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Short Communication

C-reactive protein and temperament: An instrumental variable analysis

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ABSTRACT

Background: Temperament is associated with circulating inflammatory biomarkers, such as C-reactive protein (CRP), which has been associated with various health conditions, including depression. This study aims to investigate whether genetic disposition for increased circulating CRP concentration may influence temperament over the life-course.

Methods: Using a longitudinal cohort that began in 1980—the Cardiovascular Risk in Young Finns Study (YFS)—we included 920 participants (59.8% female) aged 3–12 years old at baseline (childhood), and the same participants again at ages 30–39 years old (adulthood) in this study. We used both ordinary least-squares regression (OLS linear regression) and instrumental variable (IV) regression to assess associations between CRP concentration and temperament dimensions (negative emotionality, activity, and sociability). To represent genetically determined risk for increase in circulating CRP concentration, we calculated a weighted genetic risk score (GRS) which reflects risk for increased circulating CRP concentration.

Results: In OLS linear regression analyses, we found that increased circulating CRP concentration in childhood was associated with slightly higher scores for sociability in childhood (19% increase, CI = 7–32%) and adulthood (13% increase, CI = 2–27%), and lower activity scores in adulthood (15% decrease, CI = 3–25%). For all IV regressions, there were no apparent associations between GRS and temperament in either childhood or adulthood (all $p>0.3$). The Durbin-Wu-Hausman test for endogeneity produced p-values (all>0.05) that suggest there is no evidence for disagreement between the OLS and IV estimates.

Conclusions: We found no clear evidence for an association of GRS for elevated CRP with childhood or adulthood emotionality, activity, or sociability, although circulating CRP was associated with some of these traits.

1. Introduction

Inflammation and immune system activation have important roles in defence against infection and tissue damage. Recent research suggests that inflammatory processes are also associated with certain behaviours and temperament traits. Epidemiological studies have reported that individuals with elevated circulating concentrations of C-reactive protein (CRP: a biomarker of systemic inflammation) demonstrate increased harm avoidance and decreased self-directedness. In interventional studies, experimentally-induced elevation in CRP has been associated with subsequent social withdrawal behaviour (Eisenberger et al., 2017). A longitudinal observational study found that negative emotionality and effortful control predicted elevated CRP concentrations in adolescents (Nelson et al., 2018). One mechanism that could link CRP and inflammation to temperament traits is stress: for example, individuals with certain temperament traits (e.g. high emotionality) may be particularly sensitive to stress, which in turn is associated with chronic inflammation and increased CRP.

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Based on the currently available evidence, the long-term associations of inflammation with temperament are unclear. Also, though many studies in this area adjusted their estimates for potential confounders (e.g. infection and depressive symptoms), it is possible that some of the reported findings have been influenced by disease and lifestyle-related factors (e.g. smoking). Through exploring the role of genetically determined inflammatory activity on behaviour, we may also shed light on the contribution of environmental factors on influencing behaviour. The aim of our investigation was to examine the association of CRP with temperament dimensions emotionality, activity and sociability in childhood and adulthood, using a genetic risk score as an instrument for CRP to overcome potential confounding from environmental factors.

2. Methods

We used data from the Cardiovascular Risk in Young Finns Study (YFS), a longitudinal cohort study that followed participants from childhood (1980) to adulthood (2007) (Raitakari et al., 2008). Individuals were included in our analyses if they had complete data on age, sex, and childhood as well as adulthood temperament measures. Data on baseline (childhood) circulating CRP was available for 1022 individuals and data on GRS for 1115 individuals. Participants with CRP values outside of the normal range (0.01-10.0 mg/L, n = 25) (Pearson et al., 2003) and those with missing data on temperament measures (n = 1121) were excluded (Fig. 1).

Temperament dimensions (emotionality, activity, and sociability) were measured using questionnaires adapted from the Health Examination Survey, following Buss and Plomin's theory of temperament (Wells, 1980). Childhood temperament was assessed at study baseline (when the participants were 3–12 years old) and adulthood temperament at follow-up (at age 30–39 years). Circulating CRP concentration (mg/L) was quantified from baseline blood samples using a turbidimetric immunoassay (Wako Chemicals, Neuss, Germany) (Juonala et al., 2006). At time of blood collection, participant's caregivers were asked about the health of the participant—all indicated that the participant was well.- Genotyping was done using Illumina Human 670 k BeadChip and genotypes called using Illuminus clustering algorithm. Genotype imputation was performed using Minimac3 and 1000G phase3 reference set on Michigan Imputation Server (Fuchsberger et al., 2015). Genetic risk score (GRS) was calculated using R-package predictABEL (Kundu et al., 2011), and relfects a weighted calculation of that are associated with elevated CRP. A weighted genetic risk score (GRS) was calculated using R-package predictABEL(Kundu et al., 2011), which represents a sum of short nucleotide polymorphism (SNP) values weighted by effect size based on large scale genome-wide association studies done by Ligthart and colleagues (Ligthart et al., 2018).

We used ordinary least-squares (OLS) linear regression to examine the associations of log-transformed circulating CRP with temperament dimensions. In order to maximize statistical power, we conducted separate complete-case analyses for each temperament dimension and covariates. Thus, each model was based on data from participants who had complete data for the relevant temperament dimension, CRP (circulating or GRS) and covariates (Fig. 1). The direction of the associations between CRP and temperament was examined using instrumental variable (IV) regression, with the GRS as an instrument for CRP. This approach is based on the assumption that the GRS—in being associated with circulating CRP concentrations but not with environmental and behaviour-related confounders, and exerting an effect on temperament dimensions only through its effect on CRP—can be used as an instrument for circulating CRP (Burgess and Thompson, 2013). IV regression was implemented using the two-stage least squares estimator, with the Stata command *ivregress* 2sls. The strength of the instrument was assessed using the F-statistic. We used Durbin-Wu-Hausman test to examine whether the OLS and IV estimates differed.

Covariates we examined were age, sex, BMI, heart condition, diabetes, convulsions, atopic dermatitis, allergic rhinitis, asthma, repeat urinary tract infection (UTI). Associations of covariates with CRP, GRS, and childhood and adulthood temperament scores were investigated using linear regression; covariates that were associated with both exposure (circulating CRP concentration and/or CRP genetic risk score) and outcome (childhood or adulthood temperament dimensions) in the unadjusted analyses, with a p-value <0.1, were included in the multivariable models. All analyses were performed using Stata IC 15.1 (Stata Corporation, College Station, Texas, United States).

3. Results

The analyses of circulating CRP were based on up to 989 individuals with these data available, and the instrumental variable analyses were based on up to 920 individuals with data on GRS. All participants included in the analyses had complete data on age, sex, and a temperament measures in both childhood and adulthood (Fig. 1). A small proportion (<6%) had significant health conditions (e.g. heart condition, diabetes, asthma or recurrent infections) at baseline. Age, sex and BMI

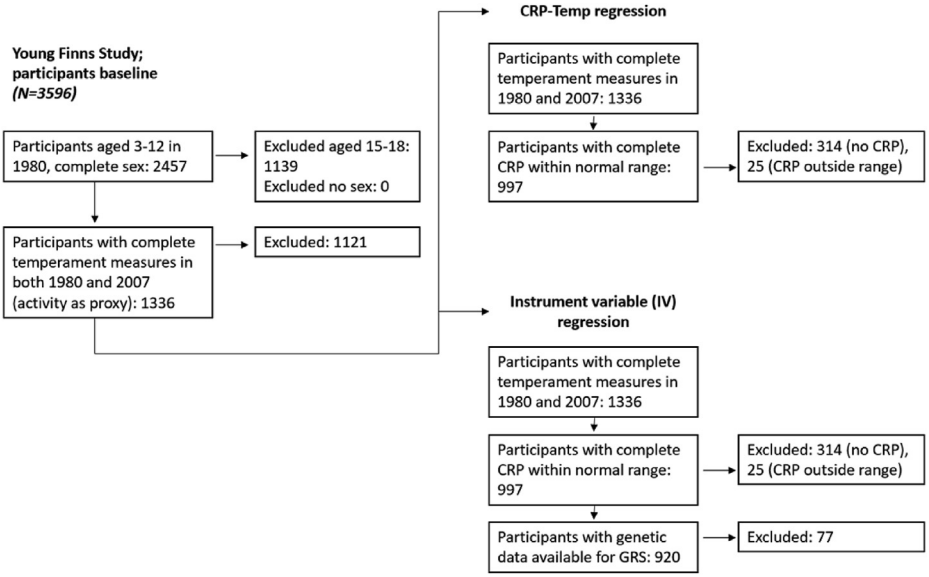

Fig. 1. Participant flow chart.

were associated with CRP and temperament dimensions, and multivariable models were adjusted for these covariates. Baseline health conditions were not associated with CRP, GRS, or temperament dimensions at $p<0.1$ level, therefore, multivariable models were not adjusted for these. All participants' circulating CRP concentrations were within the normal range mean: 0.63 mg/L; 95% CI: (0.55-0.71) (Table 1).

We found no clear evidence for an association between circulating CRP and childhood emotionality or activity (Table 1). Increased circulating CRP concentrations were associated with slightly higher scores for sociability in childhood. In adulthood, circulating CRP was unrelated to emotionality. Higher circulating CRP was associated with lower activity and higher sociability in adulthood.

The IV analyses provided no evidence for associations of GRS with either childhood or adulthood temperament dimensions (Table 1). The F-statistics (ranging from 36.1 to 40.8) suggested that the GRS was a reasonably strong instrument for CRP. Durbin-Wu-Hausman test p-values (all>0.05) provided no evidence for disagreement between the OLS and IV estimates.

Table 1
Summary of associations of CRP with temperament dimensions.

Variable summary	
CRP	*Mean (95% CI)*
Circulating CRP (mg/L) at baseline	0.63 (0.55–0.71)
CRP GRS (n = 920)	1.88 (1.87–1.90)
Temperament	*Mean (95% CI)*
Childhood temperament dimensions	
Negative Emotionality (n = 886)	1.07 (1.06–1.08)
Activity (n = 920)	2.04 (2.00–2.08)
Sociability (n = 894)	2.47 (2.42–2.51)
Adulthood temperament dimensions	
Negative Emotionality (n = 886)	2.51 (2.47–2.54)
Activity (n = 920)	3.05 (3.01–3.09)
Sociability (n = 894)	3.31 (3.27–3.36)
Covariates	
Sex (number female, %) (n = 920)	550 (59.78)
Age at baseline (mean, SD years) (n = 920)	7.87 (3.32)
BMI (mean, SD) (n = 913)	16.55 (2.21)
Ordinary linear regression analyses	
Associations of circulating CRP with temperament dimensions (adjusted)	*Coefficient (95% CI)*
Childhood	
Emotionality (n = 959)[a]	0.95 (0.61–1.48)
Activity (n = 989)[b]	0.94 (0.83–1.06)
Sociability (n = 969)[c]	**1.19 (1.07–1.32)**
Adulthood	
Emotionality (n = 959)[a]	0.95 (0.83–1.09)
Activity (n = 997)[a]	**0.85 (0.75–0.97)**
Sociability (n = 969)[c]	**1.13 (1.02–1.27)**
Instrumental variable analyses	
Associations of GRS with temperament dimensions	*Coefficient (95% CI)*
Childhood	
Emotionality (n = 886)	0.98 (0.93–1.03)
Activity (n = 920)	1.02 (0.87–1.19)
Sociability (n = 894)	0.98 (0.80–1.18)
Adulthood	
Emotionality (n = 886)	0.99 (0.85–1.16)
Activity (n = 920)	1.02 (0.88–1.19)
Sociability (n = 894)	0.92 (0.76–1.11)

Notes to Table 1: CI: confidence interval. GRS: genetic risk score. SD: standard deviation.
[a] Adjusted for sex.
[b] Adjusted for age and BMI.
[c] Adjusted for age and sex.

4. Discussion

In our analyses, we found no evidence for an association of the CRP genetic risk score with childhood or adulthood emotionality, activity, or sociability. This suggests that subsequent associations between CRP and temperament are unlikely to be genetically determined. On the other hand, we found that higher baseline circulating CRP was associated with higher sociability in childhood and adulthood, and lower activity in adulthood.

Our findings require cautious interpretation. It is possible that they are chance findings or represent residual confounding from unknown or unmeasured confounders. Other possibilities are that the elevated circulating CRP among individuals with certain temperament traits reflect behaviour-related factors or unmeasured underlying disease.

Our findings regarding emotionality and CRP differ from previous studies' reports of elevated circulating CRP being associated with emotionality and social withdrawal (Eisenberger et al., 2017; Nelson et al., 2018). For our findings on sociability, an association of higher baseline circulating CRP and sociability in childhood could be reflective of higher levels of immune system activity to counter the increased exposure to pathogens as consequence of increased social contact. Increased interferon-gamma—another cytokine involved in immune response—has been postulated to be protective factor for those with more social contacts (Leschak and Eisenberger, 2019). Social exclusion and loneliness have been associated with elevated CRP (Leschak and Eisenberger, 2019). However, a systematic review and meta-analysis has found the relationship between social isolation and CRP less clear and inconsistent across the literature (Smith et al., 2020). We did not find an association between lower sociability and elevated CRP. If lower sociability is a temperamental disposition, then participants with lower sociability may desire to be less sociable, therefore, the decreased social interaction would not be appraised as threat and would not induce a state of elevated CRP. Regarding temperamental activity, the observed association of higher baseline CRP and lower temperamental activity in adulthood could reflect sedentary behaviour, or a long-term health condition that reduces physical activity, which may be marked by increased CRP and low temperamental activity. While temperamental activity should not be confused with physical activity, lower extremes of temperamental activity could be a proxy for individuals who are generally more sedentary and low on energy (Kushner et al., 2006; Wium-Andersen et al., 2013).

Taken together, our findings and those of previous studies may reflect an association between inflammatory processes and certain behaviours (Eisenberger et al., 2017), rather than a link between inflammation and temperament.

An important strength of our investigation was that we used prospectively collected data with emotionality, activity and sociability measured in childhood and adulthood. It is unlikely that population stratification has biased our findings, for although CRP varies by ethnicity (Shah et al., 2010), our study population is genetically homogeneous (Kääriäinen et al., 2017). The modest sample size (just over 900 individuals) is a limitation, as it reduces the precision of the estimates. It is also possible that excluding individuals who did not have data available on childhood and adult temperament measures has introduced bias to our analyses if those with incomplete data had temperament traits that systematically differed from those of our study population. However, we did not consider it reasonable to attempt to impute temperament data based on covariates.

5. Conclusion

We found no clear evidence for an association of GRS for elevated CRP with childhood or adulthood emotionality, activity, or sociability, although circulating CRP was associated with some of these traits.

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Ethics statement

Cardiovascular Risk in Young Finns Study precedes the current legislation on ethics in medical research, and no formal ethics committee approval was required at study baseline in 1980. In 2007, Cardiovascular Risk in Young Finns Study was approved by Varhais-Suomi Hospital Intermunicipal ethics committee. At study baseline, all participants and their parents/carers received written information about the aims and purpose of the study and the use and storage of the data collected and were told in writing that participation was voluntary. Agreeing to take part in the baseline examination was taken to indicate informed consent.

Declaration of competing interest

None declared.

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