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Original Research Article

High-Sensitivity C-Reactive Protein, Adiposity, and Blood Pressure in the Yakut of Siberia

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ABSTRACT C-reactive protein (CRP), an acute-phase reactant and marker of inflammatory response, is known to be an important predictor of future cardiovascular mortality, independent of other risk factors. The purpose of this research was to investigate the association between CRP, adiposity, and blood pressure in the Yakut, an indigenous Siberian population undergoing rapid cultural change. We conducted a cross-sectional study of 265 healthy Yakut adults in six villages in rural northeastern Siberia. Plasma CRP was measured by high-sensitivity immunoturbidimetric assay. The median CRP value was 0.85 mg/l, with values for the 25th, 50th, and 75th percentiles of 0.30, 0.85, and 2.28 mg/l, respectively. CRP was positively associated with age ($r = 0.19$; $P = 0.002$), but not plasma lipids or smoking status. CRP was associated with measures of central adiposity and characteristics of the metabolic syndrome, particularly in women. We found significantly higher CRP across quintiles (Q) of waist circumference for women (difference = 0.7 mg/l; $P = 0.035$), but not men (difference = 0.36 mg/l; $P = 0.515$). CRP was significantly associated with systolic blood pressure in men (difference, Q1 vs. Q5 = 1.1 mg/l; $P = 0.044$) but not women (difference, Q1 vs. Q5 = 0.03 mg/l; $P = 0.713$) after adjusting for age, waist circumference, and smoking status. CRP in the Yakut was considerably lower than was reported for other populations. The low CRP levels may be explained in part by a low prevalence of abdominal obesity. Among the Yakut, the high physical-activity demands of a traditional herding lifeway likely play a role through high energy expenditure and maintenance of negative energy balance. Our findings underscore the need for further research on the metabolic activity of adipose tissue, blood pressure, and inflammatory activation in non-Western populations. Am. J. Hum. Biol. 18:766–775, 2006. © 2006 Wiley-Liss, Inc.

C-reactive protein (CRP) is an acute-phase reactant activated by cellular injury or infection, produced by hepatocytes and regulated primarily by interleukin-6 (IL-6) (Roberts et al., 2000). Upon activation, CRP levels in circulation increase rapidly up to 1,000-fold (Danesh et al., 2000). CRP is a highly sensitive marker of systemic inflammation, infection, and tissue injury. The recognition in recent years of the critical role of the inflammatory process in atherogenesis (Gotto and Pownall, 1999; Ross, 1999), insulin resistance syndrome (Yudkin et al., 1999), and hypertension (Bautista et al., 2005; Chae et al., 2001) has generated intense interest in the role that CRP and other inflammatory cytokines play in the multifactorial etiology of these diseases (Chae et al., 2001;

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Mohamed-Ali et al., 1997, 1998; Ridker, 2001).

Several investigators showed that baseline elevations (>2–3 mg/l) of CRP detected by high-sensitivity assay (Roberts et al., 2000) are associated with atherosclerotic disease risk (Lagrand et al., 1999; Libby and Ridker, 1999). These low levels are approximately one order of magnitude lower than those seen in infection or in chronic inflammatory diseases such as rheumatoid arthritis. In a recent American Heart Association/Centers for Disease Control and Prevention scientific statement on inflammatory markers and cardiovascular disease (CVD), it was suggested that a CRP cutpoint of >3.0 mg/dl is associated with increased risk of CVD, a range of 1.0–3.0 mg/dl with average risk, and <1.0 mg/dl with low risk (Pearson et al., 2003). These values represent the approximate tertiles of the US adult population distribution. In multiple prospective studies, elevated CRP was linked with future risk of myocardial infarction, stroke, peripheral artery disease, and sudden cardiac death, independent of other CVD risk factors (Koenig et al., 1999; Ridker et al., 1998, 2000, 2002; Rifai and Ridker, 2003).

Current research suggests that adiposity plays a key role in the association between chronic inflammation, elevated CRP, and risk for CVD (Danesh et al., 2000; Ford, 1999; Visser et al., 1999; Yudkin et al., 1999). This is in part due to the production of IL-6 and other proinflammatory cytokines by adipocytes, leading to increased hepatic CRP production and chronic low-level inflammation. Body-fat patterning appears to be important in this process, as abdominal body fat (in particular, visceral adipose tissue) is more metabolically active than peripheral subcutaneous tissue (Mohamed-Ali et al., 1998).

Recent studies found a link between hypertension, inflammation, and CRP levels, suggesting a direct link between elevated blood pressure and atherogenesis (Blake et al., 2003; Chobanian and Alexander, 1996; Sesso et al., 2003), yet the precise mechanisms and possible linkages with body fat and other metabolic risk factors are unclear.

Several researchers proposed the use of CRP as a screening tool for cardiovascular risk assessment in the general population (Ridker, 2001; Ridker et al., 2000), but little is known about variation in high-sensitivity CRP in relation to cardiovascular risk among non-European populations. Commercially available assays and standardized laboratory procedures for measuring CRP have become available in the past 5 years (Hutchinson et al., 2000; Rifai et al., 1999; Roberts et al., 2000), and the stability and sample preservation characteristics of CRP and other cytokines were recently investigated (Pai et al., 2002), yet to date, relatively few population studies have been conducted in non-European populations using a high-sensitivity assay.

This study contributes to this emerging research by investigating variation in CRP in relation to adiposity, blood pressure, and other physiologic CVD risk markers in a circumpolar population undergoing rapid cultural, socioeconomic, and lifestyle changes. The purpose of this paper is to examine the potential link between body fat, blood pressure variation, and CRP in an indigenous North Asian population, and to compare CRP in the Yakut to values found in other populations.

STUDY POPULATION

The Sakha (Yakut) are a Turkic-speaking population of nearly 400,000 residing in the Sakha (Yakutia) Autonomous Republic of the Russian Federation in northeastern Siberia, from 56–73° North and 107–172° East. Traditionally, the Yakut subsist by herding cattle and horses in the Lena River Valley. In more remote parts of the boreal forest, the Yakut engage in hunting and fishing, and in the extreme north, practice nomadic reindeer herding (Tokarev and Gurvich, 1956). There are three ethnographically defined Yakut groups, based on subsistence patterns and clan origins: North reindeer herders, Viliui cattle-breeder, and Central Sakha (*Kangalas*) (Tokarev, 1940). The present study was conducted among the Central Sakha. The *Kangalas* practice cattle and horse breeding and reside primarily in the Lena River Valley, its tributaries, and surrounding regions.

The Yakut are experiencing rapid acculturation following the breakup of the Soviet Union and the disbanding of the collective farming system, resulting in a dramatic increase in cardiovascular mortality. In 1999, the total mortality rate for all cardiovascular diseases was 390.7 per 100,000, compared to a rate of 268.5 per 100,000 in 1985 (Sorensen, 2003).

The study design and methods for this work were described previously (Sorensen et al., 2005). Briefly, this study was conducted in collaboration with the Ministry of Health of the Republic of Sakha (Yakutia) and the Institute of Health of the Academy of Sciences of the

Republic of Yakutia (Sakha). In 2001, the Ministry of Health conducted a household survey to measure the economic, health, and nutritional status of the population in a representative cross-sectional study. For the present study, three villages (population $\leq$1,000) and three towns (population $>$1,000) in two districts were selected for investigation of CRP, plasma lipids, blood pressure, and other physiological parameters. The study districts were rural, with economies based on milk production and herding of cattle, horses, and reindeer. The study communities were Dikimdye (n = 55, population 850), Asyma (n = 33, population 1,000), and Berdygestiakh (n = 58, population 4,000) in the Gorny district, and Khorobut (n = 54, population 650), Maia (n = 32, population 11,000), and Nizhny Bestakh (n = 33, population 5,000) in the Megino-Kangalassky district.

The study was designed to provide a representative sample from each district. Seventy households were selected at random from the household census register for each community for inclusion in the study. All healthy men and nonpregnant, nonlactating women in selected households were eligible to participate. Alternate households were contacted in cases where a household was vacant. Women were overrepresented in the sample because of the timing of data collection. The study was conducted during an important subsistence period in late summer, when men travel deep into the boreal forest to cut hay for the winter. Consequently, in some communities, many of the men were absent.

Data collected by questionnaire, and the interview included basic sociodemographic and household economic characteristics. CRP data were collected from 178 female and 87 male adults. Informed consent was obtained upon study recruitment. This project was approved by the Office for the Protection of Human Subjects Institutional Review Board at Northwestern University, and by the Ministry of Health of the Republic of Sakha (Yakutia).

METHODS

Fasting blood samples were collected by venipuncture, using 5-ml EDTA vacutainers and siliconized needles. Blood samples were collected one time from each subject. Plasma was separated in the field by centrifugation for 3–4 hr following sample collection, and aliquoted into 2.5-ml polypropylene containers and frozen at -20°C for storage and transport to the US.

CRP does not appear to show seasonal or diurnal variation (Meier-Ewert et al., 2001), and in the absence of inflammatory stimulus, repeated measures in an individual are relatively constant and cluster around a characteristic value (Wilkins et al., 1998). CRP is a very stable protein (Rifai and Ridker, 2003). Several studies evaluated the reproducibility and stability of CRP under a variety of conditions, and generally found limited sample degradation ($<$3–5%, with coefficients of variation of $\sim$10%) after up to 3 weeks at room temperature, after multiple freeze-thaw cycles, and after up to 20 years at -70°C (Aziz et al., 2003; Giltay et al., 2003; Ledue and Rifai, 2003; van Eijsden et al., 2005; Wilkins et al., 1998).

Samples were collected in a single 6-week field season, and transported frozen on ice packs to the US. Assays were conducted 4 months after data collection. We found no systematic variation between CRP concentrations and the timing or order of sample collection, and all samples were handled in the same manner.

C-reactive protein (CRP) was analyzed at the Clinical Chemistry Laboratory at the Children's Hospital, Harvard Medical School. The concentration of CRP was determined by immunoturbidimetric assay, using a Hitachi 911 analyzer (Roche Diagnostics, Indianapolis, IN), using reagents and calibrators from Denka Seiken (Niigata, Japan). The day-to-day variability of the assay at concentrations of 0.065 and 1.338 mg/dl is 9.4% and 1.1%, respectively.

Serum lipids

Lipid fractions (total (TC) and high density lipoprotein (HDL) cholesterol and triglycerides (TG)) were determined using standard enzymatic techniques at the Clinical Diagnostic Laboratory of the Northwestern University Feinberg School of Medicine. Low-density lipoprotein cholesterol (LDL) was estimated using the Freidewald equation: LDL = TC – HDL – TG/5.

Anthropometry

Anthropometric measurements were taken using standard techniques (Gibson, 2005). Stature was measured to the nearest 1 mm, using a GPM anthropometer (Seritex, Inc., East Rutherford, NJ); weight was measured to the nearest 100 g, using an electronic scale (Tanita Corp., Tokyo, Japan). Waist circumference was measured midway between the lowest

TABLE 1. Descriptive characteristics of study sample

	Females (n = 178) (67%)	Males (n = 87) (33%)
Age	44.7 (14.9)	45.5 (14.8)
Geometric mean CRP	0.90 (1.4)	0.80 (1.5)
Current smoker	34 (18%)	38 (42%)
CRP <1.0 mg/l	97 (54%)	51 (59%)
CRP between 1.0–3.0 mg/l	47 (26%)	20 (23%)
CRP >3.0 mg/l	34 (20%)	16 (18%)
Metabolic syndrome[1]	53 (30%)	21 (24%)
Waist circumference (cm)	99.7 (10.5)	99.0 (8.4)
Body mass index (kg/m^2)	25.1 (5.3)	25.3 (4.7)
Percent body fat (four skinfolds)[2]	36.6 (6.1)*	23.2 (6.9)
Total cholesterol (mg/dl)	175.8 (35.6)	171.9 (37.5)
High-density lipoprotein (mg/dl)	49.3 (14.1)	44.8 (14.3)
Triglycerides (mg/dl)	75.0 (41.8)	84.6 (43.5)
Low-density lipoprotein (mg/dl)	111.7 (30.1)	110.2 (31.8)
Systolic blood pressure	135.8 (25.5)	143.5 (25.5)
Diastolic blood pressure	81.0 (13.2)	85.7 (14.6)

[1]Metabolic syndrome criteria as defined in Methods.
[2]Sum of triceps, biceps, subscapular, and suprailiac skinfolds.
*$P < .001$. Statistically significant difference between males and females; independent samples *t*-test.

rib and the lateral iliac crest (Gibson, 2005). Skinfold measurements (triceps, biceps, subscapular, suprailiac, and periumbilical) were taken to the nearest 0.5 mm, using Lange calipers (Beta Technology, Inc., Santa Cruz, CA). Derived indices included percent body fat, calculated using four skinfolds (triceps, biceps, subscapular, and suprailiac) and age- and sex-specific equations (Durnin and Womersley, 1974), and body mass index (BMI, kg/m^2).

Metabolic syndrome

Metabolic syndrome (MS) is typically defined as the presence of three or more of the following characteristics: 1) abdominal obesity (waist circumference >88 cm for women and >102 cm for men); 2) hypertriglyceridemia (≥150 mg/dl); 3) low HDL (<50 mg/dl for women and <40 mg/dl for men); 4) high blood pressure (≥135/85 mm Hg); and 5) high fasting glucose (≥110 mg/dl) (Grundy et al., 2004). Since we did not collect data on fasting glucose, we used the first four criteria in our analysis of the association between metabolic syndrome and CRP. The use of only four criteria may lead to an underclassification of metabolic syndrome in this study.

Statistical analyses

Statistical analyses were conducted using SAS (SAS Institute, Cary, NC), and $P \leq 0.05$ was considered statistically significant. CRP values greater than 10.0 mg/l were considered to indicate current infection, and were excluded from the analysis. One subject was excluded based on this criterion, with a CRP value of 157 mg/l. The CRP distribution was log-normal, and geometric mean values were similar to median values for both sexes. Spearman's rho was used to examine associations between CRP and sociodemographic and anthropometric dimensions, serum lipids, and blood pressure. Group comparisons were evaluated using Wilcoxon's two-sample test (i.e., the Mann-Whitney union test). Analysis of covariance was used to examine associations between CRP and age, sex, anthropometric dimensions, serum lipids, and blood pressure variables. For these analyses, log-transformed CRP was used, and statistical tests were conducted on log-transformed least squares means. For some analyses, key independent variables were analyzed as quintiles of the distribution. The values were then converted to geometric means by exponentiating the log values. The distribution of CRP was explored using cutpoints identified by Pearson et al. (2003).

RESULTS

Descriptive statistics for key physiological parameters are presented in Table 1. Twenty percent of women and 18% of men were in the "high-risk" CRP group. The prevalence of smoking was 18% for women and 42% for men, similar to US women (20.0%), and higher than the prevalence among US men (25.2%) (Centers for Disease Control and Prevention, 2004). Thirty percent of women and 24% of men had three or more characteristics of metabolic syndrome, compared to 23% of US women and 24% of US men (Ford et al., 2002). Women had a significantly higher percent body fat (14% higher, $P < 0.001$), but not BMI or waist circumference. The percentage of sub-

jects with BMI ≥30 was 14% in men and 13% in women; the percentage with BMI ≥25 and <30 was 27% in men and 29% in women (data not shown in Table 1). Geometric mean CRP concentrations were 0.90 mg/l for women and 0.80 mg/l for men. Female smokers had higher CRP than nonsmokers (0.80 mg/l vs. 1.14 mg/l), whereas CRP was higher in male nonsmokers (0.99 mg/l vs. 0.62) (data not shown in table). Increasing education was associated with lower CRP in women, and with higher CRP in men (data not shown in table).

The CRP distribution was highly skewed, with values for the 25th, 50th, and 75th percentiles of 0.30, 0.85, and 2.28 mg/l, respectively. There was a significant increase with age in women ($P = 0.011$), but not men ($P = 0.188$) (Table 2). For women, median values increased from 0.97 to 1.47 mg/l between ages 18–34 and 55 and older ($P = 0.022$). CRP concentrations were lowest for women aged 35–44 (0.56 mg/l); the highest values were among women aged 55–64 (1.47 mg/l). For men, median CRP was 0.60 for ages 18–34, and 1.00 for ages 55 and older. The highest values were for men aged 55 and older (1.00 mg/l), followed by ages 45–54 (0.69 mg/l).

TABLE 2. Serum C-reactive protein by age group, raw data values

Age group	N	Geometric mean	Median
Men			
18–34 years	20	0.58 (2.2)	0.60
35–44 years	26	0.46 (1.7)	0.40
45–54 years	22	0.84 (2.1)	0.69
55 and older	19	1.04 (2.0)	1.00
All ages	87	0.80 (1.4)	0.64
Women			
18–34 years	42	0.75 (1.9)	0.97
35–44 years	52	0.53 (1.2)	0.56
45–54 years	48	0.98 (1.7)	0.86
55 and older	36	1.22 (2.3)	1.47
All ages	178	0.90 (1.4)	0.91

In women, CRP levels were significantly higher with increasing quintiles of BMI and waist circumference, but not percent body fat (Table 3). Geometric mean values increased from 0.70 mg/l for the lowest quintile of both BMI and percent body fat to 1.30 mg/l for the upper quintile of both measures. The difference in means from the lowest to the highest quintile group was similar for BMI, percent body fat, and waist circumference (0.60 mg/l for BMI and percent body fat; 0.70 mg/l for waist circumference). The difference was significant for BMI and waist circumference, but not percent body fat. For men, we found no evidence of a trend in CRP across quintiles of adiposity measures.

CRP was significantly associated with plasma triglycerides ($P = 0.002$) in women, but not with total, LDL, or HDL cholesterol. In men but not women, CRP was significantly associated with systolic blood pressure ($P = 0.043$).

Metabolic syndrome (MS) was associated with significantly higher median CRP in women (1.15 vs. 0.67 mg/l; $P = 0.010$), but not in men (0.92 vs. 0.60 mg/l; $P = 0.288$). There was a consistent increase in CRP with increasing number of MS characteristics. Median CRP concentrations for those with 1, 2, 3, or 4 MS criteria were 0.39, 0.60, 0.95, 1.11, and 0.56, respectively ($P = 0.034$ for trend).

We conducted regression analyses to examine the effects of adiposity variables and systolic blood pressure, controlling for the potential confounders of age and smoking status. This analysis indicated that abdominal fat, as measured by waist circumference, was the strongest predictor of plasma CRP concentration in the sample, followed by age, both of which showed a significant positive association

TABLE 3. Least squares mean CRP values by quintile of body mass index, percent body fat, and waist circumference for Yakut males and females, with values adjusted for age

	Geometric mean CRP value						
	Q1	Q2	Q3	Q4	Q5	*P*-value[1]	*P*-value for trend[2]
Men							
Quintile of BMI	0.66	0.72	1.06	1.04	0.75	0.797	0.810
Quintile of percent body fat	0.48	1.02	1.08	0.92	0.82	0.326	0.537
Quintile of waist circumference	0.62	1.00	1.23	0.67	0.84	0.599	0.623
Women							
Quintile of BMI	0.69	0.66	0.75	1.33	1.31	0.042	0.045
Quintile of percent body fat	0.68	0.95	0.78	0.78	1.26	0.059	0.368
Quintile of waist circumference	0.62	0.63	0.84	1.35	1.29	0.016	0.024

[1]*P*-value is for the difference in least squares means, Q1 vs. Q5.
[2]*P*-value for trend is based on the F test for simultaneous equality for means.

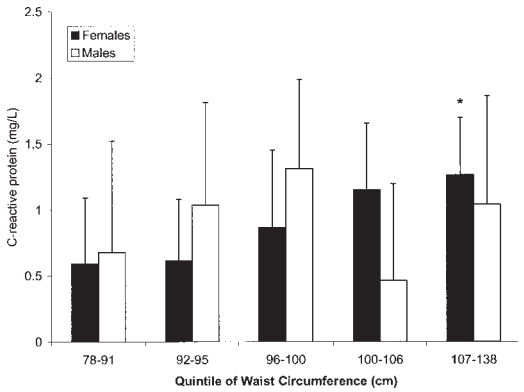

Fig. 1. Geometric mean CRP by quintile of waist circumference for males and females, adjusted for age and smoking status. *$P < 0.05$, Q5 vs. Q1, within sex.

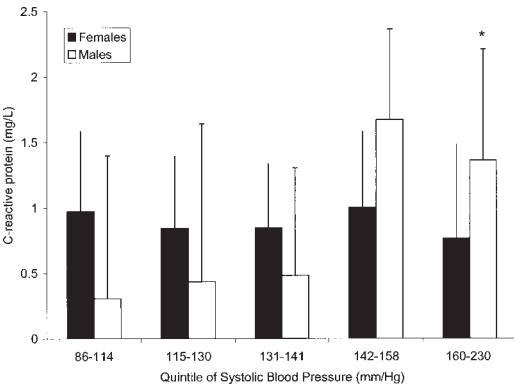

Fig. 2. Geometric mean CRP by quintile of systolic blood pressure for males and females adjusted for age, waist circumference, and smoking status. *$P < 0.05$, Q5 vs. Q1, within sex.

with log-transformed CRP values. CRP for women at the highest quintile of waist circumference was 0.67 mg/l higher than at the lowest quintile ($P = 0.036$). There was a consistent increase in CRP with increasing waist circumference in women, but in men, the highest CRP values were found with the second and third quintiles of waist circumference (Fig. 1).

Systolic blood pressure (SBP) was significantly positively associated with CRP in men after adjusting for potential confounders including age, smoking status, and waist circumference. CRP was significantly higher for the upper vs. lower SBP quintile (Q) for men alone and men and women together (geometric least squares mean CRP was 0.30 mg/l for Q1 vs. 1.36 mg/l for Q5, $P = 0.044$). The results are shown in Figure 2. This finding indicates an association between inflammation and blood pressure for Yakut men.

Comparison of CRP in the Yakut to other populations

Comparison of median CRP in the Yakut relative to the US and various European populations is shown in Table 4. Median concentrations for the Yakut were lower than for the other populations, particularly in older age groups. We compiled data on CRP in several non-European populations to contextualize our study findings. These studies did not report on CRP distributions, but provided medians or geometric means which can be used for comparison. The largest non-European study conducted to date is the Jichi Medical Cohort Study from Japan (Yamada et al., 2001), which examined 2,275 men and 3,832 women aged 30 and older. The authors reported geometric mean values for the Japanese population of 0.83 and 0.59 mg/l for men and women, respectively. These concentrations are similar to those in Yakut men, but are lower than those in Yakut women. In a study on CRP in 113 South Asians and European residents of London aged 40–55, Forouhi et al. (2001) reported geometric mean values of 1.07 and 1.35 mg/l for South Asian men and women, respectively. In the Turkish Adult Risk Factor Survey of 1,046 adult men and women, Onat et al. (2001) reported geometric mean values of 1.9 and 2.0 mg/l for men and women, respectively. In our study, median values were higher in women than in men, especially those 45 and older, whereas in the Scottish (Imhof et al., 2003) and Japanese population samples, the values were higher in men. CRP concentrations were similar for men and women in the US sample and in Germany (Imhof et al., 2003).

DISCUSSION

As in prior studies of high-sensitivity CRP, the values were highly right-skewed, with a log-normal distribution. Approximately 90% of the values were less than 5.0 mg/l for both sexes, and less than 5% of values were greater than 10.0 mg/l. Geometric mean values were 0.90 mg/l for women, and 0.80 mg/l for men. The 25th, 50th, and 75th percentiles were 0.40, 0.90, and 2.20 for women, and 0.30, 0.60, and 2.60 for men. In a recent publication with data from four separate US population-based studies for 22,403 healthy US men and women, the 25th, 50th, and 75th percentiles of CRP were 0.80, 1.50, and 3.20 mg/l for men, and 0.61,

TABLE 4. Distribution of CRP (mg/l) for Yakut and various comparative populations

Study	N	Age	Median	References
Men				
Present study	46	25–44	0.54	
Present study	41	45–74	0.92	
PHS/AFCAPS/WHI/WHS (USA)	[1]	40–84	1.50	Rifai and Ridker, 2003
MONICA, Augsburg, Germany	869	25–44	0.90	Imhof et al., 2003
	1,424	45–74	1.60	
MONICA, Glasgow, Scotland	158	25–44	0.80	Imhof et al., 2003
	256	45–74	1.40	
MONICA/KORA, Germany	800	25–44	0.70	Imhof et al., 2003
	1,256	45–74	1.50	
Women				
Present study	94	25–44	0.59	
Present study	84	45–74	1.20	
PHS/AFCAPS/WHI/WHS (USA)	[1]	40–84	1.52	Rifai and Ridker, 2003
MONICA, Augsburg, Germany	624	25–44	0.70	Imhof et al., 2003
	1,031	45–74	1.70	
MONICA, Glasgow, Scotland	168	25–44	0.60	Imhof et al., 2003
	297	45–74	1.20	
MONICA/KORA, Germany	645	25–44	0.70	Imhof et al., 2003
	865	45–74	1.60	

[1]Sample size for men and women not reported in paper, combined sample 22,403.

1.52, and 3.48 for women (Rifai and Ridker, 2003). In a European study with values from 2,291 healthy men and 2,203 healthy women from Augsburg, Germany, and 604 men and 650 women from Glasgow, Scotland, median CRP values ranged from 0.75–2.40 mg/l across age groups (Hutchinson et al., 2000). CRP values for the Yakut were lower than values found in the US population.

Geometric mean CRP values were similar for men and women (0.80 vs. 0.90 mg/l). We found a positive association with age for women but not men, most likely because of the smaller male sample size. CRP was found to be positively associated with age in some studies (Hutchinson et al., 2000; Yamada et al., 2001), but not in others (Forouhi et al., 2001). CRP values tend to be lower in younger subjects (Roberts et al., 2000), and the inconsistent association with age may be related to differences in the median age of subjects in different studies. The association with sex was inconclusive in previous work. In a study of healthy Japanese men and women, plasma CRP was significantly and substantially higher in men (Yamada et al., 2001), whereas Rifai and Ridker (2003) found no sex differences in CRP in their study of more than 22,000 US adults. Hutchinson et al. (2000) found significantly higher CRP values among women in Germany, but no sex difference in Scotland.

The lack of association with smoking in our study is puzzling and warrants further investigation. Male and female smokers in our study were younger, with lower adiposity, waist circumference, total cholesterol, HDL, and triglycerides but higher blood pressure.

We found sex-specific patterns of variation in CRP. For women, the strongest associations were with measures of centripetal adiposity, BMI, and waist circumference. Waist circumference is an indirect measure of visceral fat, which is believed to be an important source of the proinflammatory cytokines (TNF-α and IL-6) that increase hepatic CRP production (Forouhi et al., 2001). These associations may explain the relationship between CRP and measures of adiposity found in this study. For women, we found significant associations between CRP and triglycerides, but not TC or LDL. The presence of elements of metabolic syndrome was associated with significantly higher CRP in women but not in men. Our results are similar to other studies that found associations with triglycerides and markers of insulin resistance syndrome, but not total or LDL cholesterol. We found no associations with HDL and systolic or diastolic blood pressure in women.

The associations with measures of centripetal and total adiposity for women suggest that increased central adiposity (and by implication, visceral adipose tissue) in women is metabolically active and results in inflammatory activation, resulting in increased CRP production by the liver. Proinflammatory cytokines produced by adipose tissue (TNF-α and IL-6) were not measured in this study, but the

higher CRP values found across levels of increasing waist circumference suggest that these cytokines may also show an increase with higher waist circumference in women.

In men, CRP was associated with systolic blood pressure. Blood pressure was very high in the study, and the rate of hypertension was 50% among men and 36% in women. In the most isolated communities, the rate of hypertension approached 70% in men. The prevalence of hypertension and high normal blood pressure was higher in men, and the association between CRP and systolic blood pressure indicates a different clustering of CVD risk than for women.

The association with blood pressure but not with abdominal fat in men is suggestive of a hypertension-induced activation of the inflammatory response. There are several pathways through which high blood pressure may lead to elevated CRP. Hypertension may directly cause inflammation in vascular smooth muscle cells through mechanical stress on vessel walls, leading to increased proinflammatory cytokine production (Blake et al., 2003). The renin-angiotensin system may also play a role. Angiotensin II stimulates production of IL-6 and other inflammatory chemokines by vascular smooth muscle cells (Han et al., 1999; Kranzhofer et al., 1999). In a cross-sectional study of 508 healthy men, Chae et al. (2001) found strong associations between blood pressure and IL-6, an upstream regulator of hepatic CRP production. Bautista et al. (2001) found CRP to be independently associated with blood pressure after adjusting for age, sex, BMI, and other potential confounders in 300 Colombian men. Alternatively, it is possible that CRP may promote hypertension directly by stimulating a variety of chemokines with vasoconstrictive effects, including endothelin-1 and soluble intercellular adhesion molecule-1 (Blake et al., 2003; Verma et al., 2002).

For men, we found no association between CRP and adiposity measures. The lack of association in men may indicate lower visceral fat depots in men relative to women for a given BMI and waist circumference. BMI and waist circumference were similar for male and female subjects, but men had significantly lower percent body fat. These differences may be the result of greater physical activity among men and are reflective of a more general pattern in Siberia, with women at greater risk for CVD (Leonard et al., 1994; Sorensen et al., 2005).

The plasma CRP values found among the Yakut are lower than those found in previous studies, with the exception of the Jichi Medical Cohort Study in Japan (Yamada et al., 2001). The geometric mean values are lower than those found among the US and European general populations, yet show a similar modest and significant rise with age.

This study has several limitations. Our study was cross-sectional, and it was not possible to determine a causal relationship between CRP and blood pressure. The research was based on a single measurement of CRP, which may limit our understanding of a subject's long-term values. CRP shows considerable intraindividual variability, more so than cholesterol or other CV risk factors, and two separate measurements may be required to account for this variability (Pearson et al., 2003).

The high rates of cardiovascular mortality among the Yakut suggest a high degree of atherosclerotic burden, yet CRP concentrations were low relative to other populations, despite the prevalence of abdominal obesity. Among the Yakut, the high physical-activity demands of a traditional herding lifeway may play a role through high levels of energy expenditure and maintenance of a negative energy balance. Snodgrass (2004) found physical-activity levels consistent with light to moderate workloads in a study of 28 residents of Berdygestiakh, one of the towns in the present study. Previous work with other Siberian populations found higher physical-activity levels in small villages and settlements, and lighter workloads in larger towns (Leonard, 2003; Leonard et al., 2005). Emerging evidence indicates that increased energy expenditure and induction of a negative energy balance have a suppressive effect on circulating levels of inflammatory cytokines and markers of insulin resistance syndrome (Esposito et al., 2003; Klein et al., 2004; You et al., 2004), suggesting that chronic low-level inflammatory activation may explain in part the increased prevalence of cardiovascular disease and the insulin resistance syndrome found among populations undergoing modernization and rapid cultural change. Increased abdominal obesity is a key element of the biological response to modernization, and results from declining physical activity and consumption of a hypercaloric diet high in saturated fats and simple sugars (Leonard et al., 2002; McGarvey et al., 1989; Shephard and Rode, 1996). Further research is needed on the distribution of CRP, other inflammatory cytokines, and their lifestyle correlates among populations in transition.

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