# Is very high C-reactive protein in young adults associated with indicators of chronic disease risk?

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Summary
*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 field-workers assessed BMI, waist circumference, blood-pressure, and medication use, and collected bloodspots from which high-sensitivity CRP (hs-CRP) was assayed.
*Results:* Logistic regression analyses 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.
*Conclusion:* Especially among females, the exclusion of cases with very high CRP could result in an underestimation of "true" associations of CRP with both, chronic disease risk indicators and morbidity/mortality. In many instances, very high CRP could represent an extension of the lower CRP range when it comes to chronic disease risk.
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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 during adulthood (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.

# 1. Correlates of very high CRP

## 1.1. 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.

## 1.2. 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.

## 1.3. 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) on CRP, 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.

# 2. Methods and materials

## 2.1. 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 30 students enrolled. 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 in the Add Health documentation (Whitsel et al., 2013). Dried blood spots were mailed to and assayed at the University of Washington Department of Laboratory Medicine. Written consent was obtained from parents/guardians (Wave I) and young adults (Wave IV); written assent was obtained from adolescents (Wave I).

## 2.2. Assessment

### 2.2.1. C-reactive protein (Wave IV)
An in-depth documentation of the Add Health hs-CRP assay and quality control is 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 ($r = 0.98$) 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 ($0 = \leq 10$ 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.

### 2.2.2. Potential covariates of very high CRP
_Demographic variables_. Dummy variables coded different racial/ethnic groups (assessed at Wave I): 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 $0 = \leq 8th$ _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 _subject's 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-International Personality Item Pool (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 variable_ 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.

## 2.3. Missing data

$N$ = 1640 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., $N$ = 1802 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.

## 2.4. 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) in terms of 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 parental 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 and health/health behaviors 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.

## 3. Results

Twelve percent ($N$ = 1693) of young adults in the analytic sample 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 ($N$ = 1297) 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 increased 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 ≤ 10 mg/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).

Table 2 also reports results from multivariate analyses. 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

**Table 1**  Weighted % and means 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 $N$ = 1693 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 |
| Alcohol use | 2.37 | 1.82 |
| Physical activity | 1.75 | 1.50 |
| Number of children | 0.87 | 0.95 |
| No. of sexually transmitted diseases | 0.30 | 0.40 |
| Body mass index (BMI) | 28.36 | 35.66 |
| Waist circumference | 96.95 | 111.66 |
| Systolic blood pressure | 124.96 | 125.97 |
| Diastolic blood pressure | 79.31 | 80.58 |

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.

### 3.1. 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 significant covariate by 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 ($p < 0.001$) and being married ($p < 0.01$). Other variables were associated with increased risk for very high CRP in females, but not males: BMI ($p < 0.05$), BMI$^2$ ($p < 0.05$), 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 ($p < 0.001$), recent surgery ($p < 0.01$), and medication use ($p < 0.001$). In addition, waist circumference was positively associated with very high

**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) Demographic | (2) Parental SES/health | (3) Subject SES | (4) Psychological | (5) Health behavior | (6) Reproductive | (7) Illness/ medications | (8) BMI | (9) MetS indicators |
|---|---|---|---|---|---|---|---|---|---|---|
| **(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) Parental 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] |
| 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) Psychological characteristics** | | | | | | | | | | |
| 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 behavior** | | | | | | | | | | |
| 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] |
| Alcohol use | 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] |

**Table 2** (*Continued*)

| | Bivariate CRP > 10 vs. ≤10 | (1) Demographic | (2) Parental SES/health | (3) Subject SES | (4) Psychological | (5) Health behavior | (6) Reproductive | (7) Illness/ medications | (8) BMI | (9) MetS indicators |
|---|---|---|---|---|---|---|---|---|---|---|
| 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) Reproductive behavior** | | | | | | | | | | |
| 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] |
| No. 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] |
| **(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 [0.99–1.01] | | | | | | | | | 0.99 [0.98–1.00] |
| Diastolic BP | 1.01*** [1.01–1.02] | | | | | | | | | 1.01 [0.99–1.02] |
| Cholesterol | 1.53** [1.18–1.99] | | | | | | | | | 1.09 [0.80–1.48] |

MetS = Metabolic syndrome; STD = sexually transmitted disease; BP = blood pressure.

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.
[1]Male = Reference group.
[2]White = Reference group.

CRP in males, but not females ($p < 0.05$). 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.

## 3.2. Follow up analyses

Sensitivity analyses excluded participants with $\geq 1$ acute illness and also with $\geq 2$ 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 $\geq 3$ 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 greatest in the female subsample. Specifically, the size of the association for the following (dichotomized) variables was underestimated by $\geq 10\%$ in females when the very high CRP group was excluded (see Table 1a on pg. 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.

## 4. 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/ethnicity; 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 with very high CRP 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 with CRP data 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.

## 4.1. 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. 506, Pearson et al., 2003). Our results, however, suggest that in research studies 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 the 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 cut-off 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 distribution of the continuous CRP variable needs 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. Furthermore, the possibility of participants not being aware of or failing to report recent illness needs to be carefully considered.

Clinical settings have the option to repeat CRP measurements two weeks later, and 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.

### 4.2. 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 to forgetting and likely result in under-reporting (e.g., 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 (p. 303, 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 $p < 0.01$ or $p < 0.001$ 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.

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### Conflict of interest statement

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

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### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2013.10.019.

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