Population differences in associations between C-reactive protein concentration and adiposity: comparison of young adults in the Philippines and the United States[1–3]

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ABSTRACT

Background: Inflammation may be an important mediator of the association between nutrition and cardiovascular diseases, but most studies have been conducted in Western populations with high rates of overweight and obesity and low levels of infectious disease.

Objectives: This study sought to investigate the predictors of C-reactive protein (CRP) in young adults living in the Philippines and to examine patterns of association with adiposity compared with young adults in the United States.

Design: Maximum likelihood logistic regression models were used to predict elevated high-sensitivity CRP (>3 mg/L) in relation to anthropometric measures of adiposity, symptoms of infectious disease, and proxy measures of pathogen exposure in men and women from the Philippines ($n = 1648$; age: 20–22 y). Comparative data were drawn from a nationally representative sample in the United States (National Health and Nutrition Examination Survey; $n = 616$; age: 19–24 y).

Results: Median concentrations of CRP were substantially lower in the Philippines (0.2 mg/L) than in the United States (0.9 mg/L), and the likelihood of elevated CRP was lower in the Philippines than in the United States at the same level of waist circumference or skinfold thickness. In the Philippines, infectious symptoms and pathogen exposure predicted elevated CRP, independent of adiposity.

Conclusions: Adiposity and infectious exposures are associated with elevated CRP in the Philippines; other populations undergoing comparable lifestyle and dietary changes associated with increasing rates of overweight and obesity are likely experiencing similar double burdens of inflammatory stimuli. Low concentrations of CRP in this Philippine sample raise the question of whether CRP cutoffs based on European or European-American reference populations are appropriate for predicting disease risk in populations undergoing the nutrition transition. *Am J Clin Nutr* 2009;89:1237–45.

INTRODUCTION

High-sensitivity measurement of C-reactive protein (CRP)—indicating low-grade inflammation—has emerged as an important predictor of subsequent incidence of cardiovascular disease (CVD), type 2 diabetes (1), the metabolic syndrome (2), late-life disability (3), and mortality (4). This rapidly growing literature has drawn attention to the important role that inflammatory processes may play in the pathophysiology of a wide range of chronic diseases, even as uncertainty regarding the causal nature of these associations remains (5, 6). However, the vast majority of research on CRP has been conducted in relatively affluent industrialized settings, where rates of overweight and obesity are high. Whereas CRP measurement is increasingly applied in routine clinical practice, there is recognition that ''normal'' values derived from European or European-American reference populations may not apply universally, and that additional comparative data are needed (7).

Comparative research provides an opportunity to investigate the extent to which CRP concentrations differ across populations, and to evaluate differences in patterns of association with known predictors of CRP. For example, waist circumference or other measures of central adiposity are among the strongest predictors of elevated CRP in European and European-American populations (8–10), but such associations are not universally reported (11). Pathogen exposure is also an important predictor of CRP, because CRP is a central component of the acute phase response to infection and plays an important role in activating complement, promoting phagocytic activity, and opsonizing bacteria, fungi, and parasites (12, 13). However, infectious exposures are relatively infrequent in European or European-American populations and are therefore not considered in most analyses of CRP.

Considerable insights into the dynamics of inflammation may be gained, therefore, by investigating CRP in a different ecological context characterized by burdens of infectious disease as well as excess weight gain. The Philippines is a lower-middle-income nation undergoing significant economic, dietary, and

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[2] Supported by the National Institutes of Health (RO1 HL085144 and 5 RO1 TW05596); biomarker data collection was supported by pilot funds from the Interdisciplinary Obesity Center (RR20649) and the Center for Environmental Health and Susceptibility (ES10126; project 7-2004-E).

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Received October 9, 2008. Accepted for publication January 18, 2009.

First published online February 18, 2009; doi: 10.3945/ajcn.2008.27080.

lifestyle changes characteristic of the nutrition transition, and it exemplifies current trends toward rising prevalences of overweight, CVD, and the metabolic syndrome associated with these changes globally (14, 15). At the same time, infectious disease accounts for >30% of all mortality in Southeast Asia, with pneumonia, diarrhea, and tuberculosis being major contributors (16). In the Philippines, respiratory infections rank beside ischemic heart disease as the top causes of mortality (17).

This burden of pathogen exposure, in combination with recent trends toward increased body weight, is characteristic of many transitional populations globally and thus provides an important setting in which to investigate the predictors of CRP. The specific objectives of this article are 3-fold: *1*) to document concentrations of CRP in young adults in the Philippines, *2*) to investigate associations between CRP and anthropometric measures of nutritional status and proxy measures of pathogen exposure, and *3*) to compare CRP results in the Philippines with data from a nationally representative sample of young adults in the United States. In addition to considering population differences in CRP concentration, these analyses compare the strength of association between CRP and body fat in 2 populations inhabiting different ecologies of nutrition and infectious disease.

SUBJECTS AND METHODS

Participants and data collection

The Cebu Longitudinal Health and Nutrition Survey (CLHNS) began in 1983 with the recruitment of 3327 pregnant women representative of the childbearing population in Cebu City (18). The women and their children have been followed through multiple rounds of data collection since 1983, and the data for the present analyses came from the most recently completed survey, conducted in 2005, when the offspring were 20–22 y of age. Complete anthropometric, environmental, sociodemographic, and CRP data were available for 1678 participants, and 30 women who were pregnant at the time of survey were excluded from the analyses. Participants provided information on household demographics and income levels, economic activities and resources, environmental quality, and health behaviors in face-to-face interviews conducted in their homes.

We evaluated how our sample differed from the original cohort as assessed when the study started in 1983. Compared with those lost to follow-up, participants remaining in the study were born to fathers with less formal education [mean (SE) difference = 0.50 (0.15) y], to mothers with less formal education (0.25 (0.13) years), and into homes in slightly more rural communities [2.09 (0.45) points on 70-point urbanicity scale (19)]. Participants did not differ with respect to household income, assets, or size.

Standard anthropometric techniques were used to measure body weight, height, waist circumference, and triceps, subscapular, and suprailiac skinfold thicknesses (20). Body mass index (BMI) was calculated as the ratio of weight (kg) to height squared (m).

Following prior research in the Philippines and elsewhere (21–23), we collected multiple proxy measures of the likelihood of exposure to infectious microbes, including household density (number of persons/number of rooms), type of toilet (no toilet, pit, flush/water sealed), and source of drinking water (bottled, piped municipal supply, closed well with pump, open sources: uncovered well, spring, river, rain). We also constructed a pathogen exposure scale based on 5 variables, each scored on a 3-point scale (0 = low exposure, 1 = moderate, 2 = high): cleanliness of the food preparation area, means of garbage disposal, presence of excrement near the house, and level of garbage and excrement present in the neighborhood surrounding the household. Scores across these 5 variables were averaged to construct a summary pathogen exposure scale with Cronbach's α of 0.71, which suggests a relatively high degree of reliability. Low correlations between these variables and our measures of household density, toilet type, and water access suggested that these measures were capturing different dimensions of environmental quality and were thus considered separately. Prior analyses in the CLHNS have documented significant associations between comparable measures of environmental quality and risk of infant diarrhea, which attests to their utility as proxies for pathogen exposure (23).

In addition to measures of pathogen exposure, at the time of blood collection we asked participants whether they were currently experiencing any symptoms of infection. Symptoms included runny nose, cough, fever, diarrhea, sore throat, and the more general categories of flu, cold, and sinusitis. Responses were used to construct a summary variable indicating the presence or absence of any infectious symptoms at the time of blood collection.

In an attempt to capture other unmeasured aspects of environmental quality and lifestyle that may be related to CRP, we considered 4 measures of socioeconomic status (SES): highest grade completed, household income, household assets, and home ownership. We also used a previously validated measure of the degree of urban development in the community in which participants lived (19). This scale is based on population size and density, availability of communications (eg, telephone, Internet), transportation infrastructure, and presence of educational facilities, health services, and markets for food and other consumer goods. Higher scores (range: 0–70) on the scale indicate a higher degree of urban development.

CRP analysis

Blood samples were collected into EDTA-coated evacuated tubes in the participants' homes in the morning after an overnight fast. Blood samples were kept in coolers on ice packs for $\leq$ 2 h and were then centrifuged to separate plasma before freezing at −70°C. Samples were express-shipped to Northwestern University on dry ice and stored frozen at −80°C until analyzed. CRP concentrations were determined by using a high-sensitivity immunoturbidimetric method (Synchron LX20, lower detection limit: 0.1 mg/L; Beckman Coulter, Fullerton, CA) with between-assay CVs <7.6 across the assay range (24).

Data analysis

We performed a series of maximum likelihood logistic regression analyses to predict, first, the likelihood of CRP >10 mg/L and then CRP >3 mg/L, excluding individuals with CRP concentrations >10 mg/L. These cutoffs were selected based on recommendations issued by a recent joint scientific statement from the American Heart Association and the Centers for Disease Control and Prevention (7). Concentrations of CRP >10 mg/L

are presumed to be the result of acute inflammatory processes (eg, infectious disease), whereas CRP concentrations >3 mg/L but <10 mg/L indicate an increased risk of CVD due to chronic low-grade inflammation. Recent research, however, has suggested that CRP concentrations >10 mg/L are also predictive of CVD risk (25). We therefore conducted a final series of analyses predicting the likelihood of CRP >3 mg/L in the entire sample.

Analyses proceeded in 3 stages. First, we considered anthropometric measures of nutritional status as predictors of elevated CRP. We began with crude associations, followed by models that considered additional factors shown previously to influence CRP (smoking, alcohol consumption, oral contraceptive use). Adjusted models also evaluated measures of SES and urbanicity in an attempt to account for omitted variables related to lifestyle and/or environmental quality that might confound associations between CRP and our more proximate measures of nutritional status and pathogenicity. Second, in a separate set of models, we evaluated measures of pathogen exposure and infectious disease. Finally, we considered a combined model with significant nutritional status and pathogenicity variables to evaluate their independent and combined contributions to explaining elevated CRP. The criterion for statistical significance was set as an $\alpha < 0.05$; variables with $P < 0.10$ were retained in models to explore trends in the data. All statistical analyses were conducted with Stata for Windows, version 10 (StataCorp, College Station, TX).

Comparisons with NHANES

Data from the National Health and Nutrition Examination Survey (NHANES 2003–2004) were used for comparisons with data from the Philippines. NHANES is a stratified, multistage probability sample of the noninstitutionalized civilian US population, and the 2003–2004 survey included >10,000 individuals (26). Participants were interviewed in their homes and provided a blood sample at a mobile examination center. After processing, serum samples were frozen and shipped to the University of Washington Medical Center (Seattle, WA), where concentrations of CRP were determined by latex-enhanced nephelometry (BNII; lower detection limit: 0.1 mg/L; Dade Behring, Deerfield, IL) (27).

To maximize comparability, we restricted the analyses of NHANES data to an age-matched subsample of 19–24-y-olds (mean age: 21.5 y) for whom CRP and anthropometric data were available. Women pregnant at the time of the survey were excluded, which resulted in a final sample of 616 individuals ($n =$ 291 females). All analyses used 2003–2004 sampling weights and design variables to account for unequal probabilities of selection, nonresponse adjustments, clustering, and stratification.

As with data from the Philippines, we modeled the likelihood of CRP concentrations >3 mg/L, excluding individuals with CRP concentrations >10 mg/L. We investigated CRP in relation to 2 measures of adiposity: waist circumference and the sum of triceps and subscapular skinfold thicknesses. We selected these 2 measures because of their significant associations with CRP in the Cebu survey (*see* below). All models included variables for smoking and oral contraceptive use to control for their associations with CRP.

We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research. All data were collected under conditions of informed consent with institutional review board approval from the University of North Carolina, Chapel Hill.

RESULTS

Predictors of CRP in the Philippines

The young adults in this sample were lean and had a low mean waist circumference compared with young adults in the United States (28), and mean BMI values at the low end of "normal" as defined by recent Centers for Disease Control and Prevention guidelines (**Table 1**). The median CRP concentration for the entire sample was 0.2 mg/L. Of note was the absence of a significant sex difference in CRP. As expected, measures of SES were positively associated with waist circumference, including household income (Pearson's $R = 0.07$, $P < 0.01$) and household assets ($R = 0.12$, $P < 0.001$). Similar associations were

TABLE 1
Descriptive statistics for female and male participants in the Cebu Longitudinal Health and Nutrition Survey[1]

	Females ($n = 732$)	Males ($n = 916$)	Total ($n = 1648$)
Age (y)	20.9 ± 0.4[2]	20.9 ± 0.3	20.9 ± 0.3
Household income, weekly (pesos)	662.4 ± 1690.0	572.4 ± 884.3	612.3 ± 1305.2
Highest grade of school completed	11.2 ± 2.3	9.9 ± 3.2[3]	10.5 ± 3.1
BMI (kg/m^2)	20.3 ± 3.2	21.1 ± 3.0[3]	20.7 ± 3.2
Waist circumference (cm)	68.0 ± 7.6	72.2 ± 7.5[3]	70.3 ± 7.8
Sum of 3 skinfold thicknesses (mm)	62.1 ± 19.7	37.7 ± 18.1[3]	48.5 ± 22.3
Pathogen exposure scale (0-2)	0.54 ± 0.39	0.55 ± 0.41	0.55 ± 0.40
Presence of infections symptoms (%)	14.6	13.6	14.1
Current smoker (%)[4]	3.3	43.0[3]	25.4
Oral contraceptive use (%)	3.7		
C-reactive protein (mg/L)	0.2 (0.1, 0.9)[5]	0.3 (0.1, 0.9)	0.2 (0.1, 0.9)

[1] Two-sample *t* tests (continuous variables) and Pearson chi-square tests (categorical variables) were used to evaluate differences between females and males.
[2] Mean ± SD (all such values).
[3] Significantly different from females, $P < 0.0001$.
[4] Defined as ≥1 cigarette/d.
[5] Median; 25th and 75th percentile in parentheses (all such values).

also found with other anthropometric measures of adiposity. Conversely, socioeconomic measures were negatively related to scores on our pathogen exposure scale, including household income ($R = -0.15$, $P < 0.001$) and household assets ($R = -0.33$, $P < 0.001$).

Fifty-four participants, or 3.3% of the sample, had concentrations of CRP >10 mg/L. The presence of infectious disease symptoms at the time of blood collection [odds ratio (OR) = 3.83; 95% CI: 2.16, 6.78; $P < 0.001$] was the only significant predictor of CRP > 10 mg/L. No anthropometric, socioeconomic, or other environmental quality variables were significantly related to this concentration of CRP.

We next modeled the likelihood of CRP >3 mg/L, excluding the 54 participants with CRP >10 mg/L. One hundred sixteen participants (7.3%) had CRP >3 mg/L. We found evidence of sex-specific associations between CRP and our measures of adiposity, with a significant interaction term between sex and waist circumference and sex and skinfold thickness (**Table 2**). This latter interaction term was only significant when the interaction with waist circumference was included in the model. We thus conducted a subset of analyses stratified by sex to investigate these associations further.

BMI and waist circumference were highly correlated in the entire sample (Pearson's $R = 0.89$, $P < 0.001$). Both were significant predictors of elevated CRP in females, although waist circumference was a stronger predictor and was the only adiposity measure that remained significant when all measures were considered simultaneously. When considered separately, a 1-cm increase in waist circumference for females was associated with a 6.0% increase in the likelihood of CRP >3 mg/L (OR: 1.060; $P < 0.001$).

For males, skinfold thickness was the only adiposity measure that was nearly significant in predicting elevated CRP. A 1-mm increase in the sum of 3 skinfold measures was associated with a 1.1% increase in the likelihood of elevated CRP (OR: 1.011; $P = 0.09$). This association strengthened to 2.5% when waist circumference was included in the model (OR: 1.025; $P < 0.05$). For neither males nor females did we find any evidence of threshold relations between adiposity measures and CRP. Subsequent analyses combined females and males and included interaction terms to capture sex-specific associations with adiposity measures. We found no evidence of sex interactions with other independent variables.

Associations with adiposity were not altered by the addition of health behaviors or SES variables (Table 2, model 1). Smoking, alcohol consumption, and oral contraceptive use were not associated with CRP ($P > 0.1$). Of the SES variables, only current school attendance was a significant predictor of CRP: nearly 29% of all participants were still attending school at the time of the 2005 survey, and school attendance was associated with a lower likelihood of elevated CRP.

Even though individuals with CRP concentrations >10 mg/L were not included in the analyses, symptoms of infectious disease at the time of blood collection were positively associated with CRP >3 mg/L, as were higher values on our pathogen exposure scale. Symptoms of infection were associated with a >3-fold increase in the likelihood of elevated CRP. In a model including sex and infectious symptoms, a 1-point increase in pathogen exposure (3-point scale) was associated with a 69% increase in the likelihood of elevated CRP. However, this association was attenuated with the addition of current school attendance to the model (Table 2, model 2). Similar patterns of association were found for each of the variables included in the pathogen exposure scale. Household density, toilet type, and water source did not predict elevated CRP.

Finally, we considered simultaneously the associations between elevated CRP and measures of adiposity, pathogen exposure, and SES (Table 2, model 3). ORs in the full model did not change substantially when all variables were considered simultaneously, which indicated that their individual associations with CRP were relatively independent. Results were very similar when models were rerun including individuals with

TABLE 2
Maximum likelihood multiple logistic regression model predicting C-reactive protein concentrations >3 mg/L in the Cebu Longitudinal Health and Nutrition Survey[1]

	Model 1		Model 2		Model 3	
	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
Sex (female = 1)	0.00[2]	0.00, 0.10	1.00	0.68, 1.47	0.00[2]	0.00, 0.10
Waist circumference (cm)	0.95	0.90, 1.01	—	—	0.96	0.90, 1.01
Skinfold thickness (mm)	1.03[3]	1.01, 1.05	—	—	1.03[2]	1.01, 1.05
Female × waist circumference	1.12[4]	1.05, 1.20	—	—	1.12[2]	1.04, 1.20
Female × skinfold thickness	0.96[3]	0.94, 0.99	—	—	0.97[3]	0.94, 0.99
Pathogenicity scale (0–2)	—	—	1.48[5]	0.92, 2.38	1.56[4]	0.96, 2.53
Symptoms of infection (0, 1)	—	—	3.54[4]	2.30, 5.44	3.71[4]	2.40, 5.74
School enrollment (0, 1)	0.34[2]	0.17, 0.69	0.34[2]	0.17, 0.69	0.34[2]	0.16, 0.68
Likelihood ratio chi-square statistic	30.36	—	43.73	—	63.90	—
Model P value	<0.0001	—	<0.0001	—	<0.0001	—

[1] $n = 1594$ for all models. Subjects with C-reactive protein concentrations >10 mg/L were excluded. The following variables were evaluated but did not enter into the models ($P > 0.1$): smoking, oral contraceptive use, alcohol consumption, highest grade of school completed, household income, household assets, home ownership, urbanicity, BMI, household density, toilet type, and water source.

[2] $P < 0.01$.

[3] $P < 0.05$.

[4] $P < 0.001$.

[5] $P < 0.10$.

CRP >10 mg/L, although all associations were attenuated with the exception of infectious symptoms (data not shown).

Comparisons with NHANES

Concentrations of CRP among young adults in Cebu were dramatically lower than in the United States. According to data from NHANES, the median CRP concentration for 19–24-y-olds was 0.9 mg/L (25th percentile: 0.4; 75th percentile: 3.5), >4 times the concentration in Cebu. There was also a significant sex difference in CRP concentration for young adults in the United States; females (median: 2.0 mg/L; 25th percentile: 0.5; 75th percentile: 4.8) had a substantially higher concentration of CRP than did males (median: 0.7 mg/L; 25th percentile: 0.4; 75th percentile: 1.9). Women in the United States were 3 times as likely to have CRP >10 mg/L and 3.9 times as likely to have CRP >3 mg/L (and <10 mg/L) than were women in Cebu (**Figure 1**). American men were 2.3 and 1.6 times as likely to have CRP >10 mg/L and >3 mg/L than were Filipino men, respectively.

As noted above, young adults in Cebu were lean compared with young adults in the United States, which raises the question of whether low CRP concentrations in Cebu were primarily due to lower levels of adiposity, a qualitatively different relation between adiposity and CRP, or both. To address this question we plotted the probability of CRP >3 mg/L as a function of waist circumference (**Figure 2**) and skinfold thickness (**Figure 3**) for males and females, excluding individuals with CRP >10 mg/L. We chose these 2 adiposity measures because both were significant predictors of CRP in Cebu and in NHANES. We ran separate models for males and females and adjusted for smoking and oral contraceptive use. We evaluated waist circumference and skinfold thickness in separate models with these control variables. Analyses of the association between CRP and skinfold thickness used the sum of 2 skinfold-thickness measures (triceps and subscapular), because NHANES 2003–2004 collected only these 2 measures. To ensure that differences between Cebu and NHANES were not solely due to the use of 3 mg/L as a cutoff or to an artifact of model fitting, particularly given the relatively limited range of variation in waist circumference in Cebu compared with NHANES, we also plotted median CRP concentrations by category of waist circumference (**Figure 4**) and skinfold thickness (**Figure 5**). Median values are not reported for categories with <15 observations.

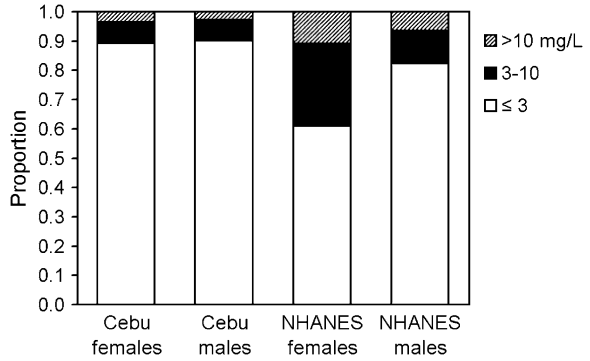

FIGURE 1. Proportion of young adults with C-reactive protein >3 mg/L and >10 mg/L in the Philippines (n = 1648) and the United States (n = 616), by sex. NHANES, National Health and Nutrition Examination Survey.

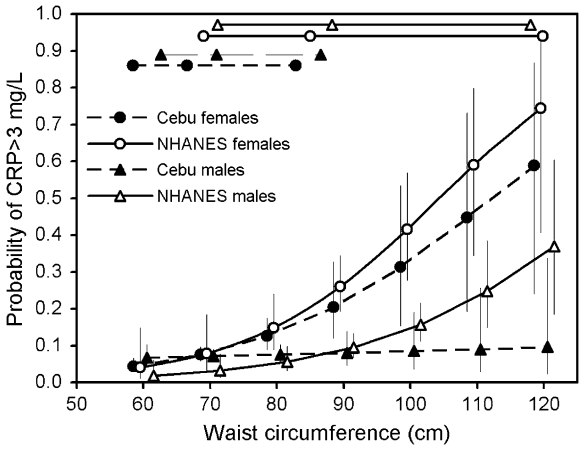

FIGURE 2. Probability of C-reactive protein (CRP) concentrations >3 mg/L (95% CI) in relation to waist circumference (cm) in the Philippines and the United States (excluding individuals with CRP >10 mg/L). The population-specific distribution of waist circumference (5th percentile, median, 95th percentile) is presented at the top of the figure. Probabilities are based on predictions from a maximum likelihood regression model including variables for smoking and oral contraceptive use. For the Philippines, n = 705 and 889 for females and males, respectively; for the National Health and Nutrition Examination Survey (NHANES), n = 246 and 295 for females and males, respectively.

In Cebu, the median waist circumference for women was 66.5 cm, and >95% of Cebu women had a waist circumference that was lower than the median value of 85.0 for young adult women in the United States. At waist circumferences of ≥70 cm, NHANES women were 5–33% more likely to have CRP > 3 mg/L than were women in Cebu. In Cebu, the median CRP concentration was 0.1 mg/L for women with a waist circumference <70 cm, compared with 0.3 mg/L in NHANES. For women with a waist circumference <80 (and ≥70 cm), median

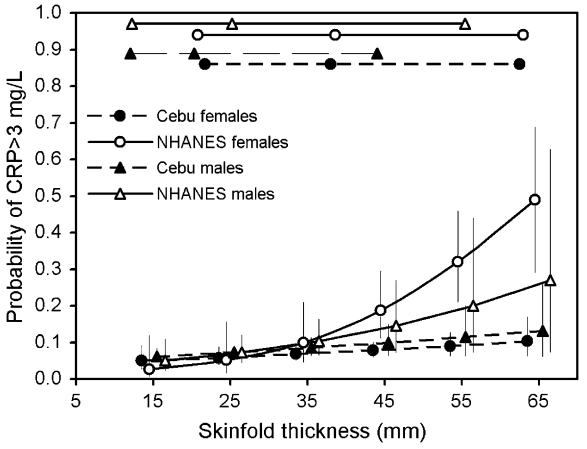

FIGURE 3. Probability of C-reactive protein (CRP) concentrations >3 mg/L (95% CI) in relation to skinfold thickness (triceps + subscapular) in the Philippines and the United States (excluding individuals with CRP >10 mg/L). The population-specific distribution of skinfold thickness (5th percentile, median, 95th percentile) is presented at the top of the figure. Probabilities are based on predictions from a maximum likelihood regression model including variables for smoking and oral contraceptive use. Probabilities are based on predictions from a maximum likelihood regression model including variables for smoking and oral contraceptive use. For the Philippines, n = 705 and 889 for females and males, respectively; for the National Health and Nutrition Examination Survey (NHANES), n = 246 and 295 for females and males, respectively.

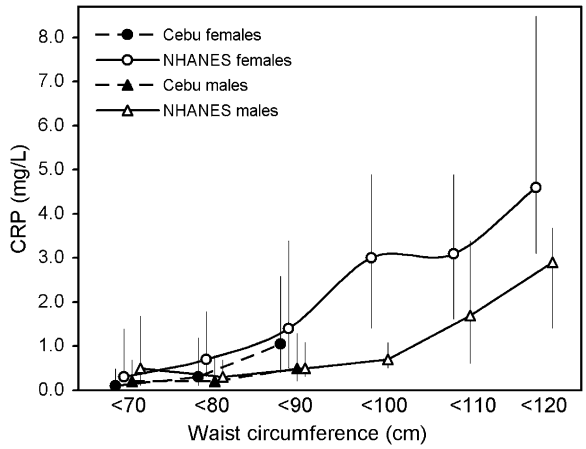

FIGURE 4. Median C-reactive protein (CRP) concentrations (25th and 75th percentiles) in relation to waist circumference in the Philippines and the United States; individuals with CRP concentrations >10 mg/L were excluded. For the Philippines, $n = 705$ and 889 for females and males, respectively; for the National Health and Nutrition Examination Survey (NHANES), $n = 246$ and 295 for females and males, respectively.

CRP concentrations in Cebu and NHANES were 0.3 and 0.7 mg/L, respectively. At waist circumferences ≥80 and <90 cm, encompassing the highest end of the distribution in Cebu, the median CRP concentration was 1.05 mg/L, compared with 1.4 mg/L in NHANES.

The distributions of skinfold thickness were similar for women in Cebu and the United States, with median values of 38.0 and 38.6 mm, respectively. At the low end of the distribution, women from both Cebu and NHANES had comparably low probabilities of elevated CRP. However, as skinfold thickness increased for American women, the likelihood of elevated CRP relative to Cebu women doubled at ≈40 mm and quadrupled after 60 mm. The association between skinfold thickness and CRP was relatively flat for women in Cebu across the entire range of values. Median CRP concentrations followed a similar pattern of increase with skinfold thickness in NHANES, with only slight increases in Cebu. For women with a skinfold thickness <25 mm, median concentrations of CRP in Cebu and NHANES were 0.1 and 0.5 mg/L, respectively. At skinfold thicknesses ≥55 and <65 mm, median CRP concentrations were 0.5 and 2.9 mg/L, respectively.

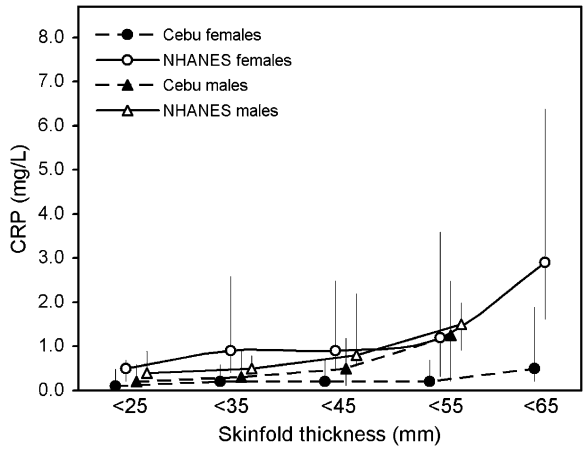

FIGURE 5. Median C-reactive protein (CRP) concentration (25th and 75th percentiles) in relation to skinfold thickness (mm; triceps + subscapular) in the Philippines and the United States. For the Philippines, $n = 705$ and 889 for females and males, respectively; for the National Health and Nutrition Examination Survey (NHANES), $n = 246$ and 295 for females and males, respectively.

For men in Cebu, median waist circumference was 70.9 cm, with >95% of all men in Cebu having a waist circumference lower than the NHANES median of 88.2. Below this value the probability of elevated CRP was very low for both populations, with NHANES men less likely to have CRP > 3 mg/L than men in Cebu. However, as waist circumference increased, the likelihood of CRP > 3 mg/L increased rapidly for NHANES men: relative to Cebu, the risk of elevated CRP doubled after 100 cm and nearly quadrupled at 120 cm. However, these differences should be interpreted with caution because median CRP concentrations in Cebu and NHANES were comparable across overlapping areas of the waist circumference distribution. For men with a waist circumference ≥70 and <80 cm, the median CRP concentration was 0.2 mg/L in Cebu and 0.3 mg/L in NHANES. For a waist circumference <90 (and ≥80 cm), the median CRP concentration was 0.5 mg/L in both populations. Above 90 cm, CRP concentrations increased rapidly in NHANES, but too few men in Cebu had a waist circumference >90 cm to allow comparison.

Skinfold thickness was lower among men in Cebu than in the United States, with median values of 20.3 and 25.2 mm, respectively. For both groups the association between skinfold thickness and elevated CRP was similar, <35 mm. Above this value, the likelihood of CRP > 3 mg/L remained relatively flat for men in Cebu and increased steadily for American men. Compared with men in Cebu, the risk of elevated CRP increased by a factor of 1.5 at 45 cm and doubled at ≈60 mm for NHANES men. Median concentrations of CRP increased with skinfold thickness for both Cebu and NHANES men, and NHANES men had higher concentrations at each level of skinfold thickness. For men with a skinfold thickness <25 mm, median concentrations of CRP in Cebu and NHANES were 0.2 and 0.4 mg/L, respectively. At skinfold thicknesses ≥45 and <55 mm, median CRP concentrations were 1.25 and 1.5 mg/L, respectively.

In the United States, the pattern of association between increasing adiposity and likelihood of elevated CRP was similar for women and men, although NHANES women were more likely to have high CRP at just about every level of adiposity. Cebu women followed a similar pattern for waist circumference, but differed with respect to associations with skinfold thickness. Cebu men stood out for their lack of strong association between adiposity and the likelihood of elevated CRP, regardless of measure.

DISCUSSION

Consistent with prior research on high-sensitivity CRP, measures of adiposity and pathogen exposure were associated with elevated CRP among young adults in the Philippines. The positive association between SES and adiposity in this population and the negative association between SES and pathogen exposure suggest that Cebu is an interesting setting in which to investigate the independent contributions of adiposity and pathogenicity to variation in CRP. Comparisons with data from NHANES indicate relatively low concentrations of CRP in the Philippines that cannot be explained by higher levels of overweight/obesity in the

United States. This pattern of results is very similar to prior analysis of CRP in older women in Cebu (29), which suggests that some combination of genetic differences, environmental differences, and/or developmental factors may have long-term implications for the regulation of inflammation.

A limitation of our study was the use of a single CRP measurement to indicate low-grade inflammation. Whereas serial CRP measurements have reported a relatively high degree of intraindividual consistency that is comparable with other serum markers of CVD risk, multiple measures would provide a more stable estimate of chronic inflammation (30, 31). In addition, the CLHNS initially recruited a sample representative of the childbearing population in Cebu, but the offspring in our sample were slightly, but significantly, more likely to come from rural households with less educated parents.

Waist circumference was a strong predictor of elevated CRP for young women in the Philippines, whereas skinfold thickness was the only significant anthropometric predictor for men. Waist circumference has been shown to be among the strongest correlates of CRP across a wide range of populations, consistent with the established importance of visceral adipose tissue as a source of proinflammatory cytokines (32, 33). However, several studies have documented sex differences in patterns of association between CRP and waist circumference and other measures of adiposity (34–36). The Pelotas Birth Cohort Study in Brazil, for example, reported stronger associations between central obesity and CRP in young adult women than in young men (37). In a lean population of young adults in north India, CRP concentrations were low (0.5 mg/L for males, 0.4 mg/L for females) and were more strongly associated with waist circumference in females than in males and more strongly associated with skinfold thickness in males than in females (38). For young men in the United States, waist circumference and peripheral skinfold-thickness measures were comparably strong correlates of CRP in whites, but peripheral skinfold thickness did not predict CRP concentrations in individuals of Asian Indian ancestry (39). These studies, as well as the results of our comparisons with NHANES, suggest the possibility of population-specific sex differences in the associations between body fat stores and inflammation that merit further investigation.

Intensity of pathogen exposure and symptoms of infectious disease were independent predictors of elevated CRP, consistent with the hypothesis that infectious exposures may be significant sources of proinflammatory stimuli in the Philippines. The presence of excreta, unsanitary means of garbage disposal, and an unhygienic food preparation area were all associated with an increased risk of elevated CRP. Although few studies using high-sensitivity CRP as an indicator of chronic, low-grade inflammation have considered measures of infection/pathogenicity, prior research has shown elevated concentrations of CRP in relation to proxy measures of pathogen exposure and infection as well as direct measures of seropositivity for common viruses and bacteria (40–45). These associations underscore the importance of pathogen pressure and infectious disease as determinants of variation in CRP and suggest that additional attention should be given to quantifying pathogen exposure in epidemiologic analyses of inflammation.

It is not clear why CRP concentrations were lower in the Philippines than in the United States, even after considering population differences in adiposity. CRP data from the Philippines and for NHANES were both generated by using automated high-sensitivity immunoassay protocols routinely applied in clinical practice, and prior comparisons indicate good agreement between results across these platforms, particularly with respect to identification of CVD risk based on CRP cutoffs (24). However, the Synchron LX20—used to generate CRP results in the Philippines—has been shown to produce slightly lower CRP results than the Dade Behring BNII method used in the NHANES population (24). The magnitude of this difference is small, but it may nonetheless account for a portion of the unexplained difference in CRP concentrations. This difference raises the broader issue that comparisons of results produced by different laboratories, at different points in time, and across analytic platforms should always be made with caution.

An additional possibility is population variation in fat patterning and body composition that contributes to differential levels of production of adipocyte-derived, proinflammatory cytokines. However, this is not likely to account for low CRP concentrations in the Philippines, because prior research suggests a higher proportion of visceral adipose tissue in Filipinos than in European Americans or African Americans at the same level of waist circumference (46).

Compared with young adults in the United States, our results suggest that young adults in Cebu produce less CRP at comparable levels of adiposity. The different pattern of association between waist circumference and CRP may be due in part to the relatively limited range of variation in waist circumference values in young adults in Cebu compared with the United States. However, associations with skinfold thickness also differed despite a high degree of overlap in the range of values. Among older women in Cebu (mean age: 47.7 y), 41.4% of whom were classified as overweight or obese, the median CRP concentration was 0.9 mg/L, which was substantially lower than the median concentration of 2.02 mg/L recently reported for European-American participants in the Women's Health Study (29, 47). These results suggest that the population differences reported in this article are not solely the result of focusing on young adults or individuals with low levels of central obesity.

Genetic factors may also account for a portion of population differences in CRP concentrations. For example, in a multiethnic study in the United States, women of Asian descent living in the United States had the lowest concentration of CRP (1.12 mg/L), whereas African American women had the highest concentration (2.96 mg/L) (47). BMI was the strongest predictor of elevated CRP and accounted for much of the ethnic group differences in CRP, although concentrations in Asian American women remained ≈25% lower after BMI and other anthropometric and metabolic variables are controlled for (37). In Japan, similar patterns of association between CRP and BMI and smoking have been reported as those seen in US populations, but mean CRP concentrations are much lower in Japan (48). Polymorphisms related to the regulation or production of CRP may contribute to these population differences.

In addition, environmental exposures early in development may have long-term implications for the regulation of CRP production in adulthood. Experimental animal models as well as observational data from population-based studies have established that conditions early in life—prenatal and early postnatal environments in particular—shape the risk of CVD and metabolic disease later in life through developmental modifications to

critical physiologic systems (49). Previously, we have shown that birth weight, growth in infancy and early childhood, and infectious disease exposure are significantly related to CVD risk factors and immune function in adolescence (18, 50, 51). If conditions early in life are significant determinants of CRP in adulthood, then differences in developmental environments across the United States and the Philippines could contribute to population differences in CRP.

To the extent that inflammation contributes to the pathophysiology of CVD or metabolic disease, CRP may be an important mediator of the link between the recent increase in obesity prevalence in the Philippines and rising rates of chronic degenerative diseases (14, 52). However, the low concentrations of CRP raise the question as to whether inflammation is a major contributor to CVD in this population and whether CRP cutoffs based on European or European-American reference populations are appropriate for predicting disease risk in populations in the midst of the nutrition transition. Additional prospective data from diverse ecological settings will be required to answer this question. In the meantime, our results highlight the value of comparative perspectives for identifying population differences in the dynamics of inflammation and underscore the need for additional research on the contributions of pathogenicity, adiposity, and inflammation to the global epidemic of CVD and metabolic diseases.

The authors' responsibilities were as follows—TWM: conducted data analysis and prepared the manuscript; JNR: assisted with data analysis and manuscript preparation; and LA and CK: assisted with data analysis and manuscript preparation and implemented data collection in the Philippines. None of the authors declared a conflict of interest.

REFERENCES

1. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001;286:327–34.
2. Ridker PM, Buring JE, Cook NR, Rifai N. 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 2003;107:391–7.
3. Kuo H-K, Bean JF, Yen C-J, Leveille SG. Linking C-reactive protein to late-life disability in the National Health and Nutrition Examination Survey (NHANES) 1999–2002. J Gerontol A Biol Sci Med Sci 2006;61:380–7.
4. Jenny NS, Yanez ND, Psaty BM, Kuller LH, Hirsch CH, Tracy RP. Inflammation biomarkers and near-term death in older men. Am J Epidemiol 2007;165:684–95.
5. Sattar N, Lowe GD. High sensitivity C-reactive protein and cardiovascular disease: an association built on unstable foundations? Ann Clin Biochem 2006;43:252–6.
6. Ross R. Atherosclerosis: an inflammatory disease. N Engl J Med 1999;340:115–26.
7. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice. Circulation 2003;107:499–511.
8. Ford ES. The metabolic syndrome, and C-reactive protein, fibrinogen, and leukocyte count: findings from the Third National Health and Nutrition Examination Survey. Atherosclerosis 2003;168:351–8.
9. Ford ES, Giles WH, Mokdad AH, Myers GL. Distribution and correlates of C-reactive protein concentrations among adult US women. Clin Chem 2004;50:574–81.
10. Lee K, Song Y-M, Sung J. Which obesity indicators are better predictors of metabolic risk?: healthy twin study. Obesity (Silver Spring) 2008;16:834–40.
11. Forouhi NG, Sattar N, McKeigue PM. Relation of C-reactive protein to body fat distribution and features of the metabolic syndrome in Europeans and South Asians. Int J Obes 2001;25:1327–31.
12. Ballou SP, Kushner I. C-reactive protein and the acute phase response. Adv Intern Med 1992;37:313–36.
13. Black S, Kushner I, Samols D. C-reactive protein. J Biol Chem 2004;279:48487–90.
14. Adair LS. Dramatic rise in overweight and obesity in adult Filipino women and risk of hypertension. Obes Res 2004;12:1335–41.
15. Tanchoco CC, Cruz AJ, Duante CA, Litonjua AD. Prevalence of metabolic syndrome among Filipino adults aged 20 years and over. Asia Pac J Clin Nutr 2003;12:271–6.
16. WHO. The World Health Report 2004—changing history. Geneva, Switzerland: World Health Organization, 2004.
17. WHO. Mortality country fact sheet 2006. Geneva, Switzerland: World Health Organization, 2006.
18. Adair LS, Kuzawa CW, Borja J. Maternal energy stores and diet composition during pregnancy program adolescent blood pressure. Circulation 2001;104:1034–9.
19. Dahly DL, Adair LS. Quantifying the urban environment: a scale measure of urbanicity outperforms the urban-rural dichotomy. Soc Sci Med 2007;64:1407–19.
20. Lohman TG, Roche AF, Martorell R. Anthropometric standardization reference manual. Champaign, IL: Human Kinetics Books, 1988.
21. Prado MS, Strina A, Barreto ML, Oliveira-Assis AM, Paz LM, Cairncross S. Risk factors for infection with Giardia duodenalis in pre-school children in the city of Salvador, Brazil. Epidemiol Infect 2003;131:899–906.
22. Nurgalieva ZZ, Malaty HM, Graham DY, et al. Helicobacter pylori infection in Kazakhstan: effect of water source and household hygiene. Am J Trop Med Hyg 2002;67:201–6.
23. VanDerslice J, Popkin B, Briscoe J. Drinking-water quality, sanitation, and breast-feeding: their interactive effects on infant health. Bull World Health Organ 1994;72:589–601.
24. McWhorter VC, Ford LC, Butch AW. Analytical performance of the Synchron LX20 Pro, BN(TM)II and IMMAGE high sensitivity C-reactive protein assays and concordance in cardiovascular risk stratification. Clin Chim Acta 2004;347:71–9.
25. Ridker PM, Cook N. Clinical usefulness of very high and very low levels of C-reactive protein across the full range of Framingham risk scores. Circulation 2004;109:1955–9.
26. CDC. NHANES 2003-2004 public data general release file documentation. Hyattsville, MD: National Center for Health Statistics, 2005.
27. CDC. Laboratory procedure manual: CRP. Atlanta, GA: CDC, 2000.
28. Okosun IS, Chandra KMD, Boev A, et al. Abdominal adiposity in U.S. adults: prevalence and trends, 1960-2000. Prev Med 2004;39:197–206.
29. McDade TW, Rutherford JN, Adair L, Kuzawa C. Adiposity and pathogen exposure predict C-reactive protein in Filipino women. J Nutr 2008;138:2442–7.
30. Ockene IS, Matthews CE, Rifai N, Ridker PM, Reed G, Stanek E. Variability and classification accuracy of serial high-sensitivity C-reactive protein measurements in healthy adults. Clin Chem 2001;47:444–50.
31. Macy EM, Hayes TE, Tracy RP. Variability in the measurement of C-reactive protein in healthy subjects: implications for reference intervals and epidemiological applications. Clin Chem 1997;43:52–8.
32. Lyon CJ, Law RE, Hsueh WA. Minireview: adiposity, inflammation, and atherogenesis. Endocrinology 2003;144:2195–200.
33. Schaffler A, Muller-Ladner U, Scholmerich J, Buchler C. Role of adipose tissue as an inflammatory organ in human diseases. Endocr Rev 2006;27:449–67.
34. Shemesh T, Rowley KG, Jenkins A, Brimblecombe J, Best JD, O'Dea K. Differential association of C-reactive protein with adiposity in men and women in an Aboriginal community in northeast Arnhem Land of Australia. Int J Obes 2007;31:103–8.
35. Sorensen MV, Leonard WR, Tarskaya LA, et al. High-sensitivity C-reactive protein, adiposity, and blood pressure in the Yakut of Siberia. Am J Hum Biol 2006;18:766–75.
36. Thorand B, Baumert J, Chambless L, et al. Elevated markers of endothelial dysfunction predict type 2 diabetes mellitus in middle-aged men and women from the general population. Arterioscler Thromb Vasc Biol 2006;26:398.
37. Nazmi A, Oliveira IO, Victora CG. Correlates of C-reactive protein levels in young adults: a population-based cohort study of 3827 subjects in Brazil. Braz J Med Biol Res 2008;41:357–67.

38. Vikram NK, Misra A, Dwivedi M, et al. Correlations of C-reactive protein levels with anthropometric profile, percentage of body fat and lipids in healthy adolescents and young adults in urban North India. Atherosclerosis 2003;168:305–13.
39. Chandalia M, Cabo-Chan AV Jr, Devaraj S, Jialal I, Grundy SM, Abate N. Elevated plasma high-sensitivity C-reactive protein concentrations in Asian Indians living in the United States. J Clin Endocrinol Metab 2003; 88:3773–6.
40. McDade TW, Leonard WR, Burhop J, et al. Predictors of C-reactive protein in Tsimane' 2-15 year-olds in lowland Bolivia. Am J Phys Anthropol 2005;128:906–13.
41. Adiloglu AK, Can R, Nazli C, et al. Ectasia and severe atherosclerosis: relationships with *Chlamydia pneumoniae, Helicobacter pylori*, and inflammatory markers. Tex Heart Inst J 2005;32:21–7.
42. Zhu J, Quyyumi AA, Norman JE, et al. Effects of total pathogen burden on coronary artery disease risk and C-reactive protein levels. Am J Cardiol 2000;85:140–6.
43. Zhu J, Quyyumi A, Norman J, Costello R, Csako G, Epstein S. The possible role of hepatitis A virus in the pathogenesis of atherosclerosis. J Infect Dis 2000;182:1583–7.
44. Muhlestein JB, Horne BD, Carlquist JF, et al. Cytomegalovirus seropositivity and C-reactive protein have independent and combined predictive value for mortality in patients with angiographically demonstrated coronary artery disease. Circulation 2000;102:1917–23.
45. Coutinho HM, Leenstra T, Acosta LP, et al. Pro-inflammatory cytokines and C-reactive protein are associated with undernutrtion in the context of *Schistosoma japonicum* infection. Am J Trop Med Hyg 2006;75:720–6.
46. Araneta MRG, Barrett-Connor E. Ethnic differences in visceral adipose tissue and type 2 diabetes: Filipino, African-American, and white women. Obes Res 2005;13:1458–65.
47. Albert MA, Glynn RJ, Buring J, Ridker PM. C-reactive protein levels among women of various ethnic groups living in the United States (from the Women's Health Study). Am J Cardiol 2004;93:1238–42.
48. Yamada S, Gotoh T, Nakashima Y, et al. Distribution of serum C-reactive protein and its association with atherosclerotic risk factors in a Japanese population: Jichi Medical School Cohort Study. Am J Epidemiol 2001;153:1183–90.
49. Barker DJ. Mothers, babies and diseases in later life. London, United Kingdom: BMJ Publishing Group, 1994.
50. Kuzawa CW, Adair LS. Lipid profiles in an adolescent Filipino population: relationship to birth weight and maternal energy status during pregnancy. Am J Clin Nutr 2003;77:960–6.
51. McDade TW, Beck MA, Kuzawa C, Adair L. Prenatal undernutrition, postnatal environments, and antibody response to vaccination in adolescence. Am J Clin Nutr 2001;74:543–8.
52. Amos AF, McCarty DJ, Zimmet P. The rising global burden of diabetes and its complications: estimates and projections to the year 2010. Diabet Med 1998;14:S7–84.