C-Reactive Protein in Adolescent Twins: Patterns and Relationship to Adiposity

Guoying Wang, Katherine Kaufer Christoffel, Wendy J. Brickman, Xiumei Hong, Lester Arguelles, Shanchun Zhang, Binyan Wang, Zhiping Li, Houxun Xing, Gengfu Tang, Donald Zimmerman, Xiping Xu, and Xiaobin Wang

Mary Ann and J. Milburn Smith Child Health Research Program (G.W., K.K.C., X.H., L.A., S.Z., B.W., X.W.), Department of Pediatrics, and Division of Endocrinology (W.J.B., D.Z.), Department of Pediatrics, Northwestern University Feinberg School of Medicine and Children's Memorial Hospital and Children's Memorial Research Center, Chicago, Illinois 60614; Institute for Biomedicine (Z.L., H.X., G.T.), Anhui Medical University, Hefei, China 230032; and Center for Population Genetics (X.X.), University of Illinois at Chicago School of Public Health, Chicago, Illinois 60612

Context: Elevated C-reactive protein (CRP) is a marker of cardiovascular risk in adults. Patterns and determinants of CRP in adolescents have not been well described.

Objective: This study aimed to determine how CRP varies by age, gender, Tanner stage, and body fat composition in rural Chinese adolescents and to what degree adiposity-CRP associations are attributable to shared genetic and environmental factors.

Design and Setting: Data were derived from an ongoing study of metabolic syndrome in a large community-based twin cohort enrolled in Anqing, China.

Participants: The study sample included 1180 adolescent twins aged 13–21 yr.

Main Outcome Measures: Plasma CRP concentrations were measured by sandwich immunoassay using flow metric xMAP technology. Body fat composition was assessed by dual-energy x-ray absorptiometry.

Results: CRP levels linearly increased across age and Tanner stage in males ($P \leq 0.0001$), but in females, CRP exhibited no trend after adjusting for fat mass ($P > 0.05$). For males, the most explanatory measure was body mass index (partial $r^2 = 5.2\%$), whereas percent body fat (partial $r^2 = 8.8\%$) was more explanatory in females. Of the phenotypic correlations between adiposity measures and CRP (0.25–0.28), 86–89% were attributed to shared genetic factors and 11–14% to common unique environmental factors in both sexes.

Conclusions: Adiposity is a strong determinant of CRP even in this relatively lean Chinese population. There is notable gender difference for the CRP pattern and the relationship of CRP with adiposity during adolescence. To a large degree, common genetic factors may underlie the observed adiposity-CRP-phenotypic correlations. (***J Clin Endocrinol Metab*** **96: 3226–3233, 2011)**

C-reactive protein (CRP) is a sensitive objective marker of inflammation and infection (1). High-sensitivity CRP also is a powerful cardiovascular risk predictor in adults (2–5). Recent studies have shown that the atherosclerotic process begins in childhood and progresses slowly into adulthood (6, 7). Elevated circulating CRP has been related to early arterial changes in American (8) and Finnish (9) children and adolescents, supporting the hypothesis that inflammation has an impact in the pathogenesis of early atherosclerosis (10, 11). Thus, under-

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2011-0590 Received March 7, 2011. Accepted July 20, 2011.
First Published Online August 11, 2011

Abbreviations: BF, Body fat; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; DEXA, dual-energy x-ray absorptiometry; FM, fat mass; LF, leg fat; OR, odds ratio; TF, truncal fat; TLR, truncal to leg fat ratio; WC, waist circumference.

standing the pattern of CRP and its determinants during childhood and adolescence may provide information that can help to guide the prevention of cardiovascular disease (CVD) via early risk detection and amelioration.

Adipose tissue is a rich source of many immune-related mediators, such as IL-6 and TNF-α, that are involved in the inflammatory response. CRP is, in turn, under the control of these proinflammatory cytokines (12). Obesity is an established determinant of CRP in adults (13). Histological studies (14, 15), showing that white adipose tissue from obese adults is characterized by increased macrophage accumulation, also confirmed the hypothesis that obesity mediates a chronic low-grade inflammatory response, which may subsequently lead to the development of metabolic and vascular disease (16).

Population-based cohort studies of American children and adolescents have shown higher CRP concentrations in overweight subjects than in normal-weight subjects (17, 18). Several studies in obese children also have shown increases in serum CRP levels as body mass index (BMI) and waist circumference (WC) increase (19, 20). Given that obesity is a risk factor for metabolic syndrome, it is important to note that these studies did not determine whether it is obesity itself or components of the metabolic syndrome such as insulin resistance that are associated with inflammation. Thus, studying the relationship between adiposity and low-grade inflammation in nonobese adolescents may improve our understanding of the early precursors of CVD in adults.

Our ongoing twin study of metabolic syndrome in Anqing, China, provided a unique opportunity to fill in knowledge gaps related to CRP during adolescence. This report addresses the following questions in a large sample of relatively lean Chinese adolescent twins. What are the patterns of CRP by age, Tanner stage, and gender? Which adiposity measures are most closely associated with CRP levels in adolescents, and do these differ by gender? To what degree can adiposity-CRP associations be attributed to environmental and genetic factors?

Subjects and Methods

Study population

This report used data from an ongoing National Institutes of Health-funded study of metabolic syndrome in a large community-based Chinese twin cohort in Anqing, Anhui Province, China. The study protocol was approved by the Institutional Review Boards of Children's Memorial Hospital in Chicago and the Biomedical Institute, Anhui Medical University, Hefei, China. Written informed consent was obtained from the subjects or parents. The study sample was initially recruited from 1998–2000 and then followed up from 2005–2006. Detailed information on sample enrollment has been described (21). This study was based on follow-up data on twins aged 13–21 yr. All study subjects completed a questionnaire interview, physical examination, and a dual-energy x-ray absorptiometry (DEXA) scan. Tanner stages (1–5) were assessed by physicians via visual inspection of pubic hair, genitals (boys), and breasts (girls) (22).

From a total of 1280 eligible participants in whom plasma CRP was determined, 100 (66 male, 34 female) were excluded because of a plasma CRP level higher than 10 mg/liter, likely due to an acute-phase response to an infection or an immune disorder characterized by acute inflammation (23). This report includes the remaining 1180 subjects (632 males, 548 females) aged 13–21 yr. All of the twin pairs included in this study were reared together in their respective families.

Anthropometric parameters and DEXA measures of adiposity

Height and weight were measured using standard protocols without shoes and outerwear. Height was measured to the nearest 0.1 cm on a portable stadiometer and weight to the nearest 0.1 kg. WC was measured at the level of the umbilicus to the nearest millimeter. BMI was calculated as weight (kilograms)/height^2 (meters squared). A standard whole-body scan was performed by DEXA (GE Lunar DPX-MD, Madison, WI) to measure fat mass (FM), truncal fat (TF), and leg fat (LF) using a standard software calculation. Percent body fat (%BF), %TF, and %LF, were calculated as (FM in kilograms/total mass in kilograms) $\times$ 100, (TF in kilograms/FM in kilograms) $\times$ 100, and (LF in kilograms/FM in kilograms) $\times$ 100, respectively. Truncal to leg fat ratio (TLR) was calculated as truncal fat divided by leg fat. BMI and %BF reflect generalized body fat, whereas WC, %TF, %LF, and TLR are used as parameters of fat distribution.

Laboratory measurements

Plasma was separated from blood cells and refrigerated within 30 min after blood was drawn. Plasma CRP concentrations were determined using sandwich immunoassay based on flow metric xMAP technology on Luminex 200 machines (Luminex multianalyte profiling system; Luminex, Corp., Austin, TX). The immunoassay kit is commercially available from Millipore Corp. (Bedford, MA). Each sample was duplicated, and intraassay coefficient variation was less than 5.1%. Twin zygosity was determined as previously published (24).

Statistical analyses

The distribution of plasma CRP levels was positively skewed, and a logarithmic transformation was used to normalize the data for subsequent statistical analyses. Adiposity measures were analyzed as age- and gender-specific z-scores that were calculated as an observed value minus the mean value divided by SD (within each year of age and sex stratum). A two-sided P value <0.05 was regarded as statistically significant. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Sex and Tanner stage effects were analyzed by generalized estimating equation linear regressions. To systematically examine the association between CRP and adiposity, we applied CRP as either a continuous or binary variable: 1) CRP was treated as a continuous variable to estimate the relationship of CRP with a one-unit increase in each adiposity z-score or 2) CRP levels were treated as binary outcomes to access the association between the risk of elevated CRP and adiposity. Elevated plasma CRP levels were defined in two ways: 1) above the age- and gender-specific

top quartil and 2) 3–10 mg/liter, the range that identifies adults at high risk for CVD (25). To determine which adiposity measures provide the best prediction of CRP, a partial r^2 was calculated based on a maximum likelihood (26). The SAS procedure MIXED was used with the family effect treated as a random variable. Finally, to assess genetic and environmental influences on the observed associations between adiposity and CRP, structural equation modeling was used (27). We first fitted a saturated model (ACE, CE, AE, and AC models) that allowed for additive genetic (A), common environmental (C), and unique environmental (E) components for each adiposity measure and CRP. Next, we fitted the bivariate Cholesky decomposition models to calculate genetic (r_G), common (r_C), and unique environmental correlations (r_E) between CRP and adiposity measures. We calculated the phenotypic correlations between CRP levels and adiposity measures as: $r_{TP} = r_G \times \sqrt{A_1 \times A_2} + r_C \times \sqrt{C_1 \times C_2} + r_E \times \sqrt{E_1 \times E_2}$. The genetic contribution (C_{GCP}) and unique environmental contributions (C_{UCP}) to the phenotypic correlations could be estimated as $C_{GCP} = r_G \times \sqrt{A_1 \times A_2}$ and $C_{UCP} = r_E \times \sqrt{E_1 \times E_2}$, respectively. Mx software (http: www.psy.vu.nl/mxbib/) was used for the twin analysis.

Results

Demographic and anthropometric characteristics

The subjects were relatively lean. Means for BMI were at the 25–50th percentile BMI-for-age using World Health Organization child growth standards (28). Age, BMI, %BF, %TF, and TLR were higher, whereas WC, %LF, and CRP level were lower in females when compared with males (Table 1). Notably, more than 13% (males 14.4%, females 13.7%) of the children in this twin cohort had CRP concentrations in the range that identifies adults at high risk of CVD, *i.e.* 3–10 mg/liter.

TABLE 1. Demographic characteristics of 1180 Chinese children and adolescents aged 13–21 yr

	Males	Females	*P* value
n	632	548	
Age (yr)	16.4 ± 2.1	16.8 ± 2.1	0.0254
Tanner stages	3.4 ± 1.4	3.7 ± 1.1	0.0018
Active smoking [yes (%)]	9.39	0.00	<0.0001
Passive smoking [yes (%)]	81.8	76.2	0.0199
Zygosity [MZ (%)]	60.2	68.4	0.0036
WC (cm)	68.4 ± 6.1	66.1 ± 6.3	0.0056
BMI (kg/m^2)	18.7 ± 2.3	19.8 ± 2.4	<0.0001
Fat mass (kg)	5.8 ± 3.58	13.0 ± 4.14	<0.0001
%BF	11.7 ± 5.3	27.4 ± 5.6	<0.0001
%TF	45.2 ± 6.8	48.6 ± 4.3	<0.0001
%LF	40.6 ± 6.4	37.3 ± 4.3	<0.0001
TLR	1.2 ± 0.4	1.3 ± 0.3	<0.0001
%TTM	5.4 ± 3.0	13.4 ± 3.5	<0.0001
%LTM	4.7 ± 1.9	10.1 ± 1.7	<0.0001
CRP (mg/liter)[a]	0.85 (0.39–1.80)	0.75 (0.34–1.72)	0.0499
3–10 mg CRP (%)	14.4	13.7	0.7255

Unless otherwise noted, data are presented as means ± SD or percent. To test the difference of each variable between males and females, χ^2 and generalized linear regression equations were used. MZ, Monozygotic; %LTM, percent leg fat of total mass; %TTM, percent truncal fat of total mass.

[a] Median (interquartile range).

Plasma CRP patterns by age and Tanner stage

The pattern of log CRP levels was linear across all ages in males, but it reached a plateau at 17 yr of age in females (Fig. 1A). After adjustment for FM, CRP levels still linearly increased across age in males, but in females, CRP slowly increased up to age 17, peaked, and then slightly decreased over time. This also was true of CRP across Tanner stage (Fig. 1B); in males, CRP dramatically increased across Tanner stage ($P_{trend} \leq 0.0001$), but in females, CRP exhibited no trend across Tanner stage ($P_{trend} = 0.54$). The CRP value was significantly higher in males compared with females after age 17 and Tanner stage 4; log (CRP) was 0.72 mg/liter (SE = 0.16; $P < 0.0001$) higher in males than females after age 17 and after adjustment for smoking, age, Tanner stage, and FM.

Relationship of CRP with adiposity measures

After adjustment for age, Tanner stage, and smoking status, linear regression confirmed that all adiposity measures were linearly associated with log (CRP) levels in both sexes (Table 2). In males, for a one-unit increase in WC, BMI, %BF, %TF, and TLR z-scores, log (CRP) increased 0.22, 0.23, 0.15, 0.14, and 0.15, respectively; in females, the increases were greater at 0.31, 0.31, 0.31, 0.19, and 0.21, respectively. However, the association of CRP with WC and TLR disappeared after adjusting for FM in females. In contrast, %LF was inversely associated with CRP; β (SE) = −0.14 (0.04) and −0.22 (0.05) in males and females, respectively. The proportion of the variance in CRP explained by adiposity (partial r^2) was higher in females compared with males, *e.g.* 3.2–8.8% *vs.* 1.9–5.2%, respectively. For males, the most explanatory measure was BMI (partial r^2 = 5.2%), whereas %BF (partial r^2 = 8.8%) was most explanatory in females. In addition, we also examined parameters of lean mass in relation to CRP and found no association in either males or females (data not shown).

Adiposity and elevated CRP

Figure 2 shows the results of multivariate logistic regression models used to predict the risk of elevated CRP (top quartile CRP or in the range of 3–10 mg/liter) after adjusting for age, smoking and Tanner stage (model 1). For males, a one-unit increase in WC, BMI, %BF, and TLR z-score increased the risk of elevated CRP levels in the top

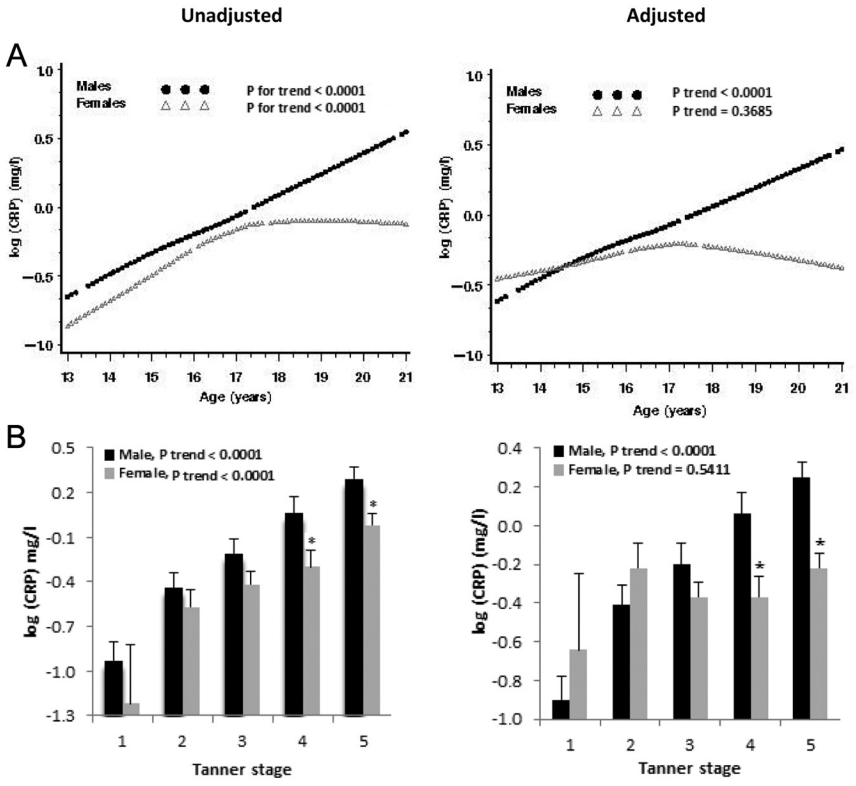

FIG. 1. Pattern of plasma CRP across age (A) and Tanner stage (B) stratified by gender in Chinese adolescent twins aged 13–21 yr. Log (CRP) levels rise with increasing age and Tanner stage in males but not in females after adjustment for fat mass. Data are given as the mean ± SEM for each Tanner stage in B. *P* trend is for log (CRP) across age or Tanner stage in each gender; *, $P < 0.05$, compared with males at same Tanner stage.

quartile from 41–66% [odds ratio $(OR)_{WC} = 1.66$ (95% confidence interval, CI = 1.28–2.03); $OR_{BMI} = 1.64$ (95% CI = 1.27–2.01); $OR_{\%BF} = 1.41$ (95% CI = 1.09–1.73); and $OR_{TLR} = 1.48$ (95% CI = 1.15–1.81)]. In females, the risk ranged from 38–95% [$OR_{WC} = 1.95$ (95% CI = 1.38–2.52); $OR_{BMI} = 1.75$ (95% CI = 1.23–2.26); $OR_{\%BF} = 1.82$ (95% CI = 1.28–2.36); and $OR_{TLR} = 1.38$ (95% CI = 1.00–1.77)]. Similarly WC, BMI, and %BF z-score all significantly increased the risk of having CRP levels over 3 mg/liter in both genders; however, %TF and TLR increased the risk of higher than 3 mg/liter CRP levels in males only. Furthermore, additionally adjusting for FM (model 2), WC and TLR were associated with the risk of top quartile CRP levels only in males. In both genders, %LF had a protective effect on the risk of top quartile CRP levels [OR = 0.68 (95% CI = 0.52–0.83) in males; OR = 0.71 (95% CI = 0.51–0.92) in females], but it significantly lowered the risk of higher than 3 mg/liter CRP levels in males only.

Genetic and environmental contributions to the adiposity-CRP correlations

Heritability estimates were based on the AE model, which was the statistically best-fitting model in our study. In Fig. 3, the heritability estimate for CRP was similar in males and females, 0.42 (95% CI = 0.29–0.54) and 0.45 (95% CI = 0.33–0.56), respectively. Heritability estimates for WC and BMI were 0.82 (95% CI = 0.76–0.86) and 0.89 (95% CI = 0.85–0.91), respectively, in males and 0.78 (95% CI = 0.72–0.83) and 0.86 (95% CI = 0.81–0.89), respectively, for females. The data suggest that the genetic contributions to BMI and WC were much higher than the genetic contributions to CRP.

Each adiposity measure and CRP were moderately correlated genetically ($r_G \approx 0.4$ in both males and females), which indicated that these paired traits share some common genetic factors. In males, WC and CRP shared 37%, whereas BMI and CRP shared 36% of common genes ($r_{GWC} = 0.37$, and $r_{GBMI} = 0.36$); in females, WC and CRP shared 41%, and BMI and CRP shared 38% ($r_{GWC} = 0.41$, and $r_{GBMI} = 0.38$). The influence of unique environmental factors on two traits (CRP-WC or CRP-BMI) was not highly correlated ($r_E = 0.10$ in males, and $r_E = 0.11$ in females).

Genetic contribution to the correlation between two phenotypes, C_{GCP}, was estimated to be 0.22 in males and 0.24 in females for both CRP-WC and CRP-BMI. The total phenotypic correlation in males was $r_{TP} = 0.25$ based on the AE model, and the proportion of the total observed phenotypic correlation that is attributable to genetic factors in males was 88% [(0.22/0.25) × 100]. Similarly, 86–89% [(0.24/0.28) × 100 or (0.24/0.27) × 100] of the total phenotypic correlations between each adiposity measure (WC and BMI) and CRP ($r_{TP} = 0.28$ and 0.27) is determined by common genes in females. Common unique environmental factors explained only 11–14% of the total phenotypic correlation in both sexes.

Discussion

In this study, we systematically characterized the impact of pubertal development, gender, and adiposity distribution on CRP levels in children and adolescents across a wide age range. Our data document prevalent subclinical inflammation in these healthy Chinese twins. Fully 13% of the children in this relatively lean cohort had CRP concentrations in the range that identifies adults at high risk

TABLE 2. Association of adiposity measures with plasma CRP level among male and female twins aged 13–21 yr

Adiposity z-score	Males					Females				
	n	β	SE	*P* value	Partial r^2	n	β	SE	*P* value	Partial r^2
Model 1										
WC	616	0.22	0.04	<0.0001	0.0366	520	0.31	0.05	<0.0001	0.0665
BMI	613	0.23	0.05	<0.0001	0.0516	518	0.31	0.05	<0.0001	0.0788
%BF	613	0.15	0.05	0.0010	0.0296	516	0.31	0.05	<0.0001	0.0881
%TF	615	0.14	0.04	0.0021	0.0185	519	0.19	0.05	0.0005	0.0317
%LF	615	−0.14	0.04	0.0014	0.0196	519	−0.22	0.05	<0.0001	0.0387
TLR	615	0.15	0.04	0.0006	0.0223	519	0.21	0.05	0.0001	0.0365
Model 2										
WC	615	0.18	0.07	0.0113	0.0107	519	0.11	0.09	0.2277	0.0075
TLR	615	0.10	0.05	0.0370	0.0073	519	0.07	0.06	0.2089	0.0033

Of 1084 participants in whom zygosity was determined, 332 pairs were monozygotic and 210 pairs were dizygotic. Model 1 was adjusted for active and passive smoking, Tanner stage, and age; model 2 was additionally adjusted for fat mass in addition to the adjustments for confounders in model 1. β, β-Coefficient.

of CVD. This is similar to the levels found in a report on native Canadian children who experience high rates of overweight (29). This surprising finding suggests that a substantial number of children from this relatively lean population may be at risk for developing atherosclerotic disease in early adulthood.

Consistent with a previous study (23), we found that although CRP rises with age, the patterns differ for males and females. We also found that pubertal development modifies CRP levels in both genders. However, in our study, CRP was associated with age and pubertal development apart from the degree of obesity in males only. One potential explanation may be due to a gender difference in adiponectin level during puberty, which may link the association between CRP and pubertal development. One recent study showed that there was a remarkable decline in adiponectin levels with the progression of puberty in boys, which was not seen in girls (30). Moreover, Winer *et al.* (31) reported that adiponectin could play a role in modulating CRP levels.

Previous results regarding circulating CRP levels in both genders were inconsistent (32–34). Some studies (32, 33) found that CRP levels were generally higher in males compared with females, whereas another study found just the opposite (34). In line with previous studies (32, 33), we found that males at later puberty had significantly higher CRP levels than females in our population, which is consistent with widely recognized evidence that men have a higher prevalence of CVD than women. The gender difference in CRP levels may presumably relate to a gender-specific regulation of CRP during puberty. The higher CRP levels of women with hyperandrogenism (35) have suggested that gender-related differences in sex steroid

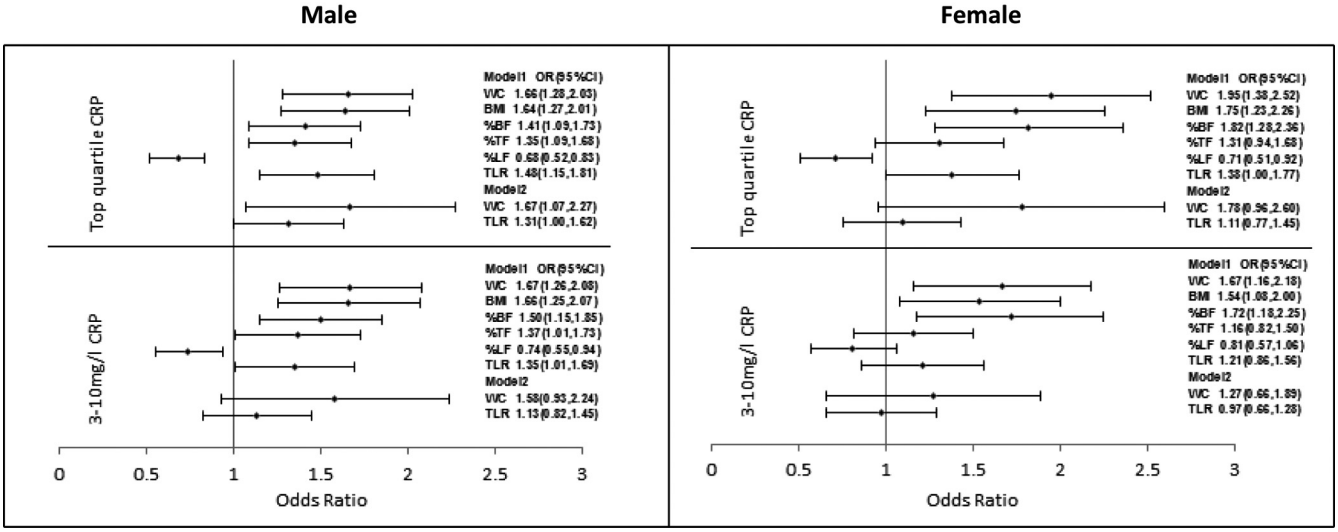

FIG. 2. Association of adiposity measures with the risk of elevated plasma CRP in adolescents aged 13–21 yr. Model 1 was adjusted for active and passive smoking, Tanner stage, and age; model 2 was additionally adjusted for fat mass in addition to the adjustments for confounders in model 1. Elevated CRP was defined in two ways: 1) above gender- and age-specific top quartile and 2) in the range of 3–10 mg/liter.

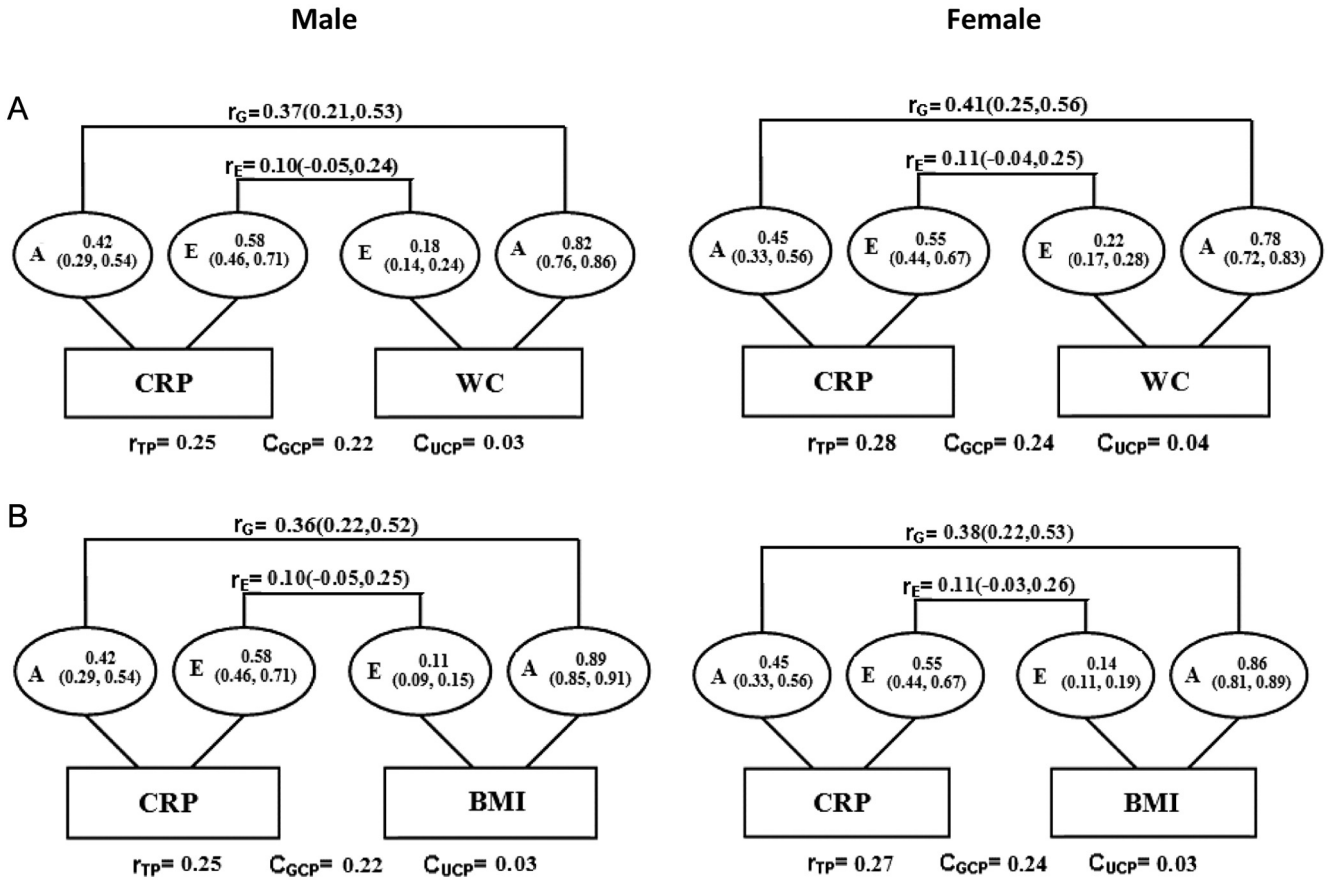

FIG. 3. Estimates of genetic and environmental correlations between CRP and WC (A) and BMI (B). Data are presented as parameter estimates (95% CI). All variance components were estimated with inclusion of age and Tanner stage as covariates in the models. A and E denote a percentage of total phenotypic variance accounted for by genetic factors and environmental factors, respectively. C_{GCP} and C_{UCP}, Genetic and unique environmental contribution to the correlation between CRP and adiposity measure, respectively; r_E, unique environmental correlation between two phenotypes; r_G, genetic correlation between two phenotypes; r_{TP}, total phenotype correlation between CRP and adiposity measures.

hormones might have a key role in low-grade chronic inflammation.

In our sample of predominantly healthy twins, the significant link between CRP and adiposity was emphasized by generally rising CRP concentrations with rising adiposity measure z-scores, irrespective of age and Tanner stage. The contribution of adiposity to CRP was of greater magnitude in females than in males, but the contribution of WC and TLR to CRP was modest compared with the impact of total fat mass in females. We also observed consistent relationships between adiposity and the risk of elevated CRP. Moreover, the results were not changed by the inclusion of individuals with CRP above 10 mg/liter (data not shown). These findings confirm and extend previous studies in pediatric cohorts that have uniformly identified adiposity as the most important determinant of CRP level (17–20) in our lean subjects. Our findings may provide a pathway underlying the interrelations among adiposity, CRP, and CVD. The mechanisms by which body fat mediates inflammation are not entirely understood. One potential mechanism is the direct sourcing of proinflammatory cytokines such as IL-6 and TNF-α from adipose tissue, driving hepatic synthesis of CRP (12, 36). Another possible explanation is that these two processes may share a common underlying mechanism, such as a common genetic vulnerability. Our heritability estimates are consistent with the study in adult twins (37) and suggest that a considerable part of the variation in CRP can be explained by genetic factors. Moreover, our findings indicated that 86–89% of the correlation between CRP and adiposity (BMI and WC) was due to shared genetic factors. These results suggest that CRP and adiposity may be the expression of a common biological pathway that is genetically modulated. We intend to follow this population beyond sexual maturity, when the relationships of CRP and adiposity are not so predominantly influenced by growth and development.

Our study also yielded another novel finding; %LF was negatively correlated with both plasma CRP and the risk of elevated CRP in both males and females. This extends the findings of previous reports showing inverse relationships between leg fat and other cardiovascular risk factors (38, 39). To the best of our knowledge, no previous epidemiological evidence is available regarding the role of

%LF in plasma CRP levels among adolescents. The reasons for this association and its implications merit further research.

This study has several strengths. First, the data were drawn from a population-based twin cohort with accurate ascertainment of zygosity. Second, adiposity measures were DEXA based. Third, study participants were healthy Chinese adolescents and young adults, with few of the confounders that affect Western studies. Our study also has limitations. First of all, the cross-sectional design precludes cause-effect conclusions. Although the twin design allowed for an estimation of the genetic correlation between two phenotypes, we cannot generalize our findings to nontwin populations. In addition, DEXA does not allow for the separate quantification of sc and visceral fat in the trunk, which may affect CVD risk. This study also is limited in that each subject had only a single CRP measurement, but day to day variability in CRP was likely reduced by using a high-sensitivity method for CRP analysis.

In conclusion, the results of this population-based study show that there are gender-specific variations in CRP level during adolescence. Both generalized and abdominal fat are associated with increased plasma CRP concentration in males, whereas the relation between abdominal adiposity and CRP levels in females is dependent on total fat mass. %LF is inversely associated with elevated CRP levels in both genders. In addition, genetic factors substantially contribute to CRP levels and also to the phenotypic correlations between CRP and adiposity measures. These results suggest that adiposity is a strong determinant of CRP during adolescence even in a nonobese population, and CRP and adiposity may be expressed by a genetically modulated common biological pathway.

Acknowledgments

We thank Tami R. Bartell for English editing.

Address all correspondence and requests for reprints to: Xiaobin Wang, M.D., M.P.H., Sc.D., 2300 Children's Plaza Box 157, Chicago, Illinois 60614. E-mail: xbwang@childrensmemorial.org.

This work was supported in part by National Institutes of Health Grants R01 HD049059, R01 HL086461, and R01 AG032227.

Disclosure Summary: None of the authors have anything to declare.

References

1. **Ross R** 1993 The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature 362:801–809
2. **Koenig W, Sund M, Fröhlich M, Fischer HG, Löwel H, Döring A, Hutchinson WL, Pepys MB** 1999 C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. Circulation 99:237–242
3. **Ridker PM, Buring JE, Cook NR, Rifai N** 2003 C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. Circulation 107:391–397
4. **Albert CM, Ma J, Rifai N, Stampfer MJ, Ridker PM** 2002 Prospective study of C-reactive protein, homocysteine, and plasma lipid levels as predictors of sudden cardiac death. Circulation 105:2595–2599
5. **Ridker PM, Stampfer MJ, Rifai N** 2001. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. JAMA 285:2481–2485
6. **Berenson GS** 2002 Childhood risk factors predict adult risk associated with subclinical cardiovascular disease. The Bogalusa Heart Study. Am J Cardiol 90:3L–7L
7. **Raitakari OT, Juonala M, Kähönen M, Taittonen L, Laitinen T, Mäki-Torkko N, Järvisalo MJ, Uhari M, Jokinen E, Rönnemaa T, Akerblom HK, Viikari JS** 2003 Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. JAMA 290:2277–2283
8. **Freedman DS, Dietz WH, Tang R, Mensah GA, Bond MG, Urbina EM, Srinivasan S, Berenson GS** 2004 The relation of obesity throughout life to carotid intima-media thickness in adulthood: the Bogalusa Heart Study. Int J Obes Relat Metab Disord 28:159–166
9. **Järvisalo MJ, Harmoinen A, Hakanen M, Paakkunainen U, Viikari J, Hartiala J, Lehtimäki T, Simell O, Raitakari OT** 2002 Elevated serum C-reactive protein levels and early arterial changes in healthy children. Arterioscler Thromb Vasc Biol 22:1323–1328
10. **Ross R** 1999 Atherosclerosis: an inflammatory disease. N Engl J Med 340:115–126
11. **Gonzalez MA, Selwyn AP** 2003 Endothelial function, inflammation, and prognosis in cardiovascular disease. Am J Med 115(Suppl 8A):99S–106S
12. **Trayhurn P, Wood IS** 2004 Adipokines: inflammation and the pleiotropic role of white adipose tissue. Br J Nutr 92:347–355
13. **Santos AC, Lopes C, Guimaraes JT, Barros H** 2005 Central obesity as a major determinant of increased high-sensitivity C-reactive protein in metabolic syndrome. Int J Obes (Lond) 29:1452–1456
14. **Cancello R, Henegar C, Viguerie N, Taleb S, Poitou C, Rouault C, Coupaye M, Pelloux V, Hugol D, Bouillot JL, Bouloumié A, Barbatelli G, Cinti S, Svensson PA, Barsh GS, Zucker JD, Basdevant A, Langin D, Clément K** 2005 Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. Diabetes 54:2277–2286
15. **Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante Jr AW** 2003 Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 112:1796–1808
16. **Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW** 1999 C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol 19:972–978
17. **Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB** 2001 Low-grade systemic inflammation in overweight children. Pediatrics 107:E13
18. **Ford ES, Galuska DA, Gillespie C, Will JC, Giles WH, Dietz WH** 2001 C-reactive protein and body mass index in children: findings from the Third National Health and Nutrition Examination Survey, 1988–1994. J Pediatr 138:486–492
19. **Wu DM, Chu NF, Shen MH, Chang JB** 2003 Plasma C-reactive

protein levels and their relationship to anthropometric and lipid characteristics among children. J Clin Epidemiol 56:94–100
20. **López-Jaramillo P, Herrera E, Garcia RG, Camacho PA, Castillo VR** 2008 Inter-relationships between body mass index, C-reactive protein and blood pressure in a Hispanic pediatric population. Am J Hypertens 21:527–532
21. **Yu Y, Lu BS, Wang B, Wang H, Yang J, Li Z, Wang L, Liu X, Tang G, Xing H, Xu X, Zee PC, Wang X** 2007 Short sleep duration and adiposity in Chinese adolescents. Sleep 30:1688–1697
22. **Marshall WA, Tanner JM** 1970 Variations in the pattern of pubertal changes in boys. Arch Dis Child 45:13–23
23. **Ford ES, Giles WH, Myers GL, Rifai N, Ridker PM, Mannino DM** 2003 C-reactive protein concentration distribution among US children and young adults: findings from the National Health and Nutrition Examination Survey, 1999–2000. Clin Chem 49:1353–1357
24. **Wang B, Necheles J, Ouyang F, Ma W, Li Z, Liu X, Yang J, Xing H, Xu X, Wang X** 2007 Monozygotic co-twin analyses of body composition measurements and serum lipids. Prev Med 45:358–365
25. **Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon 3rd RO, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith Jr SC, Taubert K, Tracy RP, Vinicor F** 2003 Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 107:499–511
26. **Demerath EW, Schubert CM, Maynard LM, Sun SS, Chumlea WC, Pickoff A, Czerwinski SA, Towne B, Siervogel RM** 2006 Do changes in body mass index percentile reflect changes in body composition in children? Data from the Fels Longitudinal Study. Pediatrics 117: e487–e495
27. **Rijsdijk FV, Sham PC** 2002 Analytic approaches to twin data using structural equation models. Brief Bioinform 3:119–133
28. **Ouyang F, Christoffel KK, Brickman WJ, Zimmerman D, Wang B, Xing H, Zhang S, Arguelles LM, Wang G, Liu R, Xu X, Wang X** 2010 Adiposity is inversely related to insulin sensitivity in relatively lean Chinese adolescents: a population-based twin study. Am J Clin Nutr 91:662–671
29. **Retnakaran R, Hanley AJ, Connelly PW, Harris SB, Zinman B** 2006 Elevated C-reactive protein in Native Canadian children: an ominous early complication of childhood obesity. Diabetes Obes Metab 8:483–491
30. **Böttner A, Kratzsch J, Müller G, Kapellen TM, Blüher S, Keller E, Blüher M, Kiess W** 2004 Gender differences of adiponectin levels develop during the progression of puberty and are related to serum androgen levels. J Clin Endocrinol Metab 89:4053–4061
31. **Winer JC, Zern TL, Taksali SE, Dziura J, Cali AM, Wollschlager M, Seyal AA, Weiss R, Burgert TS, Caprio S** 2006 Adiponectin in childhood and adolescent obesity and its association with inflammatory markers and components of the metabolic syndrome. J Clin Endocrinol Metab 91:4415–4423
32. **Wärnberg J, Nova E, Moreno LA, Romeo J, Mesana MI, Ruiz JR, Ortega FB, Sjöström M, Bueno M, Marcos A** 2006 Inflammatory proteins are related to total and abdominal adiposity in a healthy adolescent population: the AVENA Study. Am J Clin Nutr 84:505–512
33. **Vikram NK, Misra A, Dwivedi M, Sharma R, Pandey RM, Luthra K, Chatterjee A, Dhingra V, Jailkhani BL, Talwar KK, Guleria R** 2003 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 168:305–313
34. **Cook DG, Mendall MA, Whincup PH, Carey IM, Ballam L, Morris JE, Miller GJ, Strachan DP** 2000 C-reactive protein concentration in children: relationship to adiposity and other cardiovascular risk factors. Atherosclerosis 149:139–150
35. **Tosi F, Dorizzi R, Castello R, Maffeis C, Spiazzi G, Zoppini G, Muggeo M, Moghetti P** 2009 Body fat and insulin resistance independently predict increased serum C-reactive protein in hyperandrogenic women with polycystic ovary syndrome. Eur J Endocrinol 161:737–745
36. **Ramadori G, Christ B** 1999 Cytokines and the hepatic acute-phase response. Semin Liver Dis 19:141–155
37. **Wessel J, Moratorio G, Rao F, Mahata M, Zhang L, Greene W, Rana BK, Kennedy BP, Khandrika S, Huang P, Lillie EO, Shih PA, Smith DW, Wen G, Hamilton BA, Ziegler MG, Witztum JL, Schork NJ, Schmid-Schönbein GW, O'Connor DT** 2007 C-reactive protein, an 'intermediate phenotype' for inflammation: human twin studies reveal heritability, association with blood pressure and the metabolic syndrome, and the influence of common polymorphism at catecholaminergic/beta-adrenergic pathway loci. J Hypertens 25: 329–343
38. **Vega GL, Adams-Huet B, Peshock R, Willett D, Shah B, Grundy SM** 2006 Influence of body fat content and distribution on variation in metabolic risk. J Clin Endocrinol Metab 91:4459–4466
39. **Snijder MB, Dekker JM, Visser M, Bouter LM, Stehouwer CD, Yudkin JS, Heine RJ, Nijpels G, Seidell JC** 2004 Trunk fat and leg fat have independent and opposite associations with fasting and postload glucose levels: the Hoorn study. Diabetes Care 27:372–377