressure, waist circumference, BMI and LDL cholesterol levels compared with their Sephardic counterparts. It is worth noting that despite

Table I. Mean ± standard deviation (SD) of age, and age-adjusted estimated marginal mean of the other demographic variables of men by ethnic origin ($n = 3659$).

	Ashkenazi Jews ($n = 2162$)	Sephardic Jews ($n = 1497$)	p-Value
Age[a] (years)	49 ± 10	46 ± 10	<0.001
Waist (cm)	98	96	<0.001
BMI (kg m^{-2})	27.5	27.1	0.001
Heart rate (beats min^{-1})	69	71	0.002
Diastolic BP (mmHg)	79	78	<0.001
Systolic BP (mmHg)	128	125	<0.001
Haemoglobin (g l^{-1})	150	149	0.021
Glucose (mmol l^{-1})	5.37	5.42	0.248
HDL cholesterol (mmol l^{-1})	1.32	1.29	<0.001
LDL cholesterol (mmol l^{-1})	3.23	3.20	0.243
Triglycerides (mmol l^{-1})	1.53	1.58	0.138
Alcohol consumption (glass per week)	1.4	1.1	<0.001
Exercise intensity (hours per week)	2.6	2.0	<0.001
FCRS (%)	6.5	6.5	0.746
hs-CRP (mg l^{-1})	1.4	1.8	<0.001

[a]Mean ± standard deviation of age. BMI, body mass index; BP, blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FCRS, 10-year Framingham's coronary risk; hs-CRP, high-sensitivity C-reactive protein.

these metabolic differences, the age-adjusted hs-CRP level was significantly lower in the Ashkenazi population.

Table II demonstrates the characteristics of women according to their respective ethnic origins. Female volunteers of Ashkenazi ancestry were older compared with

Table II. Mean ± SD of age, and age-adjusted estimated marginal mean of the other demographic variables of women by ethnic origin ($n = 2180$).

	Ashkenazi Jews ($n = 1253$)	Sephardic Jews ($n = 927$)	p-Value
Age[a] (years)	50 ± 10	46 ± 8	<0.001
Waist (cm)	84	83	0.026
BMI (kg m^{-2})	25.8	25.9	0.606
Heart rate (beats min^{-1})	71	73	0.001
Diastolic BP (mmHg)	75	75	0.345
Systolic BP (mmHg)	121	117	<0.001
Haemoglobin (g l^{-1})	132	129	<0.001
Glucose (mmol l^{-1})	5.14	5.09	0.275
HDL cholesterol (mmol l^{-1})	1.70	1.60	<0.001
LDL cholesterol (mmol l^{-1})	3.21	3.16	0.174
Triglycerides (mmol l^{-1})	1.17	1.20	0.244
Alcohol consumption (glass per week)	0.7	0.3	<0.001
Exercise intensity (hours per week)	2.0	1.9	0.281
FCRS (%)	1.6	1.3	0.002
hs-CRP (mg l^{-1})	1.5	1.9	<0.001

[a]Mean ± standard deviation of age. BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FCRS, 10-year Framingham's coronary risk; hs-CRP, high-sensitivity C-reactive protein.

their Sephardic counterparts and had higher values for various metabolic parameters in a similar manner to that demonstrated for men.

The difference in hs-CRP values between the two ethnic groups for both genders are further emphasized after adjusting the hs-CRP for the various demographic and metabolic variables that were included in the study (Table III).

Table IV demonstrates the age-standardized rates of the different cardiovascular risk factors as well as of history of proven atherothrombotic event among the different ethnic groups. It is evident that the Ashkenazi group had higher percentages of some cardiovascular risk factors in both genders and proven atherothrombotic events in men, with the exception of smoking which was more prevalent in male volunteers of Sephardic ancestry. Of note is the finding that family history was as prevalent in both groups, and the rate of diabetes mellitus, an important cardiovascular risk factor, was the same in males of both ethnic groups.

Table V presents the age-standardized rates for the usage of different medications between the two ethnic groups according to gender. As can be seen and expected from their higher prevalence of risk factors (Table IV), the Ashkenazi group had a significantly higher percentage of medication usage in most of the categories, except for oral contraceptives which were more prevalent in Sephardic females.

Table VI highlights variables that were entered into the linear regression model as independent predictors of hs-CRP concentration. While ethnic group, BMI, waist circumference, HDL cholesterol, triglyceride concentration, use of calcium channel blockers and exercise intensity were found to explain independently the variability of hs-CRP in both genders, other factors were gender specific. Table VI also includes the partial correlation of all the variables entered into the model, controlling for all others. Interestingly, the factor that emerged as the most likely to influence hs-CRP was being a male of Sephardic descent. This factor has proven to be a stronger predictor than all other traditional factors included in the analysis.

Discussion

hs-CRP is a well-established predictor of cardiovascular risk and outcome (Ridker et al. 2002, 2003, Best et al. 2005, Laaksonen et al. 2005, Ridker et al. 2005, Khera et al. 2006, Kuller et al. 2006) and is thus of special interest from an epidemiological point of view. In this study we have demonstrated for the first time to our knowledge, CRP variation among Ashkenazi and Sephardic Jews in Israel. Subjects of Sephardic origin were found to have significantly higher adjusted mean

Table III. Mean ± standard error of the mean (SE) concentrations of inflammatory markers of men and women by ethnic origin after adjustment for demographic and metabolic variables.

	Ashkenazi Jews	Sephardic Jews	*p*-Value
Men ($n=3659$)			
n	2162	1497	
hs-CRP	1.5 ± 1.1	2.0 ± 1.1	<0.001
Women ($n=2180$)			
n	1253	927	
hs-CRP	2.9 ± 1.2	3.9 ± 1.3	<0.001

hs-CRP, high-sensitivity C-reactive protein.

Table IV. Age-standardized[a] percentage of the different cardiovascular risk factors among the two ethnic groups plus the statistical significance between them in men and women.

	Ashkenazi Jews	Sephardic Jews	χ^2 *p*-Value
Men ($n=3659$)			
n	2162	1497	
Dyslipidaemia	32.4	25.8	<0.001
Family history	14.7	12.7	0.081
Hypertension	27.7	20.7	<0.001
Diabetes mellitus	5.0	4.4	0.384
Current smoker	18.2	20.4	0.024
Past smoker	24.0	26.3	
Atherothrombotic event	5.3	3.9	0.045
Women ($n=2180$)			
n	1253	927	
Dyslipidaemia	26.9	20.5	0.001
Family history	16.2	15.3	0.546
Hypertension	20.1	15.1	0.003
Diabetes mellitus	4.2	1.8	0.001
Current smoker	20.9	19.3	<0.001
Past smoker	24.3	13.2	
Atherothrombotic event	4.3	3.7	0.470

[a]Age standardization was based on the average Jewish population in 2004 in men and women, by the direct method.

hs-CRP levels (2.0 mg l^{-1} for men and 3.9 mg l^{-1} for women) compared with Ashkenazi Jews (1.5 mg l^{-1} for men and 2.9 mg l^{-1} for women). The above mean hs-CRP levels are adjusted for known and presumed factors that influence hs-CRP

Table V. Age-standardized[a] percentages of the different medications among the two ethnic groups plus the statistical significance between them in men and women.

	Ashkenazi Jews	Sephardic Jews	χ^2 *p*-Value
Men ($n=3659$)			
n	2162	1497	
Statins	11.7	6.9	<0.001
Fibrates	1.4	0.6	0.025
Beta-blockers	6.7	4.6	0.007
Calcium channel blockers	4.3	2.7	0.010
ACE inhibitors	4.6	2.9	0.009
Aspirin	11.1	8.0	0.002
Women ($n=2180$)			
n	1253	927	
Statins	8.7	8.6	0.908
Fibrates	0.9	0.1	0.007
Beta-blockers	6.4	4.0	0.015
Calcium channel blockers	1.7	1.1	0.280
ACE inhibitors	3.8	1.4	0.001
Aspirin	3.1	3.8	0.401
Oral contraceptives	18.4	22.2	0.026
Hormone replacement therapy	7.7	7.5	0.840

[a]Age standardization was based on the average Jewish population in 2004 in men and women, by the direct method. ACE, angiotensin-converting enzyme.

Table VI. Variables that were entered into the linear regression model with hs-CRP as the dependent variable and all other potential variables including ethnic group as the independent variables for men and women.

Parameter	Unstandardized coefficient B	Standardized coefficient Beta	*p*-Value	Partial correlation
Men ($R^2 = 0.18$)				
Sephardic Jew	0.125	0.142	<0.001	0.149
Waist	0.007	0.160	<0.001	0.094
BMI	0.018	0.155	<0.001	0.092
LDL cholesterol	0.001	0.088	<0.001	0.091
HDL cholesterol	−0.003	−0.073	<0.001	−0.071
Current smoker	0.068	0.058	<0.001	0.063
Exercise intensity	−0.009	−0.058	<0.001	−0.062
Glucose	0.001	0.046	0.005	0.048
Systolic blood pressure	0.001	0.046	0.007	0.046
Statins	−0.057	−0.043	0.008	−0.045
Log (triglycerides)	0.081	0.041	0.021	0.039
CCB	0.080	0.035	0.029	0.037
Family history of CHD	0.036	0.031	0.045	0.034
Women ($R^2 = 0.38$)				
Oral contraceptives	0.462	0.230	<0.001	0.270
BMI	0.037	0.345	<0.001	0.230
Log (triglycerides)	0.383	0.159	<0.001	0.174
Sephardic Jew	0.129	0.127	<0.001	0.153
Hormone replacement therapy	0.183	0.117	<0.001	0.144
Waist	0.005	0.121	<0.001	0.081
Diabetes mellitus	0.146	0.054	0.002	0.067
Diastolic blood pressure	0.001	0.047	0.008	0.058
Alcohol consumption	−0.016	−0.043	0.017	−0.053
Exercise intensity	−0.007	−0.039	0.026	−0.049
CCB	0.124	0.036	0.038	0.046
HDL cholesterol	−0.001	−0.039	0.047	−0.044

BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CCB, calcium channel blocker; CHD, coronary heart disease.

levels. Ethnic origin has also emerged in the multivariate regression analysis as a very important independent predictor of hs-CRP level among the different groups, beyond the known predictors.

It is interesting to point out that although Sephardic Jews demonstrated a higher mean hs-CRP value than their Ashkenazi counterparts, they held lower rates of almost all other established atherothrombotic risk factors (with the exception of smoking) with varying degrees of significance. To further emphasize this discrepancy, we found that Ashkenazi Jews of male gender demonstrated a significantly higher percentage of a past history of a proven atherothrombotic event as compared with their Sephardic counterparts. A similar non-significant trend was demonstrated in the female group (Table IV). This finding necessitates the investigation for other unknown factors which may contribute to these differences. In this case of ethnic differences, genetic heterogeneity is the likely candidate. In addition, these findings highlight the need to interpret an individual's hs-CRP level in the context of their other cardiovascular risk factors as well as their ethnic origin. In practice, the derivation of different and specific

reference ranges of hs-CRP for different ethnic groups might improve the diagnostic and prognostic yield of measuring hs-CRP concentrations in patients from specific ethnic groups.

Our study findings correlate with past studies which have shown an ethnic-based variation among North American, European and Asian communities (Chambers et al. 2001, Albert et al. 2004, Anand et al. 2004, Berliner et al. 2005). Albert et al. investigated hs-CRP variation among 24 455 Caucasian, 254 Hispanic and 475 African-American women in the USA in a large cross-sectional study. They demonstrated that median hs-CRP levels are significantly higher among African-American women (2.96 mg l^{-1}) than among their Caucasian and Hispanic counterparts (2.02 mg l^{-1} and 2.06 mg l^{-1}, respectively) and that Asian women have significantly lower median hs-CRP levels (1.12 mg l^{-1}) (Albert et al. 2004). These changes were still significant after adjusting for known factors that influence hs-CRP levels. Another study by Anand et al. showed significant hs-CRP variation in Canada among 1250 men and women of various ethnic origins. Aborigines had the highest mean hs-CRP levels (3.74 mg l^{-1}) followed by South Asians and Europeans (2.59 mg l^{-1} and 2.06 mg l^{-1}, respectively). The lowest mean hs-CRP levels were demonstrated among the Chinese ethnic group (1.18 mg l^{-1}). Differences in hs-CRP among the various groups were diminished, but not eliminated after adjustments were made for metabolic factors (Anand et al. 2004). Chambers et al. demonstrated ethnic-based hs-CRP differences by comparing 518 Indian Asians with 507 European Caucasians. hs-CRP levels (1.47 mg l^{-1} for European Caucasians and 1.71 mg l^{-1} among Indian Asians, $p = 0.03$) remained statistically significant after adjusting for age, cigarette smoking, BMI and other conventional CHD risk factors. However, the difference in CRP concentrations between the racial groups was eliminated by adjusting for waist–hip ratio or insulin-resistance score (Chambers et al. 2001). A small study in Israel demonstrated that Yemenite Jews have enhanced concentrations of hs-CRP compared with the general population, indicating that the benign hereditary leukopenia–neutropenia present in this ethnic group does not represent an absence of low-grade inflammation (Berliner et al. 2005).

In our study we found various factors other than ethnicity which independently predict elevated hs-CRP levels (Table VI). These include BMI, waist circumference, low HDL cholesterol and high triglyceride concentrations, use of calcium channel blockers and low exercise intensity in both genders. In addition, for men specifically, LDL cholesterol, smoking status, glucose concentration, systolic blood pressure, use of statins and a family history of CHD were relevant factors. For women, oral contraceptives, hormone replacement therapy, diabetes mellitus, diastolic blood pressure and alcohol consumption were found to be statistically significant factors contributing to the variability of hs-CRP. All of these factors correlate with known risk factors and variables that influence the concentration of hs-CRP. Furthermore, the finding that ethnic group enters the models in addition to all of these variables and has a powerful influence on hs-CRP concentrations, emphasizes the importance of ethnic group in this regard.

Although a very large cross-sectional cohort was investigated in this study, only a prospective, long-term study will be able to shed light upon the complex relationship linking ethnicity, inflammatory makers and cardiovascular morbidity and mortality. Future studies investigating CRP trends in immigrants compared with their native

offspring will provide a unique opportunity to further understand environmental versus genetic contributions to hs-CRP levels.

References

Albert MA, Glynn RJ, Buring J, Ridker PM. 2004. C-reactive protein levels among women of various ethnic groups living in the United States (from the Women's Health Study). American Journal of Cardiology 93:1238–1242.

Anand SS, Razak F, Yi Q, Davis B, Jacobs R, Vuksan V, Lonn E, Teo K, McQueen M, Yusuf S. 2004. C-reactive protein as a screening test for cardiovascular risk in a multiethnic population. Arteriosclerosis, Thrombosis. and Vascular Biology 24:1509–1515.

Berliner S, Shapira I, Toker S, Melamed S, Shirom A, Rogowski O. 2005. Benign hereditary leukopenia–neutropenia does not result from lack of low grade inflammation. A new look in the era of microinflammation. Blood. Cells Molecules & Disease 34:135–140.

Best LG, Zhang Y, Lee ET, Yeh JL, Cowan L, Palmieri V, Roman M, Devereux RB, Fabsitz RR, Tracy RP, Robbins D, Davidson M, Ahmed A, Howard BV. 2005. C-reactive protein as a predictor of cardiovascular risk in a population with a high prevalence of diabetes: the Strong Heart Study. Circulation 112:1289–1295.

Central Bureau of Statistics. 2005. Population by population group, religion, age and sex, district and sub-district. Statistical abstract of Israel 2005. No. 56. Jerusalem: Central Bureau of Statistics.

Chambers JC, Eda S, Bassett P, Karim Y, Thompson SG, Gallimore JR, Pepys MB, Kooner JS. 2001. C-reactive protein, insulin resistance, central obesity, and coronary heart disease risk in Indian Asians from the United Kingdom compared with European whites. Circulation 104:145–150.

Crawford DC, Sanders CL, Qin X, Smith JD, Shephard C, Wong M, Witrak L, Rieder MJ, Nickerson DA. 2006. Genetic variation is associated with C-reactive protein levels in the Third National Health and Nutrition Examination Survey. Circulation 114:2458–2465.

DellaPergola S, Even J. 2001. Papers in Jewish Demography 1997. Jerusalem: The Hebrew University of Jerusalem.

Friedlander Y, Kark JD, Sinnreich R, Tracy RP, Siscovick DS. 2006. Fibrinogen and CRP in Israeli families: genetic and environmental sources of concentrations and longitudinal changes. Atherosclerosis 189:169–177.

Frohlich M, Imhof A, Berg G, Hutchinson WL, Pepys MB, Boeing H, Muche R, Brenner H, Koenig W. 2000. Association between C-reactive protein and features of the metabolic syndrome: a population-based study. Diabetes Care 23:1835–1839.

Imhof A, Froehlich M, Brenner H, Boeing H, Pepys MB, Koenig W. 2001. Effect of alcohol consumption on systemic markers of inflammation. Lancet 357:763–767.

Kerner A, Avizohar O, Sella R, Bartha P, Zinder O, Markiewicz W, Levy Y, Brook GJ, Aronson D. 2005. Association between elevated liver enzymes and C-reactive protein: possible hepatic contribution to systemic inflammation in the metabolic syndrome. Arteriosclerosis, Thrombosis, and Vascular Biology 25:193–197.

Khera A, de Lemos JA, Peshock RM, Lo HS, Stanek HG, Murphy SA, Wians FH Jr, Grundy SM, McGuire DK. 2006. Relationship between C-reactive protein and subclinical atherosclerosis: the Dallas Heart Study. Circulation 113:38–43.

Kuller LH, Arnold AM, Psaty BM, Robbins JA, O'Leary DH, Tracy RP, Burke GL, Manolio TA, Chaves PH. 2006. 10-year follow-up of subclinical cardiovascular disease and risk of coronary heart disease in the Cardiovascular Health Study. Archives of Internal Medicine 166:71–78.

Kushner I, Rzewnicki D, Samols D. 2006. What does minor elevation of C-reactive protein signify? American Journal of Medicine 119:116:e17–e28.

Laaksonen DE, Niskanen L, Nyyssonen K, Punnonen K, Tuomainen TP, Salonen JT. 2005. C-reactive protein in the prediction of cardiovascular and overall mortality in middle-aged men: a population-based cohort study. European Heart Journal 26:1783–1789.

Larbi A, Dupuis G, Douziech N, Khalil A, Fulop T Jr. 2004. Low-grade inflammation with aging has consequences for T-lymphocyte signaling. Annals of New York Academy of Sciences 1030:125–133.

Libby P, Ridker PM, Maseri A. 2002. Inflammation and atherosclerosis. Circulation 105:1135–1143.

National Cholesterol Education Program. 2001. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 285:2486–2497.

Paffen E, DeMaat MP. 2006. C-reactive protein in atherosclerosis: A causal factor? Cardiovascular Research 71:30–39.

Pankow JS, Folsom AR, Cushman M, Borecki IB, Hopkins PN, Eckfeldt JH, Tracy RP. 2001. Familial and genetic determinants of systemic markers of inflammation: the NHLBI family heart study. Atherosclerosis 154:681–689.

Petersen AM, Pedersen BK. 2005. The anti-inflammatory effect of exercise. Journal of Applied Physiology 98:1154–1162.

Pirro M, Schillaci G, Savarese G, Gemelli F, Vaudo G, Siepi D, Bagaglia F, Mannarino E. 2004. Low-grade systemic inflammation impairs arterial stiffness in newly diagnosed hypercholesterolaemia. European Journal of Clinical Investigation 34:335–341.

Rexrode KM, Pradhan A, Manson JE, Buring JE, Ridker PM. 2003. Relationship of total and abdominal adiposity with CRP and IL-6 in women. Annals of Epidemiology 13:674–682.

Ridker PM, Buring JE, Cook NR, Rifai N. 2003. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. Circulation 107:391–397.

Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, Pfeffer MA, Braunwald E. 2005. C-reactive protein levels and outcomes after statin therapy. New England Journal of Medicine 352:20–28.

Ridker PM, Hennekens CH, Rifai N, Buring JE, Manson JE. 1999. Hormone replacement therapy and increased plasma concentration of C-reactive protein. Circulation 100:713–716.

Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. 2002. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. New England Journal of Medicine 347:1557–1565.

Rifai N, Tracy RP, Ridker PM. 1999. Clinical efficacy of an automated high-sensitivity C-reactive protein assay. Clinical Chemistry 45:2136–2141.

Rogowski O, Toker S, Shapira I, Melamed S, Shirom A, Zeltser D, Berliner S. 2005. Values of high-sensitivity C-reactive protein in each month of the year in apparently healthy individuals. American Journal of Cardiology 95:152–155.

Rogowski O, Zeltser D, Shapira I, Burke M, Zakut V, Mardi T, Ben-Assayag E, Serov J, Rozenblat M, Berliner S. 2004. Gender difference in C-reactive protein concentrations in individuals with atherothrombotic risk factors and apparently healthy ones. Biomarkers 9:85–92.

Santos AC, Lopes C, Guimaraes JT, Barros H. 2005. Central obesity as a major determinant of increased high-sensitivity C-reactive protein in metabolic syndrome. International Journal of Obesity (Lond) 29:1452–1456.

Tsioufis C, Dimitriadis K, Taxiarchou E, Vasiliadou C, Chartzoulakis G, Tousoulis D, Manolis A, Stefanadis C, Kallikazaros I. 2006. Diverse associations of microalbuminuria with C-reactive protein, interleukin-18 and soluble CD 40 ligand in male essential hypertensive subjects. American Journal of Hypertension 19:462–466.

Warnberg J, Nova E, Moreno LA, Romeo J, Mesana MI, Ruiz JR, Ortega FB, Sjostrom M, Bueno M, Marcos A. 2006. Inflammatory proteins are related to total and abdominal adiposity in a healthy adolescent population: the AVENA Study. American Journal of Clinical Nutrition 84:505–512.

Yasue H, Hirai N, Mizuno Y, Harada E, Itoh T, Yoshimura M, Kugiyama K, Ogawa H. 2006. Low-grade inflammation, thrombogenicity, and atherogenic lipid profile in cigarette smokers. Circulation Journal 70:8–13.

Zeltser D, Rogowski O, Berliner S, Mardi T, Justo D, Serov J, Rozenblat M, Avitzour D, Shapira I. 2004. Sex differences in the expression of haemorheological determinants in individuals with atherothrombotic risk factors and in apparently healthy people. Heart 90:277–281.