Published in final edited form as:
Psychoneuroendocrinology. 2014 February ; 40: 76–85. doi:10.1016/j.psyneuen.2013.10.019.

Is very high C-Reactive Protein in Young Adults Associated with Indicators of Chronic Disease Risk?

Lilly Shanahan, PhD[a,*], **Jason Freeman, MS**[a], and **Shawn Bauldry, PhD**[b]

[a]University of North Carolina at Chapel Hill, Department of Psychology, CB #3270, Davie Hall, Chapel Hill, NC, 27599-3270, USA

[b]University of Alabama at Birmingham, Department of Sociology, HHB 460H, 1720 2nd Ave South, Birmingham, AL 35294, USA

Abstract

Background—Cases with very high C-reactive protein (CRP > 10 mg/l) are often dropped from analytic samples in research on risk for chronic physical and mental illness, but this convention could inadvertently result in excluding those most at risk. We tested whether young adults with very high CRP scored high on indicators of chronic disease risk. We also tested intergenerational pathways to and sex-differentiated correlates of very high CRP.

Methods—Data came from Waves I (ages 11–19) and IV (ages 24–34) of the National Longitudinal Study of Adolescent Health (*N*=13,257). At Wave I, participants' parents reported their own education and health behaviors/health. At Wave IV, young adults reported their socioeconomic status, psychological characteristics, reproductive/health behaviors and health; trained fieldworkers assessed BMI, waist circumference, blood-pressure, and medication use, and collected bloodspots from which high-sensitivity CRP (hs-CRP) was assayed.

Results—Logistic regressions revealed that many common indicators of chronic disease risk—including parental health/health behaviors reported 14 years earlier—were associated with very high CRP in young adults. Several of these associations attenuated with the inclusion of BMI. More than 75% of young adults with very high CRP were female. Sex differences in associations of some covariates and very high CRP were observed.

*Address for Correspondence: University of North Carolina at Chapel Hill, Department of Psychology, CB #3270, Davie Hall, Chapel Hill, NC, 27599-3270, lilly_shanahan@unc.edu, phone: (919) 843-6985, fax: (919) 962-2537.

Contributors

Each author made substantive intellectual contributions to this article. Lilly Shanahan conceptualized and drafted this manuscript and supervised data analyses. Jason Freeman assisted with conceptualizing the manuscript, conducted data analyses and participated in revisions of the manuscript. Shawn Bauldry assisted in the conceptualization of the manuscript, data analyses and revisions of the manuscript.

Conflict of Interest Statement

None of the authors have biomedical financial interests or potential conflicts of interest.

Conclusion—Especially among females, the exclusion of very high CRP cases could result in an underestimation of "true" associations of CRP with both, chronic disease risk indicators and morbidity/mortality. Very high CRP could represent an extension of the lower CRP range when it comes to chronic disease risk.

Keywords

C-reactive protein; inflammation; sex differences; cardiovascular disease risk; socioeconomic status; health disparities; intergenerational pathways; Add Health

The acute phase reactant C-reactive protein (CRP) is a marker of systemic inflammation. In the developed nations, values of CRP between 3 and 10 mg/L are thought to reflect elevated chronic low-grade inflammation and to index risk for cardiovascular and metabolic disease and mortality (e.g., Ridker, 2007). Values of CRP above 10 mg/L (henceforth referred to as "very high CRP") are thought to primarily index temporary acute/recent infections or medical trauma (e.g., Pearson et al., 2003). Therefore, studies investigating the role of elevated low-grade systemic inflammation in chronic physical and mental illness often exclude cases with very high CRP (O'Connor et al., 2009) in an effort to avoid obscuring "true" association between CRP and disease risk (Pearson et al., 2003).

Recent research casts doubt on this practice, however, suggesting that very high CRP is not only associated with acute/recent medical conditions, but, in fact, is a better predictor of later cardiovascular disease (CVD) and all-cause mortality than CRP 3–10 mg/L (Cushman et al., 2005; Hamer et al., 2010; Ridker and Cook, 2004). Furthermore, very high CRP is associated with demographic factors and health behaviors indicative of chronic disease risk (Alley et al., 2006; Hamer and Chida, 2009; Ishii et al., 2012). These findings raise an important question about the consequences of excluding cases with very high CRP: *Does this convention inadvertently bias analytic samples toward the disproportionate exclusion of those who are most at risk for chronic physical and mental illness?* If so, then conclusions about the role of CRP in disease risk would be understated, especially for females—who typically have the highest levels of CRP (e.g., Ishii et al., 2012)—and for more recent cohorts—who suffer from higher levels of obesity compared to previous cohorts (Reither et al., 2011).

Here, we use a nationally representative sample to comprehensively test whether young adults in the United States with very high CRP score higher on indicators of chronic disease risk compared to their peers with lower CRP. We review 1) established correlates of very high CRP, 2) additional potential demographic, psychological, and health/health behavior correlates, and 3) potential sex differences in correlates.

Correlates of Very High CRP

Established Correlates

Several studies show that very high CRP is associated with chronic disease risk indicators that have previously been identified as correlates of CRP 3–10 mg/L (O'Connor et al., 2009), including 1) lower socioeconomic status (SES; e.g., low education, income); 2) obesity; 3) engagement in unhealthy behaviors (e.g., smoking, low exercise/physical

activity); 4) Black or Hispanic race/ethnicity, 5) hypertension, and 6) depressive symptoms (Alley et al., 2006; Hamer and Chida, 2009; Ishii et al., 2012). Several of these correlates have not yet been replicated, particularly in samples of young adults.

Additional Potential Correlates

Several correlates of CRP 3–10 mg/L have not yet been established as correlates of very high CRP. If very high CRP represented an extension of the CRP 3–10 elevated disease risk continuum, then these correlates should also be associated with very high CRP. In terms of *demographic characteristics*, American Indians are at risk for elevated CRP in the < 10 mg/L range (Shanahan et al., 2013) and also chronic CRP-associated diseases (Howard et al., 1999). Asian Americans typically have lower CRP levels and chronic disease risk (Lakoski et al., 2006). Being unpartnered/unmarried increases vulnerability to chronic disease—especially in males—and thus could also increase risk for very high CRP (e.g., Hamer and Chida, 2009; Kiecolt-Glaser et al., 2010). One final observation about demographic disease risk indicators is that both low SES and chronic disease are transmitted through generations. Thus, it is possible that dropping cases with very high CRP results in the exclusion of people who have been socioeconomically disadvantaged for more than one generation and with familial health risks.

In terms of *psychological correlates*, personality traits reflecting low self-control/conscientiousness predict later low-grade inflammation and chronic illness (e.g., Moffitt et al., 2011) and thus potentially also very high CRP. Additional *health behaviors/health* correlates of very high CRP are possible. Diabetes could raise systemic CRP levels beyond the 10 mg/L threshold (Ishii et al., 2012), as could other chronic diseases, including sexually transmitted diseases (STD). Finally, although BMI is an established correlate of very high CRP, less is known about the role of waist circumference—and also additional indicators of metabolic syndrome such as high cholesterol—over and above BMI in associations with very high CRP.

Sex Differences in Correlates

Up to 70% of the very high CRP group is female; this percentage increases when repeated occasions of very high CRP are considered (Ishii et al., 2012). Obesity and use of oral contraceptives contribute to the predominance of females in the very high CRP group. Indeed, compared to males, females in their childbearing years encounter greater numbers of pro-inflammatory influences (e.g., pregnancy, oral contraceptives), stronger effects of some pro-inflammatory factors (e.g., BMI), and also lower levels of anti-inflammatory influences such as testosterone (e.g., Shanahan et al., 2013). A characterization of sex differences in correlates of very high CRP, however, is needed.

Methods and Materials

Participants and Procedures

Data came from Waves I and IV of the National Longitudinal Study of Adolescent Health (Add Health, see Harris et al., 2009). Wave I of Add Health is a nationally representative sample of adolescents enrolled in middle school or high school in the US in 1994. The

National Quality Education Database, which lists all US high schools, provided the sampling frame. Eighty high schools were randomly selected out of all high schools with an 11th grade and at least enrolled 30 students. These 80 high schools were paired with middle schools that fed into their student body. Together, 145 schools hosted an in-school survey, yielding 90,118 student respondents in grades 7–12 in 1994.

Approximately 200 students from each school were randomly selected for in-depth in-home interviews, resulting in *N*=20,745 (Wave I). The in-home assessments included interviews with a parent (typically the mother/female head of the household). Parental reports used in our study were drawn from these interviews. Wave IV was collected when respondents were 24–34 years old (14 years after Wave I). Of the eligible respondents from Wave I, 93% were re-located and 80% were re-interviewed, resulting in 15,701 in-home interviews. Wave IV blood samples were obtained at the end of each interview by trained and certified field workers using a finger-prick procedure, as described the Add Health documentation (Harris and Udry, 2013). Dried blood spots were mailed to and assayed at the University of Washington Medical Center Immunology Lab. Written consent was obtained from parents/guardians (Wave I) and young adults (Wave IV); written assent was obtained from adolescents (Wave I).

Assessment

C-reactive Protein—An in-depth documentation of the Add Health hs-CRP assay and quality control are available online (Whitsel et al., 2013). Briefly, a sandwich ELISA method was adapted from a previously published method (McDade et al., 2004). Values from dried blood spots and paired plasma samples were highly correlated (r = .98) in a cross-validation study. Intra-assay variation was 8.1% and inter-assay variation was 11%. We created a dichotomous measure of very high CRP (0 = ≤ *10 mg/L*, 1 = > *10 mg/L*. For select supplemental analyses, we also created dichotomous elevated hs-CRP < 3 mg/L and hs-CRP 3–10 mg/L variables.

Demographics variables: Dummy variables coded different racial/ethnic groups: Hispanic, Black, Asian, American Indian, other, and White (reference category). *Parental education* (Wave I) coded the highest level of education completed by either parent, ranging from 0 = ≤ *8th grade* to 5 = *professional training beyond a four-year college/university*. Parental income had a substantial amount of missing data; therefore, it was not included here. Three dummy variables for *parental self-reports of health behaviors/health* (Wave I) coded if a residential parent reported currently smoking, and if a biological parent reported having been diagnosed with *diabetes* or being *obese*.

Young adults reported their *socioeconomic and marital/cohabitation status* (Wave IV). *Household income* measured total income from all sources before taxes/deductions, and was log-transformed to lessen the impact of extremely high incomes on statistical estimates. The coding of *subjects' education* was identical to that of parental education. Participants reported whether they were *married*, *cohabiting*, or *single* (=reference category).

Psychological Characteristics (Wave IV): *Lifetime Depression/Anxiety*: Subjects reported whether a health care provider had ever told them that they had a depressive and/or anxiety

disorder. *Conscientiousness* was assessed using the Mini-IPIP (for a description of the latent conscientiousness score used here, see Baldasaro et al., 2013). Briefly, four items, measured on a scale from 1=*strongly disagree* to 5=*strongly agree*, were used. *Health behaviors (Wave IV)*. A dummy variable coded whether participants had *smoked* ≥ 1 cigarette/day in the past month. A continuous variable coded the number of times subjects reported having participated in *physical activities* (e.g., running, bicycling, weightlifting) in the past 7 days, with 0=*no physical activity* to *3 ≥ 3 physical activities*. *Alcohol use* was assessed on a 6-point scale, with 0=*no drink in the past 12 months* to 6=*drinking (almost) every day*.

Reproductive Variables (Wave IV): A dichotomous *current pregnancy* coded whether a female reported currently being pregnant. *Number of children* counted the number of biological children to date. Females reported on their use of *oral contraceptives*. Males received a score of 0 on the pregnancy and oral contraceptives variables.

A dichotomous *Acute illness (Wave IV)* variable coded whether the participant reported having had any of the following illnesses within the previous two weeks: cold, fever, sweats, nausea, blood in stool or urine, frequent urination, or skin rash/abscess. *Surgery* indicated whether the subject had surgery in the past 4 weeks. Chronic illness was generally assessed using the following script: “Has a doctor, nurse or other health care provider ever told you that you have or had: [DISEASE].”). *Diabetes* coded self-reported lifetime diagnosis of high blood sugar or diabetes. A dichotomous *non-diabetic chronic illness* variable coded the presence of any of the following self-reported lifetime diagnoses: heart disease, cancer, asthma, migraines, hepatitis and gum disease. *Sexually transmitted disease (STD)* summed self-reported lifetime diagnoses, including chlamydia, gonorrhea, trichomoniasis, syphilis, genital herpes, genital warts, human pampilloma virus, pelvic inflammatory disease, cervicitis or mucopurulent cervicitis, urethritis, vaginitis and human immunodeficiency virus. Additional illness variables are available in Add Health, but we limited our focus to conditions that were theoretically linked with inflammation and/or showed bivariate associations with very high CRP. Follow-up analyses using illness variables provided in the Add Health online documentation showed that changes in substantive results reported here were negligible.

Medication use was primarily recorded by interviewers from medications/containers provided by participants. A minority of participants recalled their medication use. For parsimony’s sake, we created a dummy variable which coded whether any non-prescription or prescription medication had been taken. Follow-up analyses suggested that changes in substantive results were negligible when medication use was disaggregated into the more specific categories available in Add Health (e.g., non-steroidal anti-inflammatory drugs). *Body mass index (BMI; Wave IV)* was calculated as weight (kg)/height (m^2)—which were measured by trained field workers. A squared BMI term was created in order to indicate extreme obesity (Ishii et al., 2012). *Metabolic syndrome indicators (Wave IV)*. Waist circumference (in centimeters) and resting blood pressure were assessed by trained interviewers. The dichotomous cholesterol measure coded self-reported lifetime diagnosis of elevated cholesterol.

Missing Data

N=1,640 respondents did not consent to having blood samples taken or had physical injuries preventing blood sample collection; *N*=903 respondents did not have a valid sample weight; and *N*=2 subjects had missing data on sex—resulting in an analytic sample of *N*=13,257. Parental health variables had significant amounts of missing data (e.g., *N*=1,802 missing data on parental smoking), and multiple imputation by chained equations (MICE) was used to impute missing values. MICE uses a series of imputation models fitted to each variable to estimate missing cases based on the arbitrary patterns for continuous, binary, ordinal, cardinal, or count variables (e.g., White et al., 2011). Specifically, we estimated 5 datasets based on all the variables in our models, and report estimates that are averaged across these datasets.

Analytic Strategy

Analyses were conducted in Stata 12 using the survey suite of commands that use sample weights and adjust for the clustered sampling design. The primary objective of our analyses was to better understand whether and how the group that is often excluded from analytic samples (i.e., the CRP > 10 mg/L group) systematically differs from the analytic samples typically used (i.e., the CRP ≤ 10 mg/L group) on chronic disease risk indicators. Therefore, we first tested bivariate associations of all study variables with very high CRP. Specifically, we used weighted logistic regression analyses to predict membership in the very high CRP > 10 mg/l versus the lower CRP (≤ 10 mg/L) group. Next, because indicators of chronic disease risk typically covary, we conducted a series of nested logistic regression models that sequentially added demographic, psychological, and health/reproductive behavior correlates to multivariate models (Models 1–6). Model 1 included basic demographic correlates (age, sex, race/ethnicity). Model 2 included indicators of parental education and health/health behaviors. Models 3–5 included indicators of subjects' own SES, psychological characteristics, and health behaviors, thus allowing us to approximate potential intergenerational pathways from parent SES to very high CRP via subject SES, psychological characteristics, and health behaviors. Model 6 added reproductive variables.

Model 7 added acute illness, chronic illness and medication use variables. If very high CRP was an indicator of acute inflammatory conditions/medication use only, then these variables should account for any associations observed in the previous models. Finally, Models 8–9 entered BMI and metabolic syndrome indicators. If very high CRP was an indicator of chronic inflammation and disease risk, as suggested by Ishii and colleagues (2012), then many differences between the very high and lower CRP groups should no longer be significant when BMI—a major chronic disease risk that clusters with many additional disease risk indicators—is taken into account. In a final analysis, we tested interactions between all study variables and sex, testing one interaction at-a-time.

Results

Twelve percent (*N* = 1,693) of young adults had very high CRP. This estimate is similar to the 10% reported by the CARDIA study of young adults—which was calculated after excluding participants with acute illness and current pregnancy (Ishii et al., 2012). Seventy-

six percent of the very high CRP group was female, replicating the preponderance of females in this group (Ishii et al., 2012). Looking within each sex category, 18% of females (*N*=1,297) and 6% of males (*N*=396) had very high CRP. Descriptive statistics for all study variables are reported in Table 1, showing, for example, a greater than 7 point difference in BMI, and an almost 15 cm difference in waist circumference between the very high (> 10 mg/L) and lower (≤ 10 mg/L) CRP groups. Supplement 1 further breaks down basic descriptive statistics for the CRP < 3, CRP 3–10 and CRP > 10 groups. The descriptives shown in Supplement 1 illustrate that almost all chronic disease risk indicators increase across these three CRP groups, supporting the idea that in generally healthy samples from the community very high CRP may be part of a chronic disease risk continuum.

Bivariate associations of all covariates with very high CRP (versus CRP ≤ 10mg/L) are reported in the first column of Table 2; the odds ratios were derived from weighted logistic regression analyses. The majority of covariates were associated with very high CRP. Previously identified correlates of very high CRP were replicated in this nationally representative sample of young adults, and new ones were identified (e.g., non-Asian American race; low parental education; parental smoking, diabetes and obesity; lifetime depression/anxiety diagnosis; low conscientiousness; recent surgery; diabetes; STD; high waist circumference, high cholesterol).

In Model 1, females, Hispanics, Blacks, and American Indians were over-, and Asians were under-represented in the very high CRP group. In Model 2, low parental education, and parental smoking and obesity—assessed 14 years earlier—predicted very high CRP, and attenuated the effect of American Indian ethnicity in the remaining models. In Model 3 young adult SES was significant. In this model, the odds ratio for parental education was attenuated to non-significance for the remainder of the models. In Model 4, lifetime depression/anxiety disorder and low conscientiousness predicted very high CRP. In Model 5, lower levels of alcohol use and physical activity were associated with very high CRP.

In Model 6 each reproductive variable independently predicted very high CRP. Number of children had not been significant in bivariate models (but could reflect a selection effect of healthier adults having more children here). In Model 7, acute illness, recent surgery, diabetes, and medication use were associated with very high CRP, and attenuated the effect of lifetime depression/anxiety and low conscientiousness for the remaining models. Importantly, Model 7 did not attenuate any other correlates of very high CRP to non-significance. This was also the case when acute illness, chronic illness, and medication use were added in separate steps.

In Model 8, both BMI and BMI^2 were associated with very high CRP, documenting non-linear associations. In order to interpret this effect, we re-ran Model 8 with categorical BMI indicators. Results suggested that being severely obese at BMI 35+ was most strongly associated with very high CRP (OR = 8.58). In comparison, the odds ratios for underweight (BMI< 18.5), overweight (BMI=25–29.9), and obese (BMI=30–34.9) were at 0.74, 1.80 and 2.82, respectively. Importantly, adding BMI attenuated the effects of African American race, parental smoking and obesity, and young adults' income, education and diabetes to non-significance. Thus, the associations between these six indicators of chronic disease risk and

very high CRP appeared to operate through their associations with BMI. In Model 9, waist circumference was associated with very high CRP, and attenuated the effect of BMI^2 partially, but not fully. In this final comprehensive model, several differences between the very high and lower CRP groups remained. Female sex, Hispanic ethnicity, low physical activity, fewer children, use of oral contraceptives, acute illness, recent surgery, medication use, BMI/BMI^2 and waist circumference remained associated with very high CRP.

Sex Differences Analyses

We tested sex differences in covariates by including covariate by sex interactions (one-at-a-time) in the prediction of very high CRP in Model 9. We report the significant covariate X sex interactions here; Supplement 2 also shows results from bivariate models and Model 9 for females and males separately. Several variables were protective from very high CRP in males, but not females: Asian race ($p < .001$) and being married ($p < .01$). Other variables were associated with increased risk for very high CRP in females, but not males: BMI ($p < .05$), BMI^2 ($p < .05$), use of oral contraceptives and currently being pregnant. Yet other variables were more strongly positively associated with very high CRP in males than in females: acute illness ($p < .001$), recent surgery ($p < .01$), and medication use ($p < .001$). In addition, waist circumference was positively associated with very high CRP in males, but not females ($p < .05$). The results in Supplement 2 also suggest additional potential sex differences (i.e., Hispanic and American Indian race/ethnicity as significant positive covariates of very high CRP in females only), but statistical interactions between these race/ethnicity variables and sex were not significant.

Follow Up Analyses

Sensitivity analyses excluded participants with ≥ 1 acute illness and also with ≥ 2 acute illnesses and also repeated all analyses with non-imputed datasets using list-wise deletion. The overall pattern of results did not change in these sensitivity analyses. An additional set of analyses (shown in Supplement 3) gauged changes in effect sizes that occur when the very high CRP group is excluded from analytic samples. Specifically, weighted logistic regression analyses were conducted predicting CRP ≥ 3 mg/L—the conventional cut-off for high CRP—using CRP < 3 mg/L as the comparison category. In a first set of bivariate analyses, cases with CRP > 10 mg/L were excluded. In a second set of analyses, these cases were included. We compared the odds ratios from these two sets of analyses.

The full results for the overall sample, females, and males are available in Supplement 3. As expected, the changes in odds ratios were the greatest in the female subsample. Specifically, the size of the association for the following (dichotomized) variables was underestimated by ≥ 10% when the very high CRP group was excluded (see Table 1a on p. 4 in Supplement 3): Hispanic (13%), Black (15%), American Indian (28%), parental diabetes (12%), parental obesity (11%), alcohol use (15%), surgery (21%), diabetes (34%), severe obesity (46%), high waist circumference (36%), high systolic blood pressure (11%), high cholesterol (14%). In many samples—especially those smaller than the Add Health sample—these and smaller changes in effect size could contribute to whether or not a variable emerges as a significant correlate of elevated CRP.

Discussion

Approximately 5–15% of participants in adult samples in the US exceed the CRP > 10 mg/L cut-off; 18% of females and 6% of males were classified as very high CRP in Wave IV of the National Longitudinal Study of Adolescent Health. Our analyses identified novel bivariate correlates of very high CRP in young adults, including American Indian and non-Asian American race; low parental education; parental diabetes and obesity; lifetime depression/anxiety diagnosis; low conscientiousness; recent surgery; STD; high waist circumference; and high cholesterol. Several findings from our study especially warrant discussion.

First, BMI—not acute illness, medical trauma or medication use—was the key variable that accounted for a number of differences between the very high and lower CRP groups. Indeed, consistent with previous research, severely obese young adults were over-represented in the very high CRP group (Ishii et al., 2012). BMI did not appear to be an ideal indicator of health-related adiposity in males—for whom only waist circumference (not BMI) was associated with very high CRP in final models. Notably, the health-related adiposity measures did not explain all differences between the very high and lower CRP groups. Factors accounting for these remaining differences need to be investigated, including body fat distribution, endogenous sex hormones, and also genetic and epigenetic factors.

Second, we replicated the female preponderance in the very high CRP group, and were able to partially explain it. Several variables encountered by females only (e.g., oral contraceptives, pregnancy) were associated with very high CRP. Other variables (e.g., BMI, BMI^2) were more strongly associated in females than in males. Additional factors (e.g., being Asian, married) were protective from very high CRP in males, but not females. In Add Health, almost 20% of females would be excluded when following current conventions in CRP research. Our follow-up analyses suggested that potential bias from excluding the very high CRP group is most pronounced in young adult females—a group that already suffers from under-detection of CVD and for whom mortality from CVD has declined the least in recent decades (Ford and Capewell, 2007).

Indeed, what constitutes low-grade inflammation in females and the utility of using very high CRP as an indicator of disease risk for this group needs to be re-evaluated (Ishii et al., 2012; Shanahan et al., 2013). Older females with very high CRP were 8 times more likely to have future cardiovascular events compared to their lowest CRP counterparts; these results need to be followed up with younger samples (Ridker and Cook, 2004). Our findings that acute medical conditions and medication use were more strongly associated with very high CRP in males than in females suggest that, perhaps, CRP >10 mg/L is a better indicator of acute conditions in males than in females.

A third notable finding from our study was first, preliminary evidence for intergenerational effects, especially from parental health/health behaviors to young adult BMI and very high CRP. These findings point to the possibility that the exclusion of cases with very high CRP from analytic samples could disproportionally exclude those who have had elevated chronic disease risk for at least two generations. Considering the 14-year lag between the

assessments of the parental health/health behavior predictors and offspring's very high CRP outcome, these findings also further undermine the idea that very high CRP is merely reflective of acute conditions.

Consequences of Excluding the Very High CRP Group from Analytic Samples

Our study suggests that excluding the very high CRP group from analytic samples in health research disproportionally bases findings on those with the lowest levels of chronic disease risk – with better education and health behaviors/health for at least two generations, lower BMI/waist circumference and associated disease risks, and also fewer psychological characteristics that predict increased disease risk. Very high CRP is often excluded from research because of the concern that it is indicative of "random" acute illness only. If this assumption were true, then including cases with very high CRP could "obscure any prediction of coronary" and other disease risks (p. 11, Pearson et al., 2003). Our results, however, suggest that it could, in fact, be the *exclusion* of this group that could obscure associations and the "true" size of effects between CRP and chronic disease risks—especially in females. Weakened effect sizes that result from the exclusion of very high CRP group could contribute to inconsistent patterns of covariate-CRP associations across studies (e.g., significance of associations in some, but not other studies).

How can research studies address the possibility that very high CRP may be an extension of the CRP continuum past the 10 mg/L range rather than a qualitatively different state that can simply be discarded from analytic samples? Results from analyses with and also without the very high CRP group should be reported in order to allow others to gauge differences in the resultant effect sizes of associations. Alternatively, cases with very high CRP could be incorporated in studies that can adjust analyses for acute/recent infections and medication use. In such studies, the distributions of the continuous CRP variable need to be carefully inspected considering that values of CRP > 10 mg/L can be widely dispersed. The accuracy of the high-sensitivity assay could also decline in the very high CRP range; thus, the use of categorical CRP variables may be warranted.

In clinical settings, a reasonable recommendation in response to a measurement of very high CRP is to measure CRP a second time (Pearson et al., 2003). Repeated measurements of very high CRP—that co-occur with other traditional risk factors for CVD—could be useful in flagging particularly high levels of chronic disease risk, perhaps especially in females.

Limitations

The Add Health study currently only has one assessment of CRP and thus chronicity and/or predictors of future very high CRP could not be tested. Furthermore, variables not easily assessed in field research, including total amounts and distribution of body fat, physical fitness, and dietary intake were not available. The measurement of some variables was also not ideal. For example, self-reported lifetime diagnoses are subject for forgetting and likely result in underreporting (Moffitt et al., 2009). In addition, although measures assessing chronic illness asked whether a health care provider had previously diagnosed a given illness, additional standardized, physician-verified assessments of these conditions would be preferable. Nevertheless, studies comparing physician assessments with self-assessments of

health report that the latter is an “equal or superior” predictor of later health and mortality (Ferraro and Farmer, 1999). Finally, many statistical tests were conducted in our effort to comprehensively characterize the very high CRP group, increasing the risk of chance findings. However, had we applied $p < .01$ or even $p < .001$ criteria, most correlates of very high CRP identified here—including correlates in the bivariate and in the final models—would have remained significant.

Despite these limitations, our study provides a more thorough characterization of young adults with very high CRP than has previously been possible, and suggests that a careful reconsideration of how to meaningfully include these cases in studies of the development of chronic physical and mental illness is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This research uses data from Add Health, a program project directed by Kathleen Mullan Harris and designed by J. Richard Udry, Peter S. Bearman, and Kathleen Mullan Harris at the University of North Carolina at Chapel Hill, and funded by grant P01-HD31921 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, with cooperative funding from 23 other federal agencies and foundations. Special acknowledgment is due Ronald R. Rindfuss and Barbara Entwisle for assistance in the original design. Information on how to obtain the Add Health data files is available on the Add Health website (http://www.cpc.unc.edu/addhealth). No direct support was received from grant P01-HD31921 for this analysis. Support from this work also came from NICHD (R01 HD061622-01).

Role of Funding Sources

The collection of the data used here was funded by grant P01-HD31921 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, with cooperative funding from 23 other federal agencies and foundations. No direct support was received from grant P01-HD31921 for this analysis. Support from this work also came from NICHD (R01 HD061622-01).

References

Alley DE, Seeman TE, Ki KJ, Karlamangla A, Hu P, Crimmins EM. Socioeconomic status and C-reactive protein levels in the US population: NHANES IV. Brain. Behav. Immun. 2006; 20:498–450. [PubMed: 16330181]

Baldasaro RE, Shanahan MJ, Bauer DJ. Psychometric properties of the mini-IPIP in a large, nationally representative sample of young adults. J. Pers. Assess. 2013; 95:74–84. [PubMed: 22808913]

Cushman M, Arnold AM, Psaty BM, Manolio TA, Kuller LH, Burke GL, Polak JF, Tracy RP. C-reactive protein and the 10-year incidence of coronary heart disease in older men and women: the cardiovascular health study. Circulation. 2005; 112:25–31. [PubMed: 15983251]

Ferraro KF, Farmer MM. Utility of health data from social surveys: Is there a gold standard for measuring morbidity? Am. Sociol. Rev. 1999; 64:303–315.

Ford ES, Capewell S. Coronary heart disease mortality among young adults in the U.S. from 1980 through 2002: Concealed leveling of mortality rates. J. Am. Coll. Cardiol. 2007; 50:2128–2132. [PubMed: 18036449]

Hamer M, Chida Y. Associations of very high C-reactive protein concentration with psychosocial and cardiovascular risk factors in an ageing population. Atherosclerosis. 2009; 206:599–603. [PubMed: 19339014]

Hamer M, Chida Y, Stamatakis E. Association of very highly elevated C-reactive protein concentration with cardiovascular events and all-cause mortality. Clin. Chem. 2010; 56:132–135. [PubMed: 19884487]

Harris KM, Halpern CT, Whitsel EA, Hussey JM, Tabor JW, Entzel PP, Udry JR. The National Longitudinal Study of Adolescent Health: Research Design. 2009 http://www.cpc.unc.edu/projects/addhealth/design.

Harris KM, Udry JR. 2013 http://www.icpsr.umich.edu/icpsrweb/DSDR/studies/33443.

Howard BV, Lee ET, Cowan LD, Devereux RB, Galloway JM, Go OT, Howard WJ, Rhoades ER, Robbins DC, Sievers ML, Welty TK. Rising tide of cardiovascular disease in American Indians. The Strong Heart Study. Circulation. 1999; 99:2389–2395. [PubMed: 10318659]

Ishii S, Karlamangla AS, Bote M, Irwin MR, Jacobs DRJ, Cho HJ, Seeman TE. Gender, obesity and repeated elevation of C-reactive protein: Data from the CARDIA cohort. PLoS ONE. 2012; 7:e36062. [PubMed: 22558327]

Kiecolt-Glaser JK, Gouin J, Hantsoo L. Close relationships, inflammation, and health. Neurosci. Biobehav. Rev. 2010; 35:33–38. [PubMed: 19751761]

Lakoski SG, Cushman M, Criqui M, Rundek T, Blumenthal RS, D'Agostino RBJ, Herrington DM. Gender and C-reactive protein: data from the Multiethnic Study of Atherosclerosis (MESA) cohort. Am. Heart. J. 2006; 152:593–598. [PubMed: 16923436]

McDade T, Burhop J, Dohnal J. High-sensitivity enzyme immunoassay for C-reactive protein in dried blood spots. Clin. Chem. 2004; 50:652–654. [PubMed: 14981035]

Moffitt TE, Arseneault L, Belsky D, Dickson N, Hancox RJ, Harrington H, Houts R, Poulton R, Roberts BW, Ross S, Sears MR, Thomson WM, Caspi A. A gradient of childhood self-control predicts health, wealth, and public safety. Proc. Natl. Acad. Sci. 2011; 108:2693–2698. [PubMed: 21262822]

Moffitt TE, Caspi A, Taylor A, Kokaua J, Milne BJ, Polanczyk G, Poulton R. How common are common mental disorders? Evidence that lifetime prevalence rates are doubled by prospective versus retrospective ascertainment. Psychol. Med. 2009; 40:1–11.

O'Connor MF, Bower JE, Cho HJ, Creswell JD, Dimitrov S, Hamby ME, Hoyt MA, Martin JL, Robles TF, Sloan EK, Thomas KS, Irwin MR. To assess, to control, to exclude: Effects of biobehavioral factors on circulating inflammatory markers. Brain. Behav. Immun. 2009; 23:887–897. [PubMed: 19389469]

Pearson TA, Mensah GA, Alexander RW. Centers for Disease Control and Prevention, American Heart Association. 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. 2003; 107:499–511. [PubMed: 12551878]

Reither EN, Olshansky SJ, Yang Y. New forecasting methodology indicates more disease and earlier mortality ahead for today's younger Americans. Health Aff. (Millwood). 2011; 30:1562–1568. [PubMed: 21700600]

Ridker PM. C-reactive protein and the prediction of cardiovascular events among those at intermediate risk: Moving an inflammatory hypothesis toward consensus. J. Am. Coll. Cardiol. 2007; 29:2129–2138. [PubMed: 17531663]

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; 109:1955–1959. [PubMed: 15051634]

Shanahan L, Copeland WE, Worthman C, Erkanli A, Angold A, Costello EJ. Sex-differentiated changes in C-reactive protein from ages 9 to 21: The contributions of BMI and physical/sexual maturation. Psychoneuroendocrinology. 2013; 38:2209–2217. [PubMed: 23711900]

White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat. Med. 2011; 30:377–399. [PubMed: 21225900]

Whitsel EA, Cuthbertson CC, Tziakas DN, Power C, Wener MH, Killeya-Jones LA, Harris KM. Add Health Wave IV documentation: Measures of inflammation and immune function. 2013 http://www.cpc.unc.edu/projects/addhealth/data/guides/add-healthwave-iv-documentation-measures-of-inflammation-and-immune-function.

Table 1

Means (SD) and N (weighted %) of all covariates in the lower and very high CRP groups. All estimates based on datasets created with multiple imputation.

Variable	**CRP ≤ 10 mg/L N = 11,564 87.9 %**	**CRP>10 mg/L N = 1,693 12.1 %**
Categorical Variables	***Weighted %***	***Weighted %***
Female	47%	76%
White (=Reference group)	68%	60%
Hispanic	12%	15%
Black	15%	20%
Asian	4%	1%
American Indian	2%	3%
Other	1%	1%
Parental Smoking	30%	35%
Parental Diabetes	8%	11%
Parental Obesity	22%	32%
Single (= Reference group)	35%	37%
Married	43%	43%
Cohabiting	21%	20%
Depression/Anxiety	21%	29%
Smoking	25%	23%
Currently Pregnant	3%	6%
Oral Contraceptive	15%	26%
Acute Illness	33%	48%
Recent Surgery	2%	4%
Diabetes	2%	5%
Non-diabetic Chronic Illness	29%	36%
Medication Use	29%	37%
High Cholesterol	8%	11%
Continuous Variables	***Mean***	***Mean***
Age (Years)	28.42	28.45
Parental Education	2.89	2.66
Logged Household Income	10.76	10.56
Education Level	3.06	2.91
Conscientiousness	<0.01	<0.01
Drinking	2.37	1.82
Physical Activity	1.75	1.50
Number of children	0.87	0.95
# of sexually transmitted diseases	0.30	0.40
BMI	28.36	35.66

Variable	**CRP ≤ 10 mg/L N = 11,564 87.9 %**	**CRP>10 mg/L N = 1,693 12.1 %**
Waist Circumference	96.95	111.66
Systolic Blood Pressure	124.96	125.97
Diastolic Blood Pressure	79.31	80.58

Table 2

Predicting very high CRP with weighted logistic regression models. Odds ratios (95% confidence intervals). N=13,257.

	Bivariate CRP > 10 vs. ≤ 10	(1) Demo-graphic	(2) Parental SES/Health	(3) Subject SES	(4) Pycho-logical	(5) Health Behavior	(6) Repro-ductive	(7) Illness/ Medi-cations	(8) BMI	(9) MetS Indi-cators
1. Demographic										
Age	1.01 [0.96–1.06]	1.02 [0.98–1.07]	1.01 [0.97–1.06]	1.01 [0.97–1.06]	1.01 [0.97–1.06]	1.01 [0.97–1.06]	1.03 [0.98–1.07]	1.02 [0.98–1.07]	1.02 [0.97–1.07]	1.02 [0.97–1.07]
Female[1]	3.53*** [2.96–4.21]	3.55*** [2.97–4.24]	3.55*** [2.97–4.25]	3.61*** [3.00–4.35]	3.50*** [2.91–4.21]	3.25*** [2.69–3.91]	3.11*** [2.52–3.83]	2.99*** [2.41–3.69]	2.83*** [2.29–3.50]	2.92*** [2.39–3.57]
Hispanic[2]	1.49** [1.17–1.90]	1.50** [1.18–1.90]	1.43* [1.09–1.88]	1.43** [1.10–1.86]	1.46** [1.12–1.89]	1.36* [1.06–1.75]	1.40** [1.10–1.79]	1.41** [1.11–1.79]	1.35* [1.05–1.74]	1.39* [1.08–1.79]
Black[2]	1.57*** [1.31–1.89]	1.55*** [1.28–1.87]	1.50*** [1.23–1.81]	1.39** [1.13–1.71]	1.45*** [1.17–1.78]	1.31* [1.06–1.61]	1.41** [1.14–1.73]	1.49*** [1.22–1.83]	1.16 [0.94–1.44]	1.20 [0.96–1.49]
Asian[2]	0.47** [0.27–0.82]	0.46** [0.27–0.81]	0.53* [0.30–0.92]	0.54* [0.31–0.95]	0.55* [0.32–0.97]	0.52* [0.30–0.89]	0.52* [0.30–0.90]	0.51* [0.29–0.89]	0.60* [0.37–0.98]	0.61 [0.38–1.00]
American Indian[2]	1.64* [1.04–2.59]	1.78* [1.11–2.85]	1.55 [0.99–2.42]	1.49 [0.96–2.33]	1.47 [0.94–2.30]	1.48 [0.93–2.35]	1.49 [0.93–2.40]	1.44 [0.88–2.34]	1.37 [0.85–2.20]	1.37 [0.85–2.21]
Other[2]	0.98 [0.48–1.98]	1.02 [0.52–2.03]	1.00 [0.51–1.97]	1.01 [0.51–1.98]	1.05 [0.53–2.06]	1.02 [0.52–2.00]	1.01 [0.51–2.00]	1.00 [0.51–1.94]	1.35 [0.69–2.65]	1.40 [0.72–2.69]
2. Par. Education/Health										
Parental Education	0.87*** [0.82–0.92]		0.91** [0.85–0.98]	0.95 [0.88–1.02]	0.94 [0.87–1.02]	0.96 [0.89–1.04]	0.95 [0.88–1.03]	0.95 [0.88–1.03]	1.00 [0.92–1.08]	1.00 [0.92–1.08]
Parental Smoking	1.27** [1.09–1.47]		1.26** [1.08–1.48]	1.22* [1.04–1.43]	1.21* [1.03–1.42]	1.24** [1.06–1.46]	1.27** [1.08–1.50]	1.27** [1.08–1.49]	1.13 [0.96–1.33]	1.12 [0.95–1.32]
Parental Diabetes	1.52** [1.13–2.04]		1.27 [0.93–1.74]	1.24 [0.91–1.70]	1.24 [0.91–1.70]	1.20 [0.87–1.64]	1.16 [0.85–1.59]	1.13 [0.82–1.54]	0.93 [0.67–1.28]	0.91 [0.66–1.26]
Parental Obesity	1.66*** [1.42–1.95]		1.65*** [1.39–1.95]	1.63*** [1.37–1.94]	1.62*** [1.37–1.93]	1.62*** [1.37–1.93]	1.65*** [1.39–1.95]	1.65*** [1.38–1.96]	1.01 [0.83–1.22]	0.99 [0.82–1.20]
3. Subject SES										
Household Income	0.79*** [0.73–0.85]			0.91* [0.83–0.99]	0.92 [0.84–1.00]	0.93 [0.85–1.02]	0.91* [0.83–0.99]	0.91* [0.83–0.99]	0.91 [0.82–1.01]	0.92 [0.83–1.02]
Education	0.88** [0.82–0.95]			0.92 [0.84–1.01]	0.93 [0.85–1.02]	0.94 [0.86–1.02]	0.90* [0.82–0.98]	0.90* [0.83–0.99]	0.93 [0.85–1.03]	0.94 [0.85–1.04]
Married	0.96 [0.82–1.11]			0.91 [0.77–1.09]	0.93 [0.78–1.10]	0.87 [0.73–1.04]	0.98 [0.81–1.18]	0.97 [0.80–1.18]	0.94 [0.77–1.14]	0.93 [0.76–1.13]

	Bivariate CRP > 10 vs. ≤ 10	(1) Demo-graphic	(2) Parental SES/Health	(3) Subject SES	(4) Pycho-logical	(5) Health Behavior	(6) Repro-ductive	(7) Illness/ Medi-cations	(8) BMI	(9) MetS Indi-cators
Cohabiting	0.92 [0.77–1.10]			0.87 [0.71–1.05]	0.87 [0.72–1.05]	0.87 [0.71–1.05]	0.90 [0.74–1.09]	0.88 [0.73–1.08]	0.91 [0.73–1.13]	0.91 [0.73–1.13]
4. Psychol. Char.										
Depression/Anxiety	1.55*** [1.30–1.86]				1.19* [1.00–1.41]	1.19* [1.00–1.42]	1.21* [1.01–1.43]	1.09 [0.92–1.30]	1.07 [0.89–1.28]	1.06 [0.88–1.27]
Conscientiousness	0.78** [0.67–0.90]				0.85* [0.73–0.98]	0.87 [0.75–1.00]	0.86* [0.74–0.99]	0.88 [0.76–1.02]	1.03 [0.88–1.20]	1.05 [0.89–1.22]
5. Health Beh.										
Smoking	0.87 [0.74–1.04]					0.85 [0.71–1.01]	0.88 [0.74–1.05]	0.86 [0.72–1.03]	1.01 [0.84–1.21]	1.01 [0.84–1.21]
Drinking	0.84*** [0.81–0.88]					0.92** [0.88–0.97]	0.91*** [0.87–0.96]	0.91*** [0.87–0.96]	0.94* [0.89–1.00]	0.94 [0.89–1.00]
Physical Activity	0.80*** [0.75–0.85]					0.85*** [0.80–0.92]	0.85*** [0.80–0.92]	0.86*** [0.80–0.92]	0.86*** [0.80–0.92]	0.86*** [0.80–0.92]
6. Reprod. Beh.										
Pregnant	2.37*** [1.69–3.31]						1.49* [1.06–2.09]	1.53* [1.08–2.16]	1.52* [1.05–2.20]	1.44 [0.99–2.08]
# of Children	1.06 [0.99–1.13]						0.86*** [0.79–0.94]	0.87** [0.79–0.95]	0.88** [0.80–0.97]	0.88* [0.81–0.97]
Oral Contraceptive	1.93*** [1.60–2.32]						1.33** [1.08–1.64]	1.37** [1.11–1.69]	1.75*** [1.40–2.17]	1.77*** [1.42–2.20]
7. Illness										
Acute Illness	1.91*** [1.66–2.19]							1.65*** [1.43–1.90]	1.72*** [1.48–1.99]	1.71*** [1.47–2.00]
Surgery	2.12*** [1.47–3.07]							1.82** [1.24–2.69]	1.96** [1.31–2.93]	1.94** [1.30–2.91]
Diabetes	2.31*** [1.67–3.19]							1.62** [1.14–2.31]	1.16 [0.80–1.70]	1.08 [0.73–1.61]
Chronic Illness	1.41*** [1.19–1.67]							1.01 [0.84–1.22]	0.96 [0.78–1.18]	0.96 [0.78–1.18]
STD	1.20*** [1.11–1.31]							0.94 [0.85–1.04]	0.98 [0.89–1.09]	0.98 [0.89–1.09]
Medications	1.48*** [1.29–1.69]							1.33*** [1.15–1.54]	1.36*** [1.17–1.59]	1.35*** [1.16–1.57]

	Bivariate CRP > 10 vs. ≤ 10	(1) Demo-graphic	(2) Parental SES/Health	(3) Subject SES	(4) Pycho-logical	(5) Health Behavior	(6) Repro-ductive	(7) Illness/ Medi-cations	(8) BMI	(9) MetS Indi-cators
8. BMI										
BMI	1.21*** [1.14–1.29]								1.20*** [1.14–1.26]	1.14*** [1.07–1.21]
BMI[2]	0.99** [0.99–0.99]								0.99** [0.99–0.99]	0.99* [0.99–0.99]
9. MetS Indicators										
Waist Circumference	1.04*** [1.04–1.05]									1.02*** [1.01–1.02]
Systolic BP	1.01 [1.00–1.01]									0.99 [0.98–1.00]
Diastolic BP	1.01 [1.01–1.02]									1.01 [1.00–1.02]
Cholesterol	1.53** [1.18–1.99]									1.09 [0.80–1.48]

*$p < 0.05$,

**$p < 0.01$,

***$p < 0.001$

[1]Male=reference group

[2]White=reference group

MetS=Metabolic Syndrome; STD=Sexually transmitted disease; BP=Blood pressure

Psychoneuroendocrinology. Author manuscript; available in PMC 2015 February 01.