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Anthropometric Correlates of C-Reactive Protein among Indigenous Siberians

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Abstract C-reactive protein (CRP) is an inflammatory marker, which at low-level elevations is associated with increased cardiovascular risk. Although CRP has been extensively investigated in North American and European settings, few studies have measured CRP among non-Western groups. The present study used dried whole blood spot samples to examine high-sensitivity CRP concentrations among the Yakut (Sakha) of Siberia (85 females, 56 males; 18–58 years old). Our goals were: (1) to compare Yakut CRP concentrations with other populations; (2) to investigate sex differences; and (3) to explore anthropometric correlates of CRP. Results indicate that serum equivalent CRP concentrations are similar to those from industrializing nations, lower than US and European values, and greater than Japanese concentrations. Yakut men and women display similar CRP concentrations; however, CRP was significantly higher among men after adjustment for body fat, age, and smoking. Positive associations were documented between CRP and BMI, body fat, and central adiposity. *J Physiol Anthropol 26(2): 241–246, 2007* http://www.jstage.jst.go.jp/browse/jpa2
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Introduction

C-reactive protein (CRP) is a nonspecific acute phase reactant that rapidly increases in plasma concentration in response to inflammation, infection, and injury (Pepys and Hirschfield, 2003). In recent years, studies using high-sensitivity assays have linked minor CRP elevation, previously considered clinically normal, with increased cardiovascular risk in both clinical and healthy populations (Kuller et al., 1996; Danesh et al., 1998; Ridker et al., 1998; Koenig et al., 1999).

Current evidence suggests a link between body composition and CRP concentration, as excess body fat (even at low levels) is associated with higher CRP (Ford, 1999; Danesh et al., 1999; Visser et al., 1999; Yudkin et al., 1999; Rexrode et al., 2003; Greenfield et al., 2004). In part, this relationship reflects the low-level production of proinflammatory cytokines (e.g., IL-6) by adipose tissue in individuals with excess body fat. Abdominal obesity, however, appears to be more closely associated with adipokine secretion than does subcutaneous tissue (Fried et al., 1998; Yudkin et al., 2000; Fain et al., 2004).

While CRP is increasingly playing an important role in Western clinical settings, an impediment to its broader use stems from lack of data on global CRP variation. Most population-level studies of CRP have been conducted among Europeans, European-derived groups in North America, and Japanese populations. Few studies have measured CRP among different racial and ethnic groups in developed nations, and even fewer among individuals in developing nations. Some studies have documented substantial CRP variation by ethnicity (e.g., Chambers et al., 2001), yet results are not fully consistent and show sex differences. Surprisingly, this issue of variation has attracted little attention. As a result, the extent of interpopulation variation remains unknown, and it is unclear whether variation in CRP concentration reflects genetic differences, lifestyle variation (e.g., physical activity levels), developmental effects, environmental differences (e.g., air pollution exposure), or some combination of these factors. The scarcity of comparative data from non-Western groups is unfortunate given the considerable variation in diet and lifestyle factors, environmental conditions, body composition, and burden of established risk factors for CVD between different human populations. Consequently, the extent of interpopulation variation in CRP concentration, and the association between CRP and measures of body composition in different populations remain largely unknown.

In the current study, we investigated CRP concentrations among the Yakut, an indigenous high-latitude Siberian herding population. Our objectives were: (1) to compare CRP concentrations in the Yakut to other populations; (2) to investigate potential sex differences in CRP; and (3) to explore anthropometric correlates of CRP variation.

Methods

The Yakut (Sakha), members of the Turkic language family, are concentrated in northeastern Siberia. The Yakut traditionally practiced a regionally-variable subsistence strategy primarily dependent upon local ecology; subsistence activities centered on hunting and fishing in the remote taiga, and transhumant horse and cattle pastoralism in the Lena River Valley. Today, most rural Yakut populations rely on a mixture of subsistence activities (e.g., horse and cattle herding, farming, fishing, gathering, and hunting), government wages and pensions, private-sector salaries, and "cottage" industries (Craumer, 1994; Jordan and Jordan-Bychkov, 2001).

This study, conducted in the summer of 2003, was cross-sectional and included 141 healthy Yakut adult volunteers (85 females, 56 males; 18–58 years old) recruited from Berdygestiakh, Russia (62°N, 127°E; population 4,900) (Snodgrass et al., 2005). All participants were ethnically Yakut based on self-definition and reported to be healthy at the time of the study. All females were non-pregnant, non-lactating. The Institutional Review Board of Northwestern University approved the study protocol; verbal informed consent was obtained from all participants.

Whole blood spot samples were collected from fasted (>12 hours) participants in the morning or early afternoon for subsequent laboratory analysis. Each participant had their finger pricked with a sterile disposable lancet; 2 to 5 drops of blood were then collected on standardized filter paper (No. 903; Schleicher and Schuell, Keene, NC). Blood spot samples were then dried overnight, transported frozen, and were stored at −30°C until laboratory analysis.

Blood spot CRP concentrations were measured using a high-sensitivity enzyme-linked immunosorbent assay (ELISA) protocol described elsewhere (McDade et al., 2004). Assay validation indicates good sensitivity, precision, and reliability. All laboratory analyses were performed in the Laboratory for Human Biology Research at Northwestern University.

In order to compare blood spot concentrations obtained in this study to values obtained in other studies from serum or plasma samples, we used a conversion formula based on matched serum/blood spot samples. Validation of blood spot CRP (BS CRP) assay performance indicates that the method has good sensitivity, precision, and reliability; matched plasma and blood spot samples are highly correlated (McDade et al., 2004). Serum equivalent CRP for blood spot concentration was calculated as:

$$\text{Serum CRP} = 1.15 \times \text{BS CRP} + 0.13 \quad \text{(McDade et al., 2004)}$$

Serum equivalent CRP concentrations greater than 10.0 mg/L were considered clinically elevated and indicative of current infection (Pearson et al., 2003); two individuals fit this criterion and were excluded from statistical analyses. However, in order to compare CRP concentrations among the Yakut to published data for other populations, CRP concentrations for all study participants were used (including those with clinically elevated CRP values). Individuals with serum equivalent CRP concentrations above 3.0 mg/L were classified as high risk (Pearson et al., 2003).

Stature and body mass were recorded using standard procedures (Lohman et al., 1988). Body mass index (BMI) was calculated as mass divided by height in meters squared (kg/m^2). Body fat (BF) percentage was calculated from the sum of four skinfolds (triceps, biceps, subscapular, and suprailiac; Durnin and Womersley, 1974), measured using Lange calipers (Beta Technology, Santa Cruz, CA). Regional fat distribution was assessed by waist circumference (WC) and waist-to-stature ratio (WSR) following standard procedures (NIH, 2000; Ho et al., 2003).

Student's t-tests and Mann-Whitney U-tests were used to assess sex differences in anthropometric variables and CRP. Distributional assumptions were examined using Kolmogorov-Smirnov tests. CRP values were $\log_{10}$-transformed and logCRP used in subsequent analyses. Pearson's correlations were used to assess logCRP and anthropometric associations. Multiple regression analyses were used to adjust for potential confounders (i.e., age and smoking status) when considering logCRP and anthropometric variables. To assess whether sex independently predicted CRP concentration, ANCOVA was used to adjust for body composition, age, and smoking. Additional analyses were performed on males and females separately. Comparisons were considered statistically significant at $P<0.05$. All results are expressed as means±standard deviations unless otherwise noted. Statistical analyses were performed using SPSS 10.0.

Results

Descriptive statistics for 84 females and 55 males are presented in Table 1. Both sexes had positively skewed CRP distributions; however, log CRP was not significantly different from normal in females or males.

Based on serum equivalent CRP concentration, 11.9% of females and 14.5% of males were classified as high risk. Median serum equivalent CRP concentrations were higher in males than females (0.85 vs. 0.76), but did not reach significance ($P=0.607$). Sex was a significant predictor of log CRP after adjustment for BF, age, and smoking (covariates) ($P<0.001$; $F=13.95$; $r^2=0.198$). All additional analyses were performed independently by sex.

Pearson correlation coefficients for log CRP and anthropometric variables are presented in Table 2. For females, log CRP was significantly positively associated with all anthropometric dimensions (body mass, BMI, BF, WC, and

WSR) ($P<0.001$). Among males, associations were similar, though the limited sample size reduced statistical power. log CRP was significantly positively associated with BF ($P<0.05$), WC ($P<0.05$), and WSR ($P<0.05$), and approached significance for body mass ($P=0.085$) and BMI ($P=0.055$).

Age and smoking were considered as potential confounders, as suggested by most previous studies. Age was significantly correlated with log CRP among females ($P<0.001$) but not males ($P=0.395$) (Table 2). Smoking was not significantly associated with log CRP among females ($P=0.270$) or males ($P=0.799$).

In multiple regression models for females, log CRP (dependent variable) remained significantly associated ($P<0.01$) with each anthropometric variable (body mass, BMI, BF, WC, and WSR) after adjusting for age and smoking. For males, log CRP was significantly associated with BF ($P<0.05$) and approached statistical significance for WC ($P=0.084$), WSR ($P=0.06$), and BMI ($P=0.094$).

Table 1 Descriptive statistics for age, anthropometric, and C-reactive protein (CRP) data[1,2,3]

Measure	Females (n=84)	Males (n=55)
Age (years)	32.3±11.4	31.0±11.2
Current Smokers (%)	45.8	67.3
Height (cm)	156.8±5.5***	170.1±6.0
Weight (kg)	60.9±14.6*	66.7±12.8
BMI	24.7±5.6*	23.0±4.1
Body Fat (%)	36.3±6.7***	20.0±6.9
Waist Circumference (cm)	78.4±12.5	82.2±10.2
Waist-to-Stature Ratio	0.50±0.08	0.48±0.06
Mean blood spot CRP (mg/L)	1.05 (1.35)	1.38 (2.08)
Median blood spot CRP (mg/L)[4]	0.55 (0.19–1.32)	0.62 (0.23–1.35)
Mean serum equivalent CRP (mg/L)	1.34 (1.55)	1.72 (2.39)
Median serum equivalent CRP (mg/L)[4]	0.76 (0.34–1.65)	0.85 (0.40–1.68)

[1] All values are presented as mean and SD, unless noted.
[2] Excluding individuals with CRP concentration >10.0 mg/L.
[3] Sex differences statistically significant at: * $P<0.05$; *** $P<0.001$.
[4] Median and Interquartile Range.

Discussion

Among the Yakut, median serum equivalent CRP concentration was 0.79 mg/L in women and 0.86 mg/L among men (Table 3). These concentrations are similar to those we documented from venous whole blood samples among Yakut

Table 2 Pearson correlations between log CRP and anthropometric variables

Measure	Females	Males
	r(*P*)	*r*(*P*)
Age (years)	0.438 (<0.001)	0.117 (=0.395)
Weight (kg)	0.426 (<0.001)	0.235 (=0.085)
BMI	0.491 (<0.001)	0.261 (=0.055)
Body Fat (%)	0.492 (<0.001)	0.340 (<0.05)
Waist Circumference (cm)	0.487 (<0.001)	0.270 (<0.05)
Waist-to-Stature Ratio	0.513 (<0.001)	0.288 (<0.05)

Table 3 Median high-sensitivity C-reactive protein concentrations among selected populations[1]

Population	Study Year(s)	Age years	CRP mg/L	Source
Males				
Yakut[2]	2003	18–58	0.86	this study
Yakut	2001	≥18	0.64	Sorensen et al., 2006
Brazil	1998–2001	14–74	0.70	Araújo et al., 2004
Germany	1994–1995	25–44	0.90	Imhof et al., 2003
	1994–1995	45–74	1.60	Imhof et al., 2003
Japan	1992–1995	≥30	0.16	Yamada et al., 2001
Singapore	2004	20–78	0.85	Hawkins, 2004
United Kingdom	1992	25–44	0.80	Imhof et al., 2003
	1992	45–74	1.40	Imhof et al., 2003
United States	1999–2000	≥20	1.60	Ford et al., 2003
Females				
Yakut[2]	2003	18–58	0.79	this study
Yakut	2001	≥18	0.91	Sorensen et al., 2006
Brazil	1998–2001	14–74	0.90	Araújo et al., 2004
Germany	1994–1995	25–44	0.70	Imhof et al., 2003
	1994–1995	45–74	1.70	Imhof et al., 2003
Japan	1992–1995	≥30	0.09	Yamada et al., 2001
Singapore	2004	20–78	0.56	Hawkins, 2004
United Kingdom	1992	25–44	0.60	Imhof et al., 2003
	1992	45–74	1.20	Imhof et al., 2003
United States	1999–2000	≥20	2.70	Ford et al., 2004

[1] Includes individuals with clinically elevated CRP (>10.0 mg/L)
[2] Value represents serum equivalent CRP concentration.

residents of six villages in the Sakha Republic (median CRP concentrations of 0.91 mg/L in women and 0.64 mg/L in men) (Sorensen et al., 2006). The slight difference between the two Yakut studies, with that of Sorensen and colleagues (2006) documenting higher CRP concentrations among women compared to men, may in part reflect the inclusion of fewer women with clinically elevated CRP concentrations (>10.0 mg/L) in the present study. It may also reflect the inclusion of individuals from multiple communities in the Sorensen study, including participants from relatively small villages (population≤1000). Present evidence suggests that the physical activity level among indigenous Siberian men and women is shaped both by sex and community size (Leonard et al., in press). Further research is needed to better understand the sources of intrapopulation variation in CRP concentrations among the Yakut.

Yakut CRP values are similar to median CRP levels among Brazilian women (0.9 mg/L) and men (0.7 mg/L) (Araújo et al., 2004). A study from Singapore reported median CRP concentrations of 0.56 mg/L among women and 0.85 for men (Hawkins, 2004). Yakut CRP concentrations were considerably lower than those documented in population studies in the United States (Table 3). According to NHANES 1999–2000, median CRP concentration was 2.7 mg/L among women and 1.6 mg/L among men (Ford et al., 2003, 2004). Median CRP concentrations among Europeans are modestly higher than Yakut concentrations (Table 3), although published data are limited and inconsistently presented. CRP concentrations among Yakut men and women were higher than found in Japanese adults (Yamada et al., 2001) (Table 3). That study documented median CRP concentration of 0.09 mg/L among women and 0.16 mg/L among men.

Previous studies have not demonstrated a consistent pattern of CRP variation by sex (Table 3). Most US studies and one Brazilian study documented higher concentrations among women, while studies in Japan and Singapore documented lower concentrations among women. Most European studies have noted similar CRP concentrations in men and women. The underlying factors responsible for this variation remain unclear, and differences in study design (e.g., inclusion or exclusion of women taking hormone replacement therapy) may additionally contribute to discrepancies. The present study documented broadly similar CRP values between Yakut men and women. Although more men in the study were classified in the high risk category (>3.0 mg/L) (14.5% vs. 11.9%) and median serum equivalent CRP values were higher among men (0.85 vs. 0.76 mg/L), these differences did not reach statistical significance. However, after adjustment for BF, age, and smoking status, CRP concentrations were significantly higher among Yakut men compared to women.

In accordance with previous studies, the present study documented an association between CRP concentration and various measures of body composition and central fat. Measures of total body fat in Yakut women (BMI and BF) were strongly correlated with CRP concentrations; individuals with excess body fat had higher CRP. Further, anthropometric measures of central adiposity (WC and WSR) were also highly correlated with CRP concentrations among Yakut women, and these associations remained after adjustment for age and smoking status. Among Yakut men, the anthropometric correlates of CRP concentration were somewhat different, although the more limited sample size may account for these differences. Some studies (e.g., Visser et al., 1999), however, have documented stronger relationships between measures of total adiposity and CRP concentration among women. Among Yakut men, BF and central adiposity measures were significantly correlated with CRP. This relationship between adiposity and CRP remained after adjustment for age and smoking status, and showed a trend in the other anthropometric dimensions.

Despite research on anthropometric correlates of CRP, few studies have explored whether interpopulation variation in body composition and fat distribution contribute to ethnic differences in CRP. However, a recent study in the UK concluded that this may hold considerable explanatory power (Chambers et al., 2001). Considering well established global variation in obesity (e.g., Popkin and Doak, 1998; WHO, 2000) and regional fat deposition (e.g., Rode and Shephard, 1994; Deurenberg et al., 1998), this issue merits further investigation and may help explain variation in cardiovascular disease not explained by traditional risk factors. Further, additional research is needed to explore the contribution of diet, lifestyle, and genetics in structuring global variation in CRP.

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