



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

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