

# Association of Adverse Experiences and Exposure to Violence in Childhood and Adolescence With Inflammatory Burden in Young People

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**IMPORTANCE** Childhood stress exposure is associated with inflammation as measured by C-reactive protein (CRP) and interleukin 6 (IL-6). However, findings are inconsistent and effect sizes are small. The addition of soluble urokinase plasminogen activator receptor (suPAR), a new biomarker of chronic inflammation, may improve measurement of stress-related inflammatory burden.

**OBJECTIVES** To assess whether exposure to adverse experiences, stress, and violence is associated with an increase in suPAR levels in young people and to test the hypothesis that measuring suPAR in addition to CRP or IL-6 levels improves the assessment of the inflammatory burden associated with early-life stress.

**DESIGN, SETTING, AND PARTICIPANTS** This cohort study included 1391 participants from a 1994 to 1995 birth cohort of twins from the nationally representative Environmental Risk Longitudinal Twin Study in the United Kingdom. Participants were followed up until 18 years of age (93% retention). Plasma samples were analyzed in July 2018, and statistical analysis was performed from October 1, 2018, to May 31, 2019.

**EXPOSURES** Adverse childhood experiences and childhood and adolescent experience of stress and violence exposure.

**MAIN OUTCOMES AND MEASURES** Plasma CRP, IL-6, and suPAR levels at 18 years of age.

**RESULTS** Among 1391 young people (mean [SD] age, 18.4 [0.36] years; 733 [52.7%] female), those who had been exposed to stressful experiences had elevated suPAR levels by 18 years of age after controlling for sex, body mass index, and smoking: 0.03-ng/mL (95% CI, 0.01-0.05 ng/mL) increase in suPAR per each additional adverse childhood experience, 0.09-ng/mL (95% CI, 0.01-0.17 ng/mL) increase in suPAR per each additional severe childhood experience of stress or violence, and 0.04-ng/mL (95% CI, -0.02 to 0.10 ng/mL) increase in suPAR per each additional severe adolescent experience of stress or violence. Individuals exposed to multiple types of violence in both childhood and adolescence had 0.26-ng/mL (95% CI, 0.07-0.45 ng/mL) higher suPAR levels compared with children who did not experience stress or violence. These stress-exposed young people were significantly more likely to have elevated suPAR levels at 18 years of age even if they did not have elevated CRP or IL-6 levels. Measuring suPAR in addition to CRP or IL-6 increased the association between stress exposure and inflammatory burden. For example, after adjusting for CRP and IL-6 levels, each additional adverse childhood experience was associated with a 0.05-mL (95% CI, 0.03-0.07 ng/mL) increase in suPAR, each additional severe childhood experience of stress or violence was associated with a 0.14-ng/mL (95% CI, 0.06-0.22 ng/mL) increase in suPAR, and each additional severe adolescent experience of stress or violence was associated with a 0.10-ng/mL (95% CI, 0.04-0.16 ng/mL) increase in suPAR.

**CONCLUSIONS AND RELEVANCE** The results suggest that adult inflammation is associated with childhood exposure to stress. Adding information about suPAR to traditional biomarkers of inflammation may improve the measurement of inflammatory burden associated with exposure to stress and violence.

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Exposure to adverse experiences, stress, and violence during childhood and adolescence is associated with elevated risk of physical and mental health problems in adulthood,<sup>1</sup> many of which have inflammatory origins. Inflammation could constitute one of the underlying mechanisms responsible for the biological embedding of childhood stress, indicating an association between exposure to early-life adversity and adverse health outcomes in later life.<sup>2</sup>

C-reactive protein (CRP) and interleukin 6 (IL-6) are among the most commonly measured biomarkers of inflammation.<sup>3</sup> Different types of adverse experiences have been associated with increased CRP and IL-6 levels,<sup>4</sup> including maltreatment,<sup>5,6</sup> bullying,<sup>7-9</sup> and sexual abuse.<sup>10</sup> However, findings are not consistent; several studies report nonsignificant associations,<sup>4,11,12</sup> and not all associations were found after controlling for the confounding effects of smoking or obesity.<sup>10,13</sup> The Dunedin Longitudinal Study<sup>14</sup> recently found that exposure to childhood risk factors, including adverse childhood experiences (ACEs), was associated with higher levels of a novel biomarker of inflammation, soluble urokinase plasminogen activator receptor (suPAR), in adults independently of smoking and body mass index (BMI).

suPAR is released to the bloodstream during proinflammatory conditions when the membrane-bound receptor uPAR is cleaved from the surface of immunologically active cells.<sup>15</sup> Plasma levels of suPAR are thought to reflect a person's overall level of immune activity. Elevated suPAR levels are observed in many diseases and pathologic conditions<sup>16-19</sup> and are associated with development and progression of disease, adverse clinical outcomes, and mortality.<sup>20,21</sup> High suPAR levels are also positively correlated with CRP and IL-6 in general and patient populations.<sup>14,22</sup> Whereas CRP is an acute-phase reactant and a marker of acute inflammation and infections,<sup>23</sup> suPAR appears to be less affected by acute conditions.<sup>24</sup> Of interest, suPAR is associated with disease and mortality independent of CRP,<sup>21,25</sup> the criterion standard marker of inflammation, suggesting that combined use of CRP and suPAR may provide a more accurate estimate of inflammatory burden by combining information about acute and chronic inflammation. Less is known about how suPAR compares with IL-6. Interleukin 6 is an important cytokine with proinflammatory or anti-inflammatory properties depending on the specific immunologic context. In addition to the immunologic functions of IL-6 in the acute-phase response, infections, inflammation, and cancer, IL-6 exerts multiple pleiotropic effects on other cell types, thereby regulating metabolism, hematopoiesis, and the neuroendocrine system.<sup>26</sup> Although suPAR has been found to be associated with clinical outcomes independent of IL-6,<sup>25</sup> whether the combined use of IL-6 and suPAR also provides additive information about inflammatory burden is unknown.

This report extends a previous study<sup>14</sup> by investigating the association between suPAR and exposure to adverse experiences, stress, and violence during childhood and adolescence in the population-representative Environmental Risk (E-Risk) Longitudinal Twin Study followed up to 18 years of age. We assessed multiple types of adverse experiences during childhood and adolescence and cumulatively across the first 2 decades of life inside

## Key Points

**Question** Is exposure to adverse experiences, stress, and violence in childhood associated with an increase in blood levels of the inflammatory biomarker soluble urokinase plasminogen activator receptor in young people?

**Findings** In this cohort study of 1391 young people followed up to 18 years of age in the United Kingdom, exposure to adverse experiences, stress, and violence during childhood or adolescence was associated with elevated levels of the soluble urokinase plasminogen activator receptor at 18 years of age, even in children who did not have elevated C-reactive protein or interleukin 6 levels.

**Meaning** The findings suggest that stress-related inflammation begins at a relatively young age, and the measurement of this inflammatory burden may be improved by adding information about soluble urokinase plasminogen activator receptor to traditional biomarkers of inflammation.

and outside the family, including emotional, physical, and sexual abuse; emotional and physical neglect; peer bullying; cyber bullying; and crime violence. In addition to evaluating these experiences in relation to suPAR, we compared the association of stress and violence exposure with CRP and IL-6 levels and tested whether adding suPAR to the measurement of CRP or IL-6 levels provides additional information about inflammation associated with stress and violence exposure.

## Methods

### Sample

This cohort study included members of the E-Risk Longitudinal Twin Study, which tracks the development of a 1994-1995 birth cohort of 2232 British children.<sup>26</sup> In brief, the E-Risk Longitudinal Twin Study sample was constructed from 1999 to 2000, when 1116 of 1203 eligible families (92.8%) with same-sex 5-year-old twins participated in home-visit assessments. This sample comprises 1242 (55.7%) monozygotic (MZ) and 990 (44.4%) dizygotic (DZ) twins; sex was evenly distributed within zygosity (1140 [51.1%] female). Home visits were conducted when participants were aged 5, 7, 10, 12, and, most recently, 18 years of age ( $n = 2066$  [92.6%]). At 18 years of age, each twin was interviewed by a different interviewer. The Joint South London and Maudsley and the Institute of Psychiatry research ethics committee approved each phase of the study. Parents gave written informed consent, and twins gave oral assent between 5 and 12 years of age and then written informed consent at 18 years of age. Plasma samples were analyzed in July 2018, and statistical analysis was performed from October 1, 2018, to May 31, 2019.

The sample represents socioeconomic conditions in the United Kingdom, as reflected in the families' distribution on a neighborhood-level socioeconomic index (ACORN [A Classification of Residential Neighborhoods], developed by CACI Inc for commercial use): 25.6% of E-Risk Longitudinal Twin Study families live in wealthy achiever neighborhoods compared with 25.3% nationwide, 5.3% vs 11.6% live in urban prosperity neighborhoods, 29.6% vs 26.9% live in comfortably off

neighborhoods, 13.4% vs 13.9% live in moderate means neighborhoods, and 26.1% vs 20.7% live in hard-pressed neighborhoods. The E-Risk Longitudinal Twin Study underrepresents urban prosperity neighborhoods because such households are often childless.

### Exposure to Adverse Experiences in Childhood and Adolescence

We assessed 4 forms of stressful experiences in childhood: (1) ACEs, as introduced by the US Centers for Disease Control and Prevention ACEs Study<sup>1</sup> and expanded by the Philadelphia Urban ACE Survey<sup>27</sup>; (2) exposure to 6 types of severe childhood experiences of stress or violence between birth to 12 years of age; (3) exposure to 7 types of severe adolescent experiences of stress or violence at 12 to 18 years of age; and (4) exposure to cumulative stress and violence experiences throughout the life, as determined by applying latent class analysis (LCA) to stress and violence experiences data in childhood and adolescence. These measures have been reported previously<sup>28-31</sup> and are described in the **Box** and detailed in eMethods 1 to 4 in the [Supplement](#).

### Inflammatory Biomarkers

Venous blood was collected from 1700 of the 2066 participants (82.3%) with EDTA tubes. Tubes were spun at 2500g for 10 minutes and plasma samples obtained. Samples were stored at -80°C. Plasma samples were available for 1448 participants. Plasma CRP (high-sensitivity CRP) was measured using enzyme-linked immunosorbent assay (ELISA) (Quantikine ELISA Kit DCRP00, R&D Systems) following the manufacturer's protocol. The coefficient of variation was 5.6%. Plasma IL-6 levels were measured using ELISA (Quantikine HS ELISA Kit HS600C, R&D Systems) following the manufacturer's protocol. The coefficient of variation was 12.6%. Plasma suPAR levels were analyzed using ELISA (suPARnostic AUTO Flex ELISA, ViroGates A/S) following the manufacturer's protocol. The coefficient of variation was 6%.

### Other Variables Associated With Inflammation

When participants were 18 years of age, we recorded BMI (calculated as weight in kilograms divided by height in meters squared), body temperature, current daily smoking, current illness and injury (eTable 1 in the [Supplement](#)), and use of anti-inflammatory medication (corticosteroids) within the past 2 weeks. Children exposed to ACEs or stress and violence may also be exposed to unsanitary homes, which could be associated with elevated suPAR levels and potentially confound associations between ACEs or stress and violence exposure and suPAR level. The cleanliness of the homes was assessed when children were 12 years by home visitors answering the question, "Are visible rooms of the house clean?" (no, somewhat, or yes).

Childhood socioeconomic status (SES) was defined through a standardized composite of parental income, educational level, and occupation. The 3 SES indicators were highly correlated ( $r = 0.57-0.67$ ) and loaded onto 1 latent factor. The population-wide distribution of the resulting factor was divided in tertiles for analyses.<sup>35</sup>

### Box. Description of Study Measures

#### ACEs

Twenty ACEs were measured during childhood and adolescence up to 17 years of age: 10 conventional ACEs, corresponding to the 10 subcategories of childhood adversities introduced by the CDC Adverse Childhood Experiences Study,<sup>1</sup> and 10 expanded ACEs, identified from the results from the Philadelphia Urban ACE Survey and routine activity theory, as previously described.<sup>28</sup> The 10 conventional ACEs included physical abuse, sexual abuse, emotional abuse, physical neglect, emotional neglect, domestic violence exposure, household substance abuse, family history of mental illness, loss of a parent (parental death, separation, or divorce), and parental antisocial behavior. The 10 expanded ACEs included experiencing bullying, living in foster care, low childhood socioeconomic status, peer substance use, low parental monitoring (as evaluated by parents), low parental monitoring (as evaluated by children), participant-perceived unsafe neighborhood, high neighbor crime violence measured via neighbor survey, neighborhood rated as unsafe through systematic social observation, and high-crime neighborhood measured through official police records. Measurement details are provided in eMethods 1 in the [Supplement](#). Among children in this study, 197 (14.2%) had no ACEs, 238 (17.1%) had 1 ACE, 229 (16.5%) had 2 ACEs, and 727 (52.3%) had 3 or more ACEs.

#### Severe Childhood Experiences of Stress or Violence

Exposure to 6 types of severe childhood experiences of stress or violence was assessed repeatedly when the children were 5, 7, 10, and 12 years of age, including exposure to domestic intimate partner violence between the mother and her partner, frequent bullying by peers, physical maltreatment by an adult, sexual abuse, emotional abuse and neglect, and physical neglect. Exposures were coded from 12-year dossiers for each child that comprised information from home visit staff, mothers, children, family physicians, and child protection interventions. Each exposure during childhood was coded on a 3-point scale (0 indicating no exposure, 1 indicating probable or less severe exposure, and 2 indicating definite or severe exposure). Following the guidelines by Finkelhor et al,<sup>32</sup> we operationalized severe childhood experiences of stress or violence as the total number of adverse event types experienced by a child. All severe childhood experiences or stress or violence were summed. Measurement details are provided in eMethods 2 in the [Supplement](#). Among children in this study, 1004 (72.2%) had no severe childhood experiences of stress or violence, 298 (21.4%) had 1 experience, 59 (4.2%) had 2 experiences, and 30 (2.2%) had 3 or more experiences.

#### Severe Adolescent Experiences of Stress or Violence

Severe adolescent experiences of stress or violence between the ages of 12 and 18 years were assessed at age 18 years of age when the twins were interviewed using the JVQ-R2,<sup>33,34</sup> adapted as a clinical interview.<sup>29</sup> The adapted JVQ-R2 comprised 45 questions covering 7 different forms of adverse experience: crime violence, peer or sibling violence, cyber bullying, sexual abuse, maltreatment, family violence, and neglect. Like severe childhood experiences of stress or violence experiences, each exposure during adolescence was coded on a 3-point scale (0 indicating no exposure, 1 indicating probable or less severe exposure, and 2 indicating definite or severe exposure). Severe adolescent experiences of stress or violence were derived by summing the number of severe adolescent experiences of stress or violence. Measurement details are provided in eMethods 3 in the [Supplement](#). In this study,

(continued)

**Box. (continued)**

887 adolescents (63.8%) had no severe adverse experiences, 275 (19.8%) had 1 experience, 131 (9.4%) had 2 experiences, and 98 (7.0%) had 3 or more experiences.

**Cumulative Stress and Violence Experiences**

Three groups of stress or violence experiences were identified with latent class analysis combining the 6 childhood and the 7 adolescent measures of severe experiences of stress or violence, as previously described.<sup>31</sup> The latent class analysis classified participants into groups based on the degree of each participant's exposure (none, moderate, or severe), and the analysis was performed using only participants who experienced at least 1 form of stress or violence experience. The 3 groups identified were (1) individuals who were exposed primarily to parental intimate partner violence during childhood ( $n = 213$  [15.3%]), (2) individuals who were mainly bullied by peers and experienced street crime during childhood and adolescence ( $n = 354$  [25.4%]), and (3) individuals who experienced multiple types of violence during childhood and adolescence ( $n = 129$  [9.3%]). Measurement details are provided in eMethods 4 in the [Supplement](#).

Abbreviations: ACEs, adverse childhood experiences; CDC, Centers for Disease Control and Prevention; JVQ-R2, Juvenile Victimization Questionnaire, second revision.

**Statistical Analysis**

Both CRP and IL-6 levels were log-transformed to improve normality of their distributions, as commonly done.<sup>36</sup> Distributions of CRP, IL-6, and suPAR levels are shown in the eFigure in the [Supplement](#). Sex-adjusted regression coefficients were calculated to test associations between the inflammatory biomarkers with clinical characteristics of the sample. The association between ACEs or stress and violence exposure and inflammation was tested using ordinary least squares regression, with continuous measures of CRP, IL-6, and suPAR levels. Models were adjusted for sex, BMI, and smoking. Analyses of suPAR levels were adjusted for cleanliness of the home, childhood SES, CRP level, or IL-6 level. We report unstandardized B and standardized  $\beta$  coefficients, with 95% CIs adjusted to control for the nonindependence of observations of twins within families. Estimates and 95% CIs for log-transformed variables were back-transformed by exponentiating.

To analyze associations of ACEs or stress and violence exposure with combined CRP (untransformed values) and suPAR levels or combined IL-6 (untransformed values) and suPAR levels, we created groups characterized by high or low levels of CRP and suPAR or IL-6 and suPAR, as previously described.<sup>14</sup> For CRP, we used the established clinical cutoff (3 mg/L [to convert to nanomoles per liter, multiply by 9.524]) to identify participants with high CRP levels; thus, high CRP level indicates a CRP level greater than 3 mg/L ( $n = 287$  [20.6%]). Clinical cutoffs for suPAR and IL-6 have not yet been established. To identify participants with high suPAR or high IL-6 levels, we chose a cutoff for each that corresponded to a similar percentage as high CRP level; thus, high suPAR level indicates a suPAR level greater than 3.81 ng/mL ( $n = 286$  [20.6%]), and high IL-6 level indicates an IL-6 level greater than 1.48 pg/mL ( $n = 286$  [20.6%]). We created 4 groups of individuals characterized by (1) low CRP and low suPAR levels

( $n = 920$  [66.1%]), (2) high CRP and low suPAR levels ( $n = 185$  [13.3%]), (3) low CRP and high suPAR levels ( $n = 184$  [13.2%]), and (4) high CRP and high suPAR levels ( $n = 102$  [7.3%]). Similarly, we created 4 groups of individuals characterized by (1) low IL-6 and low suPAR levels ( $n = 916$  [65.9%]), (2) high IL-6 and low suPAR levels ( $n = 189$  [13.6%]), (3) low IL-6 and high suPAR levels ( $n = 189$  [13.6%]), and (4) high IL-6 and high suPAR levels ( $n = 97$  [7.0%]).

In addition, we performed an LCA that combined  $\ln(\text{CRP})$ ,  $\ln(\text{IL-6})$ , and suPAR to classify participants into groups based on each participant's levels of the 3 biomarkers, accounting for clustering of twins within families. The LCA identified 3 inflammation groups of individuals (eTable 2 and eTable 3 in the [Supplement](#)): low levels of all 3 biomarkers, elevated CRP and IL-6 levels, and elevated CRP, IL-6, and suPAR levels. The association between stress and violence exposure and the inflammation groups was tested using multinomial logistic regression, reporting odds ratios (ORs) with 95% CIs. Two-sided  $P < .05$  was a priori designated statistically significant.

**Results**

Of the 2066 children participating at 18 years of age, 1419 (68.7%) had complete data for childhood and adolescent adverse experiences; CRP, IL-6, and suPAR measurements at 18 years of age; and the covariates BMI and smoking. Participants with levels greater than 4 SDs above the means of CRP ( $n = 18$ ), IL-6 ( $n = 7$ ), or suPAR ( $n = 3$ ) levels were excluded, leaving a final sample of 1391 (mean [SD] age, 18.4 [0.36] years; 733 [52.7%] female). No significant differences were found for those with complete data included in this article vs those without in terms of mean SES (mean, 1.99 [95% CI, 1.95-2.04] vs 2.02 [95% CI, 1.97-2.08];  $P = .47$ ), ACEs (mean, 3.22 [95% CI, 3.08-3.36] vs 3.04 [95% CI, 2.86-3.21];  $P = .17$ ), severe childhood experiences of stress or violence (mean, 0.36 [95% CI, 0.33-0.40] vs 0.34 [95% CI, 0.29-0.39];  $P = .49$ ), or severe adolescent experiences of stress or violence (mean, 0.60 [95% CI, 0.55-0.65] vs 0.55 [95% CI, 0.49-0.62];  $P = .34$ ).

Correlates of CRP, IL-6, and suPAR are given in [Table 1](#). Compared with male participants, female participants had higher levels of CRP ( $r = 0.14$ ; 95% CI, 0.08-0.20;  $P < .001$ ) and suPAR ( $r = 0.23$ ; 95% CI, 0.17-0.29;  $P < .001$ ) but not IL-6 ( $r = 0.002$ ; 95% CI, -0.06 to 0.06;  $P = .95$ ). Participants with high BMIs had higher levels of all 3 inflammatory biomarkers (CRP:  $r = 0.35$ ; 95% CI, 0.30-0.40;  $P < .001$ ; IL-6:  $r = 0.19$ ; 95% CI, 0.13-0.24;  $P < .001$ ; and suPAR:  $r = 0.29$ ; 95% CI, 0.22-0.35;  $P < .001$ ). Tobacco smoking was associated with elevated levels of IL-6 ( $r = 0.06$ ; 95% CI, 0.005-0.12;  $P = .03$ ) and suPAR ( $r = 0.22$ ; 95% CI, 0.16-0.28;  $P < .001$ ) but not CRP ( $r = 0.04$ ; 95% CI, -0.02 to 0.09;  $P = .20$ ). In contrast, acute conditions, such as body temperature and current illness or injury ([Table 1](#) and eTable 1 in the [Supplement](#)), were associated with elevated levels of CRP (body temperature:  $r = 0.06$ ; 95% CI, 0.004-0.12;  $P = .04$ ; current illness or injury:  $r = 0.18$ ; 95% CI, 0.12-0.23;  $P < .001$ ) and IL-6 (current illness or injury:  $r = 0.14$ ; 95% CI, 0.08-0.20;  $P < .001$ ) but not suPAR (body temperature:  $r = 0.03$ ; 95% CI, -0.03 to 0.09;  $P = .31$ ; current illness or injury:  $r = 0.02$ ; 95% CI, -0.03 to 0.08;



Table 1. Sex-Adjusted Correlates of Plasma CRP, IL-6, and suPAR at 18 Years of Age in the E-Risk Longitudinal Twin Study

		CRP <sup>a</sup>		IL-6 <sup>a</sup>		suPAR	
Variable	Total	<i>r</i> (95% CI) <sup>b</sup>	<i>P</i> Value	<i>r</i> (95% CI) <sup>b</sup>	<i>P</i> Value	<i>r</i> (95% CI) <sup>b</sup>	<i>P</i> Value
Correlates of inflammation							
Female, No./total No. (%)	733/1391 (52.7)	0.14 (0.08 to 0.20)	<.001	0.002 (−0.06 to 0.06)	.95	0.23 (0.17 to 0.29)	<.001
BMI, mean (SE)	22.9 (0.15)	0.35 (0.30 to 0.40)	<.001	0.19 (0.13 to 0.24)	<.001	0.29 (0.22 to 0.35)	<.001
Daily smoking, No./total No. (%)	315/1391 (22.6)	0.04 (−0.02 to 0.09)	.20	0.06 (0.005 to 0.12)	.03	0.22 (0.16 to 0.28)	<.001
Body temperature, mean (SE), °C	36.3 (0.02)	0.06 (0.004 to 0.12)	.04	0.06 (−0.01 to 0.12)	.07	0.03 (−0.03 to 0.09)	.31
Current illness or injury, No./total No. (%) <sup>c</sup>	323/1390 (23.2)	0.18 (0.12 to 0.23)	<.001	0.14 (0.08 to 0.20)	<.001	0.02 (−0.03 to 0.08)	.36
Anti-inflammatory medication use, No./total No. (%) <sup>d</sup>	17/1391 (1.2)	0.01 (−0.04 to 0.06)	.65	−0.04 (−0.15 to 0.07)	.46	0.008 (−0.07 to 0.08)	.83
Cleanliness of home, No./total No. (%)	107/1342 (8.0) <sup>e</sup>	−0.04 (−0.10 to 0.02)	.22	−0.07 (−0.12 to −0.005)	.03	−0.11 (−0.17 to −0.05)	<.001
Socioeconomic status, No./total No. (%)	466/1391 (33.5) <sup>f</sup>	−0.05 (−0.11 to 0.01)	.09	−0.10 (−0.16 to −0.03)	.002	−0.16 (−0.22 to −0.10)	<.001
Inflammatory biomarkers, mean (SE)							
CRP level, mg/L <sup>a</sup>	2.34 (0.11)	NA	NA	0.39 (0.33 to 0.44)	<.001	0.25 (0.20 to 0.31)	<.001
IL-6 level, pg/mL <sup>a</sup>	1.19 (0.03)	0.39 (0.33 to 0.44)	<.001	NA	NA	0.27 (0.21 to 0.33)	<.001
suPAR level, ng/mL	3.23 (0.03)	0.25 (0.20 to 0.31)	<.001	0.27 (0.21 to 0.33)	<.001	NA	NA

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CRP, C-reactive protein; E-Risk, Environmental Risk; IL-6, interleukin 6; NA, not applicable; suPAR, soluble urokinase plasminogen activator receptor.

SI conversion factor: To convert CRP to nanomoles per liter, multiply by 9.524.

<sup>a</sup> Log-transformed (natural logarithm).

<sup>b</sup> Standardized estimated regression coefficients; all correlations were adjusted for sex, and *P* values were adjusted for clustering within families.

<sup>c</sup> The current illness or injury index is a count of 16 conditions present on the

day of blood sample obtaining. Correlations with individual illnesses and injuries are provided in eTable 1 in the Supplement.

<sup>d</sup> Any use of anti-inflammatory medication (corticosteroids) in the past 2 weeks.

<sup>e</sup> Number of homes reported to be unclean by home visitors when children were 12 years of age. A total of 205 (15.3%) were reported as somewhat clean, and 1030 (76.8%) were reported as clean.

<sup>f</sup> Number of families scored as low on the social class composite. A total of 469 (33.7%) were scored as middle social class, and 456 (32.8%) were scored as high social class.

*P* = .36). Use of anti-inflammatory medication (corticosteroids) in the past 2 weeks was not associated with any of the inflammatory biomarkers (CRP: *r* = 0.01; 95% CI, −0.04 to 0.06; *P* = .65; IL-6: *r* = −0.04; 95% CI, −0.15 to 0.07; *P* = .46; suPAR: *r* = 0.008; 95% CI, −0.07 to 0.08; *P* = .83). The 3 inflammatory biomarkers (CRP, IL-6, and suPAR) were positively intercorrelated (*r* = 0.25–0.39) (Table 1).

### Association of Adverse Experiences With Inflammatory Biomarker Levels

Children exposed to more ACEs had higher levels of suPAR and IL-6 but not CRP at 18 years of age. Only the association with suPAR remained after adjustment for sex, BMI, and smoking (CRP: *B* = 1.00; 95% CI, 0.97–1.03; IL-6: *B* = 1.01; 95% CI, 1.00–1.03; suPAR: *B* = 0.03; 95% CI, 0.01–0.05) (Table 2). In general, adverse experiences were most strongly associated with suPAR at 18 years of age. Participants who experienced stress and violence exposure as children had higher levels of suPAR and IL-6 but not CRP even after controlling for sex, BMI, and smoking (suPAR: *B* = 0.09, 95% CI, 0.01–0.17; IL-6: *B* = 1.06; 95% CI, 1.01–1.12; CRP: *B* = 1.04;

95% CI, 0.92–1.17) (Table 2). Participants who experienced stress and violence exposure as adolescents had higher levels of suPAR and CRP but not IL-6 (suPAR: *B* = 0.11; 95% CI, 0.05–0.18; CRP: *B* = 1.09, 95% CI, 1.00–1.18; IL-6: *B* = 1.02; 95% CI, 0.99–1.06), but none of these associations remained after adjustment for covariates (Table 2). Participants exposed to cumulative adverse experiences across childhood and adolescence had elevated suPAR levels. In particular, levels of suPAR (but not CRP or IL-6) were elevated among those exposed to domestic violence (suPAR: *B* = 0.25, 95% CI, 0.10–0.40; CRP: *B* = 1.04; 95% CI, 0.83–1.29; IL-6: *B* = 1.01; 95% CI, 0.91–1.13) and those who experienced multiple types of violence in childhood and adolescence (suPAR: *B* = 0.26; 95% CI, 0.07–0.45; CRP: *B* = 1.06; 95% CI, 0.81–1.38; IL-6: *B* = 1.02; 95% CI, 0.88–1.18) even after controlling for sex, BMI, and smoking (Table 2).

Correlations among different types of adverse experiences (eg, physical abuse, street crime, and cyber bullying) and CRP, IL-6, and suPAR levels are presented in eTable 4 in the Supplement. suPAR was associated with various forms of adverse experiences, suggesting that the elevation in suPAR levels among

Table 2. Associations of Childhood Adversities With Plasma CRP, IL-6, and suPAR Levels at 18 Years of Age in 1391 Participants in the E-Risk Longitudinal Twin Study

Measure	CRP <sup>a</sup>				IL-6 <sup>a</sup>				suPAR			
	Unadjusted		Adjusted <sup>b</sup>		Unadjusted		Adjusted <sup>b</sup>		Unadjusted		Adjusted <sup>b</sup>	
	B (95% CI) <sup>c,d</sup>	β (95% CI) <sup>e</sup>	B (95% CI) <sup>c,d</sup>	β (95% CI) <sup>e</sup>	B (95% CI) <sup>c,d</sup>	β (95% CI) <sup>e</sup>	B (95% CI) <sup>c,d</sup>	β (95% CI) <sup>e</sup>	B (95% CI) <sup>c</sup>	β (95% CI) <sup>e</sup>	B (95% CI) <sup>c</sup>	β (95% CI) <sup>e</sup>
Adverse childhood experiences	1.01 (0.98 to 1.04)	0.02 (−0.04 to 0.08)	1.00 (0.97 to 1.03)	0.002 (−0.06 to 0.06)	1.02 (1.01 to 1.03)	0.08 (0.02 to 0.13)	1.01 (1.00 to 1.03)	0.06 (−0.01 to 0.12)	0.05 (0.02 to 0.07)	0.13 (0.06 to 0.19)	0.03 (0.01 to 0.05)	0.08 (0.02 to 0.15)
Childhood experiences of stress or violence	1.07 (0.95 to 1.22)	0.03 (−0.03 to 0.09)	1.04 (0.92 to 1.17)	0.02 (−0.04 to 0.08)	1.08 (1.03 to 1.14)	0.09 (0.03 to 0.14)	1.06 (1.01 to 1.12)	0.07 (0.01 to 0.13)	0.15 (0.06 to 0.24)	0.11 (0.05 to 0.17)	0.09 (0.01 to 0.17)	0.07 (0.01 to 0.12)
Adolescent experiences of stress or violence	1.09 (1.00 to 1.18)	0.05 (−0.002 to 0.11)	1.05 (0.97 to 1.14)	0.03 (−0.02 to 0.09)	1.02 (0.99 to 1.06)	0.03 (−0.02 to 0.09)	1.01 (0.97 to 1.05)	0.01 (−0.05 to 0.07)	0.11 (0.05 to 0.18)	0.11 (0.05 to 0.18)	0.04 (−0.02 to 0.10)	0.04 (−0.02 to 0.10)
Groups of Cumulative Experiences of Stress or Violence												
Exposure to parental intimate partner violence in childhood <sup>f</sup>	1.10 (0.87 to 1.40)	0.07 (−0.10 to 0.24)	1.04 (0.83 to 1.29)	0.03 (−0.13 to 0.18)	1.04 (0.93 to 1.16)	0.07 (−0.11 to 0.24)	1.01 (0.91 to 1.13)	0.02 (−0.15 to 0.20)	0.33 (0.17 to 0.49)	0.36 (0.19 to 0.53)	0.25 (0.10 to 0.40)	0.27 (0.11 to 0.43)
Exposure to peer and street crime stress and violence during childhood and adolescence <sup>f</sup>	1.20 (1.00 to 1.44)	0.13 (−0.003 to 0.26)	1.06 (0.89 to 1.27)	0.04 (−0.08 to 0.17)	1.02 (0.94 to 1.11)	0.04 (−0.09 to 0.17)	0.99 (0.91 to 1.07)	−0.02 (−0.15 to 0.11)	0.16 (0.03 to 0.29)	0.17 (0.03 to 0.31)	0.02 (−0.10 to 0.13)	0.02 (−0.11 to 0.14)
Exposure to multiple types of violence during childhood and adolescence <sup>f</sup>	1.14 (0.86 to 1.52)	0.10 (−0.11 to 0.30)	1.06 (0.81 to 1.38)	0.04 (−0.16 to 0.23)	1.07 (0.93 to 1.23)	0.11 (−0.12 to 0.33)	1.02 (0.88 to 1.18)	0.03 (−0.20 to 0.26)	0.43 (0.22 to 0.64)	0.47 (0.24 to 0.69)	0.26 (0.07 to 0.45)	0.28 (0.08 to 0.48)

Abbreviations: CRP, C-reactive protein; E-Risk, Environmental Risk; IL-6, interleukin 6; suPAR, soluble urokinase plasminogen activator receptor.

<sup>a</sup> Log-transformed (natural logarithm).

<sup>b</sup> Adjusted for sex, body mass index, and smoking.

<sup>c</sup> Unstandardized B coefficient for ordinary least squares regression model, in which a 1-unit change in the variable

(eg, adverse childhood experiences) is associated with a corresponding change in B, holding all other variables constant.

<sup>d</sup> Log-transformed estimates and 95% CIs were back-transformed by exponentiating.

<sup>e</sup> Standardized β coefficients.

<sup>f</sup> Estimates represent mean differences from the no adverse experience group.

young people who underwent adverse experiences was not specific to any particular type of adverse experience but was rather a function of cumulative exposure.

Home visitor ratings allowed us to investigate whether living in a nonhygienic home during childhood and adolescence explained the association between adverse experiences and inflammation. Cleanliness of the home was negatively correlated with levels of suPAR ( $r = -0.11$ ; 95% CI,  $-0.17$  to  $-0.05$ ;  $P < .001$ ) and IL-6 ( $r = -0.07$ ; 95% CI,  $-0.12$  to  $-0.005$ ;  $P = .03$ ) but not CRP ( $r = -0.04$ ; 95% CI,  $-0.10$  to  $0.02$ ;  $P = .22$ ) (Table 1). When controlling for cleanliness of the home, all adverse experience exposures remained associated with elevated suPAR level at 18 years of age (eTable 5 in the [Supplement](#)).

Childhood SES was negatively correlated with levels of suPAR ( $r = -0.16$ ; 95% CI,  $-0.22$  to  $-0.10$ ;  $P < .001$ ) and IL-6 ( $r = -0.10$ ; 95% CI,  $-0.16$  to  $-0.03$ ;  $P = .002$ ) but not CRP ( $r = -0.05$ ; 95% CI,  $-0.11$  to  $0.01$ ;  $P = .09$ ) (Table 1). When controlling for SES, all adverse experience exposures remained associated with elevated suPAR level at 18 years of age (eTable 5 in the [Supplement](#)).

### Importance of suPAR in Adverse Experience-Associated Inflammation

Adverse experiences were associated with suPAR apart from any association with CRP and IL-6 (eTable 5 in the [Supplement](#)). Measuring suPAR in addition to CRP or IL-6 increased the association between stress exposure and inflammatory burden. For example, after adjusting for CRP and IL-6 levels, each additional adverse childhood experience was associated with a 0.05-mL (95% CI, 0.03-0.07 ng/mL) increase in suPAR, each additional severe childhood experience of stress or violence was associated with a 0.14-ng/mL (95% CI, 0.06-0.22 ng/mL) increase in suPAR, and each additional severe adolescent experience of stress or violence was associated with a 0.10-ng/mL (95% CI, 0.04-0.16 ng/mL) increase in suPAR. Young people who were exposed to more ACEs, childhood stress and violence exposure, adolescent stress and violence exposure, and cumulative stress and violence exposure were significantly more likely to have elevated levels of both CRP and suPAR at 18 years of age (ACEs: OR, 1.41; 95% CI, 1.16-1.71;  $P < .001$ ; childhood stress and violence exposure: OR, 1.33; 95% CI, 1.12-1.57;  $P = .001$ ; adolescent stress and violence exposure: OR, 1.28; 95% CI, 1.05-1.56;  $P = .02$ ; cumulative stress and violence exposure: OR, 2.51; 95% CI, 1.27-4.97;  $P = .008$ ) (Figure, A, and eTable 6 in the [Supplement](#)) as well as elevated levels of IL-6 and suPAR at 18 years of age (ACEs: OR, 1.39; 95% CI, 1.13-1.71;  $P = .002$ ; childhood stress and violence exposure: OR, 1.34; 95% CI, 1.11-1.63;  $P = .003$ ; adolescent stress and violence exposure: OR, 1.35; 95% CI, 1.12-1.64;  $P = .002$ ; cumulative stress and violence exposure: OR, 3.04; 95% CI, 1.61-5.73;  $P < .001$ ) (Figure, B, and eTable 6 in the [Supplement](#)).

However, adverse experiences were also prominent in the group of participants with low CRP and high suPAR (or low IL-6 and high suPAR) levels, who would inadvertently have been misclassified as having low inflammation if suPAR levels had not been measured. Similarly, the LCA revealed that young people who had elevated suPAR levels at 18 years of age in addition to elevated CRP and IL-6 levels had been exposed to more ACEs and childhood,

adolescent, and cumulative stress and violence experiences compared with those with low levels of all 3 inflammatory biomarkers or with those with mainly high levels of CRP and IL-6 but not suPAR (Figure, C, and eTable 7 in the [Supplement](#)).

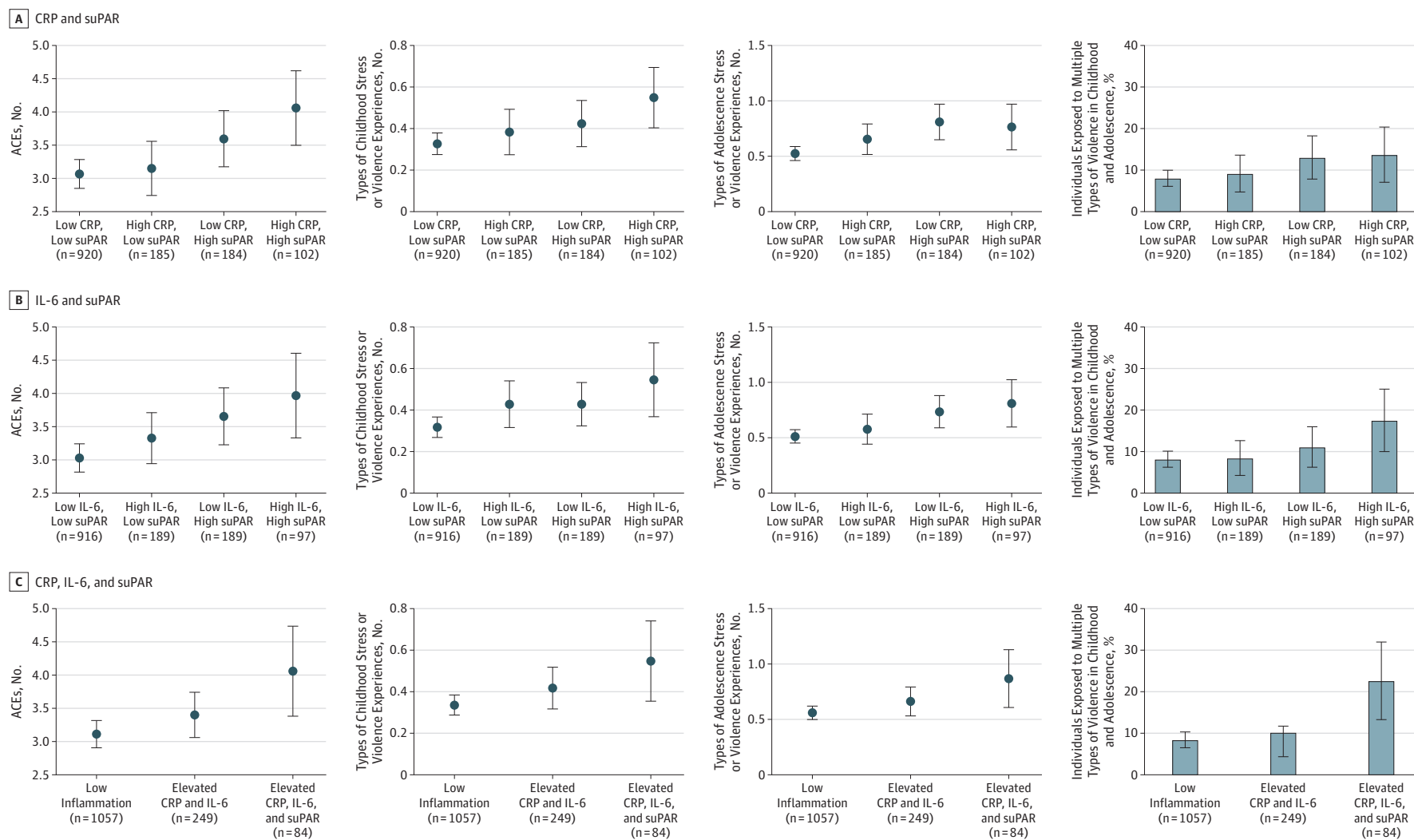
## Discussion

In this 2-decade prospective cohort study, we tested the usefulness of a new biomarker, suPAR, to understand the biological association with stress in the first part of the life course. First, children exposed to adversities and to multiple forms of stress and violence during childhood and adolescence had elevated suPAR levels by the time they reached 18 years of age. The association could not be attributed to BMI, smoking, or living in unhygienic homes during that period. Second, suPAR levels appear to add information about the health implications of stressful experiences in childhood beyond the more established biomarkers CRP and IL-6. We observed the strongest associations between stress exposure and inflammation when combining biomarkers, and we also found that adverse experiences were prominent in the group of participants with low CRP or low IL-6 level, who would have inadvertently been assigned to the low inflammation group if suPAR levels had not been assayed. These results replicate findings from the Dunedin Longitudinal Study,<sup>14</sup> which found that exposure to ACEs was associated with elevated levels of suPAR at midlife. Thus, suPAR may be a valuable adjunct to estimating inflammatory burden that may be associated with childhood stress exposure. This conclusion was supported by an LCA that revealed that young people with elevated inflammation could be separated into 2 categories: those with elevated CRP and IL-6 levels and those with elevated CRP, IL-6, and suPAR levels, the latter of which had stronger associations with adverse experiences.

Inflammation has been the target of investigation for researchers seeking to understand the biological variables associated with stress. Much of this work has relied on measuring CRP and IL-6 levels. A meta-analysis<sup>4</sup> revealed significant associations between ACEs and levels of these 2 inflammatory biomarkers. However, effects were small, and more than half of the studies, many of which were well powered, did not reveal positive associations.

Part of the difficulty may be that traditional markers of inflammation mix historical and acute effects; for example, CRP and IL-6 are involved in the acute-phase response. suPAR, the soluble form of uPAR, has been put forward as a marker of chronic inflammation. The expression and shedding of uPAR are upregulated under inflammatory conditions and in response to immunologic stimuli.<sup>37,38</sup> Thus, the suPAR level is elevated in many diseases with an inflammatory component,<sup>21</sup> whereas it is generally low, although still detectable, in healthy individuals.<sup>39</sup> Common risk factors for chronic disease, such as smoking and morbid obesity, are linked to elevated suPAR levels,<sup>40</sup> and elevated suPAR levels are associated with development and progression of disease and adverse outcomes, including mortality.<sup>20</sup> In contrast to many markers of inflammation, which are labile and rapidly upregulated and downregulated,<sup>41,42</sup> suPAR appears to be more stable and less

**Figure. Frequency of Adverse Childhood Experiences (ACEs) and Severe Experiences of Stress or Violence in Childhood or Adolescence Stratified by Inflammatory Biomarker Levels**



Mean number of ACEs, number of types of adverse experiences during childhood, number of types of adverse experiences during adolescence, or percentage of young people exposed to multiple types of violence during childhood or adolescence for individuals of the Environmental Risk (E-Risk) Longitudinal Twin Study stratified in groups of high C-reactive protein (CRP) level (>3 mg/L) and/or high soluble urokinase plasminogen activator receptor (suPAR) level (>3.81 ng/mL) (A), high interleukin 6 (IL-6) level (>1.48 pg/mL) and/or high suPAR level (>3.81 ng/mL) (B); or inflammation groups identified by latent class analysis (ie, low inflammation, elevated CRP and IL-6 levels, and elevated CRP, IL-6, and suPAR levels) (C). Error bars indicate 95% CIs.



sensitive to acute influences<sup>43</sup> and does not fluctuate with circadian rhythm.<sup>44</sup> Of the 2 categories of elevated inflammation identified by the LCA in this study, the one with elevated suPAR in addition to CRP and IL-6 was more strongly associated with stress and violence exposure during childhood and adolescence than the one with mainly elevated CRP and IL-6 levels. This finding supports the conclusion that adding suPAR to CRP and IL-6 measurement may improve the assessment of chronic inflammation associated with early-life stress.

### Limitations

This study has limitations. First, plasma samples were only available for 1448 participants in the longitudinal study. However, no significant stress-exposure differences were found between participants who did and did not provide blood samples. Second, we studied twins, who may not represent singletons. However, the same pattern of associations between adverse experiences and suPAR levels was found in the Dunedin Longitudinal Study cohort of singletons.<sup>14</sup> Third, although the distributional properties of suPAR are appealing for research purposes, the optimal threshold for its use as a diagnostic biomarker has not yet been determined. Fourth, the detected effect sizes were modest for suPAR, although this is to be expected in a sample of generally healthy young adults. Moreover, after we examined cumulative adverse experiences, effect sizes increased, a finding that underscores the importance of evaluating multiple risk factor exposures rather than any single exposure.<sup>45</sup> Fifth, we collected inflammation data for the first

time only in participants at 18 years of age, preventing us from analyzing the association of stress and violence exposure with inflammation trajectories over time. Longitudinal studies of suPAR are needed. In addition, randomized clinical trials of interventions intended to reduce effects of violence exposure should include inflammation biomarkers as outcome measures.<sup>46</sup> One study<sup>47</sup> found that favorable lifestyle changes were associated with reduced suPAR levels, suggesting suPAR as an outcome measure for studies of potential reversibility of chronic inflammation associated with early-life risk exposures. Sixth, we were able to identify risk factors associated with elevated suPAR levels, but because of the observational study design, we cannot rule out noncausal, alternative explanations of the associations.

### Conclusions

Inflammation has been suggested to fill the black box that connects childhood stress exposure to poor adult health, and it is under vigorous investigation.<sup>48</sup> The results of the present study suggest that adult inflammation is associated with childhood stress exposure,<sup>2</sup> with inflammation beginning by the time young people exposed to stress reach 18 years of age. Along with a previous report,<sup>14</sup> the present study suggests that adding information about suPAR to traditional biomarkers of inflammation may improve the measurement of stress-related inflammatory burden.

#### ARTICLE INFORMATION

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## Supplementary Online Content

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### eReferences

This supplementary material has been provided by the authors to give readers additional information about their work.



### **eMethods 1. Assessment of Adverse Childhood Experiences (ACEs)**

We have previously reported on the measurement of ACEs.<sup>1</sup> Here we summarize the method.

We measured ACEs in two categories. First, we measured conventional ACEs:<sup>2</sup> physical abuse, sexual abuse, emotional abuse and neglect, physical neglect, domestic violence exposure, parental antisocial behavior, family history of substance abuse, family history of mental health disorders, and parental separation or divorce. Second, from the results of the Philadelphia ACEs survey, we identified 10 adversities that we could test as part of the E-Risk Study: experiencing bullying, living in foster care, low childhood socioeconomic status, peer substance abuse, low parental monitoring (as evaluated by parents), low parental monitoring (as evaluated by children), participant-perceived unsafe neighborhood, high neighborhood crime victimization (as evaluated by a survey of neighbors), neighborhood rated as unsafe (as evaluated by systematic social observation), and high-crime neighborhood (as evaluated by police records).

Physical abuse, sexual abuse, emotional abuse and neglect, physical neglect, and domestic violence were assessed as described below in the section on childhood victimization (eMethods 2 "Assessment of Severe Childhood Experiences of Stress or Violence"). Only severe cases of these measures (coded as 2; see below) were used for the assessment of ACEs.

Parental antisocial behavior. Father's and mother's history of antisocial behavior was reported by the mothers when the children were 5 years old. Mothers were interviewed using the Young Adult Behavior Checklist,<sup>3</sup> which was modified to obtain lifetime data. Full details of father's and mother's history of antisocial behavior within the E-Risk Study are reported elsewhere.<sup>4</sup> A study of mother-father agreement about men's antisocial behavior in this sample showed that women provided reliable information about the behavior of their children's father.<sup>5</sup> The variable was coded as a dichotomous indicator of approximately the top quarter of the distribution of antisocial behaviors of parents (n=560).

Family history of substance abuse. Substance use for any of the child's biological mother, father, maternal grandparents, or maternal aunts and uncles was reported by the mother when the children were 12 years old. Family history algorithms follow those outlined by Milne et al., 2008.<sup>6</sup> The variable was coded as a dichotomous indicator of approximately the top quarter of the proportion of family members with a history of substance use (n=478).

Family history of mental health disorders. Family history of a report of hospitalization for psychiatric disorder or attempted or completed suicide for any of the child's biological mother, father, maternal grandparents, or maternal aunts and uncles (for additional details see Belsky et al., 2012<sup>7</sup>). Family history of mental illness was reported for 658 of the children.

Parental separation or divorce. Biological parent separation or divorce was assessed at each interview, up to 10 years of age, by questions on whether the biological parents were living in the same household. Parental separation or divorce was reported for 1,024 of the children.

Bullying victimization. Severe bullying up to age 12 years was assessed from mother's or participant's reports and was operationally defined as evidence of (a) repeated harmful actions, (b) between children, and (c) where there is a power differential between the bully and the victim (for additional details see Shakoor et al., 2012<sup>8</sup>). Bullying victimization was reported for 197 of the children.

Lived in foster care. Information from Life History Calendars was used to assess whether children had lived in foster care up to age 12 years. Living in foster care was reported for 24 children.

Low socioeconomic status. Low socioeconomic status at age 5 was assessed based on mother reports, and the variable was coded as a dichotomous indicator of approximately the top quarter of socioeconomic disadvantage, defined as follows: (a) head of household had no educational qualifications; (b) head of household was employed in an unskilled occupation or was not in the labor force; (c) total household gross annual income was less than £10,000; (d) family was receiving at least one government benefit, excluding disability benefit; (e) family housing was government subsidized; and (f) family had no access to a vehicle (for additional details see Kim-Cohen et al., 2004<sup>9</sup>). Low socioeconomic status was indicated for 442 of the children.



Peer substance abuse. Peer substance abuse was reported by participants at age 12 and coded as a dichotomous indicator of approximately the top quarter of scores on a scale of five items. The items capture, for each twin separately, the number of peers who drink alcohol, smoke cigarettes, use hash or cannabis, use pharmaceuticals, or sniff glue/gas. Participants responded with none, some, most, or all. Peer substance abuse was indicated for 421 of the participants.

Low parental monitoring (mother). Mothers were asked about their parental monitoring during the last 6 months, and low parental monitoring was coded as a dichotomous indicator of approximately the top quarter of scores on a scale of ten items from the Monitoring and Supervision Questionnaire.<sup>10</sup> The items capture, for each twin separately, whether the child needed permission to leave home or before deciding what to do on the weekend, and whether they had to report on where and who they go out with. Mothers also reported on whether they knew the friends their child hangs out with, where they go in their spare time, how they spend their money, what type of homework or tests and projects they have, and how their child performs in different subjects. Answers were recorded as “no, never” (0), “sometimes” (1), and “yes, always” (2) (for additional details see Wertz et al., 2016<sup>11</sup>). Mother-reported low parental monitoring was indicated for 396 of the participants.

Low parental monitoring (participant). Participants were asked about parental monitoring at age 12 years, and the variable was coded as a dichotomous indicator of approximately the top quarter of scores, using the same items used with mother-rated parental monitoring but worded slightly differently (e.g., “Do your parents know...”) (for additional details see Wertz et al., 2016<sup>11</sup>). Participant-reported low parental monitoring was indicated for 475 of the children.

Participant-perceived unsafe neighborhood. At age 12 years, participants reported whether they felt unsafe in their neighborhood by responding to the question: “You feel unsafe in your neighborhood” with true or false. Participant-perceived unsafe neighborhood was reported for 260 participants.

High neighborhood victimization. Neighborhood victimization was assessed in a neighbor survey when participants were age 13–14 years and coded as a dichotomous indicator of approximately the top quarter of scores on a scale of three items tapping into neighbor victimization experiences. Neighbors in the same postal code as the participant were surveyed on whether they had been a victim of 3 different types of crime (home break-in, theft from outdoor home property, violence experienced by respondent or family member in neighborhood). Neighbors were able to respond with “no”, “yes, once”, and “yes, more than once”, for each of the three types of victimization. (Complete details on the survey methodology can be found in Odgers et al., 2009<sup>12</sup>). High neighborhood victimization was indicated for 542 of the participants.

Neighborhood rated unsafe. The participant’s neighborhood was rated in a systemic social observation (SSO). Raters used Google Street View images of each participant’s neighborhood to respond to two questions on the neighborhood’s appearance: whether the raters felt that the neighborhood was “a safe place to live?” and “somewhere they would feel safe walking at night?”. Raters provided scores ranging from definitely safe (1) to definitely unsafe (5). (Complete details about the SSO methodology can be found in Odgers et al. 2009<sup>13</sup>). Unsafe neighborhoods were coded as a dichotomous indicator of approximately the top quarter of the average scores of the two items. Unsafe neighborhood was indicated for 410 of the participants.

High-crime neighborhood. Crime in the participants’ neighborhoods was assessed using police data. Local area crime was measured by mapping a 1 mile radius around each E-Risk Study family’s home and tallying the total number of crimes that occurred in the area each month. Street-level crime data, including information on the type of crime, date of occurrence, and approximate location, were accessed online as part of an open data sharing effort about crime and policing in England and Wales (<https://data.police.uk/>). An Application Program Interface (API) was used to extract street-level crime data for each of the geospatial coordinates marking the family’s home. For a full description see: <https://data.police.uk/about/#location-anonymisation>. The monthly average of the total number of crimes for the area surrounding each Study family’s home was computed for 2011, the first year for which full street-level data was available. High-crime neighborhood was coded as a dichotomous indicator of the top quarter of crime-ridden areas. High-crime neighborhood was indicated for 534 of the participants.

## **eMethods 2. Assessment of severe childhood experiences of stress or violence**

We have previously published evidence on the reliability and validity of our measurement of childhood victimization (in the present article termed “severe childhood experiences of stress or violence”).<sup>14</sup> Here we summarize the method.

A team of interviewers visited each family at home when the twins reached ages 5, 7, 10, and 12 years. Each home-visit interview was guided by a series of questions in a booklet. Based on these interviews with the mothers, each interviewer coded in the booklet her initial impression of whether or not she thought a child had been maltreated. The interviewers also recorded notes about their experiences in the home, and if an interviewer was worried about a child, she met with the fieldwork coordinator to debrief. Sometimes, the Study had to make a referral to help a child. Codes, notes, and the fieldwork coordinator’s narratives from the debriefs have been saved over the years to create a dossier for each child with cumulative information about exposure to domestic violence between the mother and her partner; frequent bullying by peers; physical abuse by an adult; sexual abuse; emotional abuse and neglect; and physical neglect. All the component measures are outlined briefly below.

Physical domestic violence. Mothers reported about perpetration of and victimization by 12 forms of physical violence (e.g., slapping, hitting, kicking, strangling) from the Conflict Tactics Scale,<sup>15</sup> on three assessment occasions during the child’s first decade of life (when the children were 5, 7, and 10 years of age). Reports of either perpetration or victimization constituted evidence of physical domestic violence. Families in which no physical violence took place were coded as 0 (55.2%); families in which physical violence took place on one occasion were coded as 1 (28.0%); and families in which physical violence took place on multiple occasions were coded as 2 (16.8%).

Bullying by peers. Experiences of victimization by bullies were assessed using both mothers’ and children’s reports. During the interview, the following standard definition of bullying was read out: “Someone is being bullied when another child (a) says mean and hurtful things, makes fun, or calls a person mean and hurtful names; (b) completely ignores or excludes someone from their group of friends or leaves them out on purpose; (c) hits, kicks, or shoves a person, or locks them in a room; (d) tells lies or spreads rumors about them; and (e) other hurtful things like these. We call it bullying when these things happen often, and when it is difficult to make it stop. We do not call it bullying when it is done in a friendly or playful way.” Mothers were interviewed when children were 7, 10, and 12 years old and asked whether either twin had been bullied by another child, responding never, yes, or frequently. We combined mothers’ reports at child age 7 and 10 to derive a measure of victimization during primary school. Mothers’ reports when the children were 12 years old indexed victimization during secondary school. During private interviews with the children when they were 12 years old, the children indicated whether they had been bullied by another child during primary or secondary school. When a mother or a child reported victimization, the interviewer asked them to describe what happened. Notes taken by the interviewers were later checked by an independent rater to verify that the events reported could be classified as instances of bullying operationally defined as evidence of (a) repeated harmful actions, (b) between children, and (c) where there is a power differential between the bully and the victim.<sup>16</sup>

Although inter-rater reliability between mothers and children was only modest ( $\kappa = 0.20\text{--}0.29$ ), reports of victimization from both informants were similarly associated with children’s emotional and behavioral problems, suggesting that each informant provides a unique but meaningful perspective on bullying involvement.<sup>16</sup> We thus combined mother and child reports of victimization to capture all instances of bullying victimization for primary and secondary school separately: reported as not victimized by both mother and child; reported by either mother or child as being occasionally victimized; and reported as being occasionally victimized by both informants or as frequently victimized by either mother or child or both.<sup>17</sup> We then combined these primary and secondary school ratings to create a bullying victimization variable for the entire childhood period (5–12 years). Children who were never bullied in primary or secondary school or occasionally bullied during one of these time periods were coded as 0 (55.5%); children who were occasionally bullied during primary and secondary school, or frequently bullied during one of these time periods were coded as 1 (35.6%); and children who were frequently bullied at both primary and secondary school were coded as 2 (8.9%).

Physical and sexual abuse by an adult. We assessed childhood physical and sexual harm in the E-Risk Study using an approach that resembles the process undertaken by child protection agencies. Essentially this is a two-stage process. In child protection, professionals such as teachers working with children typically raise concerns

if they observe signs or symptoms or if they become aware of risk that children are victims of violence. When concerns are raised, child protection officers then review the concerns and evaluate them in the context of information previously gathered on that child or family in order to determine the likelihood that abuse has taken place. In the E-Risk Study, research workers visited the home in pairs, and were extensively trained to detect signs of abuse or neglect. Each time the two research workers visited a home, they interviewed the mother using a structured interview about child harm, tested the children, and observed the family environment using the Home Observation for Measurement of the Environment (HOME).<sup>18</sup> If either research worker had any concerns, they flagged up the case for review. Immediately after each home visit, a review was performed if a family was flagged. In addition, at each wave, any family who had been flagged on a prior wave of the study was automatically reviewed again. The reviews were performed independently by at least 2 clinical psychologists or psychiatrists, and were based on comprehensive dossiers compiled across multiple home visits for each study member during the course of the ongoing longitudinal study. When the twins were aged 5, 7, 10, and 12 their mothers were interviewed about each twin's experience of intentional harm by an adult. At age 5 we used the standardized clinical protocol from the MultiSite Child Development Project.<sup>19,20</sup> At ages 7, 10, and 12 this interview was modified to expand its coverage of contexts for child harm. Interviews were designed to enhance mothers' comfort with reporting valid child maltreatment information, while also meeting researchers' responsibilities for referral under the U.K. Children Act. Specifically, mothers were asked whether either of their twins had been intentionally harmed (physically or sexually) by an adult or had contact with welfare agencies. If caregivers endorsed a question, research workers made extensive notes on what had happened, and indicated whether physical and/or psychological harm had occurred. Under the U.K. Children Act, our responsibility was to secure intervention if maltreatment was current and ongoing. Such intervention on behalf of E-Risk families was carried out with parental cooperation in all but one case. No families left the study following intervention.

Over the years of data collection, the study developed a cumulative profile for each child, comprising the caregiver reports, recorded debriefings with research workers who had coded any indication of maltreatment at any of the successive home visits, recorded narratives of the successive caregiver interviews, and information from clinicians whenever the Study team made a child-protection referral. Each time we visited a home, the research workers flagged concerns, and if there was sufficient evidence to code definite harm then, we did so. If evidence only met the level of probable harm, we kept an "ongoing concern list" and if, at a later wave, there was continued evidence of probable harm, or new evidence, the code was upgraded to definite harm. The profiles were reviewed at the end of the age-12 phase by at least two clinical psychologists or psychiatrists. Inter-rater agreement between the coders was 90% of cases for whom maltreatment was identified (100% for cases of sexual abuse), and discrepantly coded cases were resolved by consensus review. These were coded as: 0 = no physical harm at any age; 1 = probable physical harm at any age; and 2 = definite physical harm at any age. There were 15.0% of children coded as probably being exposed to physical harm and 5.1% as definitely physically harmed by 12 years of age. There were 1.5% of the children coded as being exposed to sexual abuse.

Emotional abuse and neglect. These forms of maltreatment were coded from research workers' narratives of home visit at ages 5, 7, 10, and 12. We coded quite severe examples of parental behavior observed. For example, a mother who had schizophrenia screamed and swore at the children throughout the home visit. As another example, a father who was drunk during the home visit repeatedly spoke abusively to the children in front of the research workers. We found that coders could not empirically separate emotional abuse and emotional neglect in a reliable way and thus such experiences were coded together as emotional abuse/neglect. Inter-rater agreement between the coders exceeded 85% for cases with such emotional abuse/neglect, and discrepant cases were resolved by consensus review. Children with no evidence of emotional abuse/neglect were coded as 0 (88.3%), those where there was some indication of emotionally inappropriate/potentially abusive behavior were coded as 1 (8.7%), and where there was evidence of severe emotional abuse/neglect the children were coded as 2 (3.0%).

Physical neglect. The cumulative observations of the physical state of the home environment documented by the research workers during home visits to the twins at ages 5, 7, 10, and 12 were reviewed by two raters for evidence of physical neglect. This was defined as any sign that the caretaker was not providing a safe, sanitary, or healthy environment for the child. This included the child not having proper clothing or food, as well as grossly unsanitary home environments. (However, this did not include a family living in a crime-ridden neighborhood for economic reasons.) Inter-rater agreement between the coders was 85%, and discrepantly coded cases were resolved by consensus review. Children with no evidence of physical neglect were coded as 0 (90.9%), those for whom there was an indication of minor physical neglect were coded as 1 (7.1%), and where there was evidence of severe physical neglect the children were coded as 2 (2.0%).

Childhood poly-victimization. Finkelhor et al. operationalize poly-victimization as the total number of victimization types that a child experiences.<sup>21</sup> The E-Risk poly-victimization variable was derived by summing all victimization experiences that received a code of '2'. Among children in this article, 1,004 (72.2%) children had no severe victimization experiences, 298 (21.4%) had one, 59 (4.2%) had two, and 30 (2.2%) had three or more.

### **eMethods 3. Assessment of severe adolescent experiences of stress or violence**

We have previously published evidence on the reliability and validity of our measurement of adolescent victimization (in this article termed “severe adolescent experiences of stress or violence”).<sup>22</sup> Here we summarize the method.

Within each pair of twins in our cohort, co-twins were interviewed separately at age 18 by a different research worker and were assured of the confidentiality of their responses. The participants were advised that confidentiality would only be broken if they told the research worker that they were in immediate danger of being hurt, and in such situations the project leader would be informed and would contact the participant to discuss a plan for safety.

Juvenile Victimization Questionnaire 2<sup>nd</sup> revision (JVQ-R2) interview. Our adapted version of the JVQ-R2 comprised 5 questions asking about maltreatment, 5 about neglect, 7 about sexual victimization, 6 about family violence, 10 about peer/sibling victimization, 3 about cyber victimization, and 9 about crime victimization. Each JVQ-R2 question was asked for the period “since you were 12”. Participants were given the option to say “yes” or “no” as to whether each type of victimization had occurred in the reporting period. Research workers could rate each item “maybe” if the participant seemed unsure or hesitant in their response or they were not convinced that the participant understood the question or was paying attention. Items rated as “maybe” were recoded as “no” or “yes” by the rating team based on the notes provided by the research workers. When insufficient notes were available, these responses were recoded conservatively as a “no”. Consistent with the JVQ-R2 manual,<sup>23,24</sup> participants were coded as 1 if they reported any experience within each type of victimization category, or 0 if none of the experiences within the category were endorsed. If an experience was endorsed within a victimization category, follow-up questions were asked concerning how old the participant was when it (first) happened, whether the participant was physically injured in the event, whether the participant was upset or distressed by the event, and how long it went on for (by marking the number of years on a Life History Calendar<sup>25</sup>). In addition, the interviewer wrote detailed notes based on the participant’s description of the worst event. If multiple experiences were endorsed within a victimization category, the participant was asked to identify and report about their worst experience.

Victimization dossiers. All information from the JVQ-R2 interview was compiled into victimization dossiers. Using these dossiers, each of the seven victimization categories was rated by an expert in victimology and 3 other members of the E-Risk team who were trained on using the rating criteria. Ratings were made using a 6-point scale: 0 = not exposed, then 1-5 for increasing levels of severity. The anchor points for these ratings were adapted from the coding system used for the Childhood Experience of Care and Abuse interview (CECA<sup>26,27</sup>), which has good inter-rater reliability.<sup>27,28</sup> The CECA is a comprehensive semi-structured interview whose standardized coding system attempts to improve the objectivity of ratings by basing them on the coder’s perspective (rather than relying on the participant’s judgment) and focusing on concrete descriptions rather than perceptions or emotional responses to the questions, together with considering the context in which the adverse experience occurred.

In our adapted coding scheme, the anchor points of the scale differ for each victimization category, with some focused more on the severity of physical injury that is likely to have been incurred during victimization exposure (crime victimization, family violence, maltreatment), while others are more focused on the frequency of occurrence of victimization (peer/sibling victimization and cyber victimization), the physical intrusiveness of the event (sexual victimization), or the pervasiveness of the effects of victimization (neglect). This reflects the different ways in which severity has previously been defined for different types of victimization.<sup>27,29</sup> (Given that our sample comprises twins, we also coded if any of the victimization events experienced by each twin had been perpetrated by their co-twin, as it is possible that growing up with a genetically related, same-age child could increase or decrease sibling victimization rates.) Each twin’s dossier was evaluated separately and we did not use information provided in the co-twin’s dossier about their own or shared victimization experiences to rate direct or witnessed violence exposure for the target twin.

**Reliability.** High levels of inter-rater reliability were achieved for the severity ratings for all forms of victimization: crime victimization (intra-class correlation coefficient [ICC]=0.89,  $P<.001$ ), peer/sibling victimization (ICC=0.91,  $P<.001$ ), cyber victimization (ICC=0.90,  $P<.001$ ), sexual victimization (ICC=0.87,  $P<.001$ ), family violence (ICC=0.93,  $P<.001$ ), maltreatment (ICC=0.90,  $P<.001$ ), and neglect (ICC=0.74,  $P<.001$ ).

The ratings for each type of victimization were then grouped into three classes: 0 = no exposure (score of 0), 1 = some exposure (score of 1, 2 or 3), and 2 = severe exposure (score of 4 or 5) due to small numbers for some of the rating points. Combining ratings of 4 and 5 is also consistent with previous studies using the CECA, which have collapsed comparable scale values to indicate presence of “severe” abuse (e.g., Bifulco et al., 1994, 1997, 1998;<sup>27,28,30</sup> Fisher et al., 2011<sup>31</sup>).

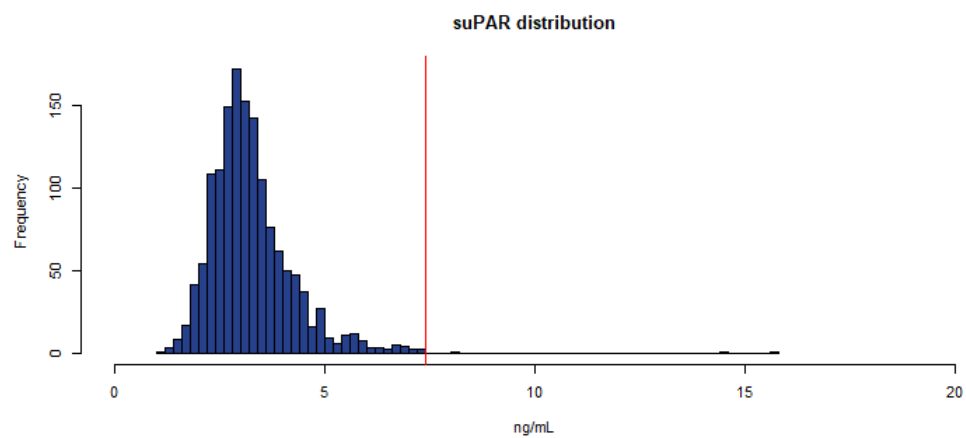
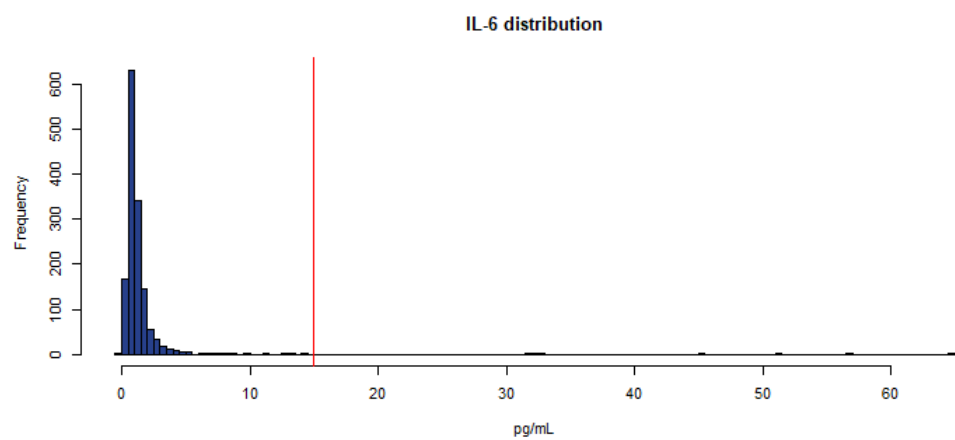
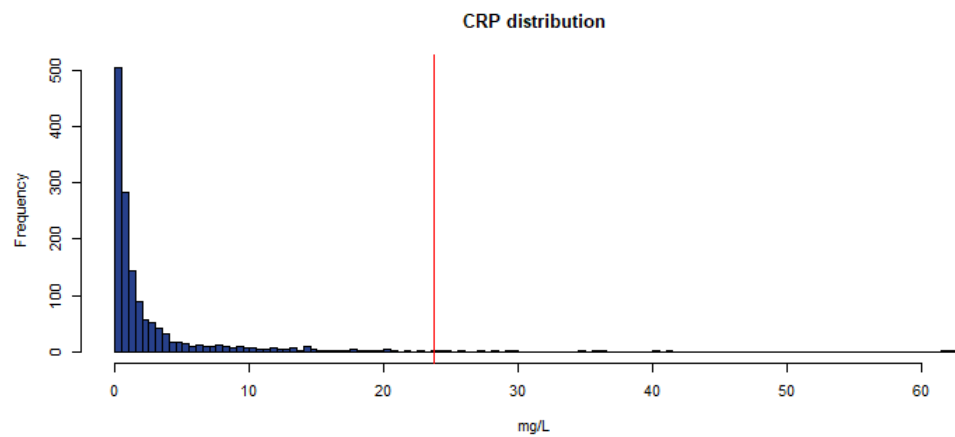
**Adolescent poly-victimization.** Adolescent victimization was derived by summing the number of severe adolescent victimization experiences. In this article, 887 (63.8%) of adolescents had no severe victimization experiences, 275 (19.8%) had one, 131 (9.4%) had two, and 98 (7.1%) had three or more.

#### **eMethods 4. Assessment of cumulative stress and violence experiences**

We have previously published on the measurement of cumulative victimization (in this article termed “cumulative stress and violence experiences”).<sup>32</sup> Here we summarize the method.

We performed a latent class analysis using longitudinal data about childhood and adolescent victimization. Latent class analysis is a person-centered technique that classifies individuals into groups based on a profile of variables, in this case the degree of each participant’s exposure (i.e., none, moderate, or severe) to the six types of childhood and seven types of adolescent victimization. The latent class analysis was performed using only participants who experienced at least one form of victimization. It was conducted in MPlus, version 7.4, accounting for clustering of twins within families. The latent class analysis identified three victimized groups: 1) individuals who were exposed primarily to parental intimate-partner violence in childhood ( $n=254$ , 15%), 2) those who were primarily victimized by peers and street crime throughout childhood and adolescence ( $n=412$ , 24.8%), and 3) those who experienced multiple types of violence in both childhood and adolescence ( $n=158$ , 9.5%). 834 individuals were not exposed to childhood or adolescent victimization.





**eFigure. Distributions of CRP, IL-6, and suPAR in the E-Risk Longitudinal Twin Study.** Blood samples were collected at age 18 years. Participants with CRP (n=18), IL-6 (n=7), or suPAR (n=3) levels greater than four standard deviations above the means were excluded; these values are indicated by the red line. CRP and IL-6 were log-transformed to improve normality of their distributions (the figure indicates the distributions of CRP and IL-6 before log-transformation). Abbreviations: CRP, C-reactive protein; IL-6, interleukin-6; suPAR, soluble urokinase plasminogen activator receptor.

**eTable 1. Correlations (Sex-Adjusted) of Plasma CRP, Plasma IL-6, and Plasma suPAR With Individual Illnesses or Injuries on the Day of Blood Sampling at Age 18 Years in the E-Risk Study (n = 1390)**

		CRP <sup>a</sup>			IL-6 <sup>a</sup>			suPAR	
Variable	n (%)	r <sup>b</sup> (95% CI)	P		r <sup>b</sup> (95% CI)	P		r <sup>b</sup> (95% CI)	P
Fever	9 (0.7)	0.08 (0.03; 0.12)	<b>&lt;.001</b>		0.04 (-0.03; 0.10)	.27		0.01 (-0.02; 0.03)	.69
Swollen lymph glands <sup>c</sup>	25 (1.8)	0.09 (0.04; 0.14)	<b>&lt;.001</b>		0.04 (0.04; 0.18)	<b>.0021</b>		0.03 (0.03; 0.09)	.29
Persistent cough	107 (7.7)	0.20 (0.14; 0.25)	<b>&lt;.001</b>		0.17 (0.11; 0.24)	<b>&lt;.001</b>		0.04 (-0.01; 0.10)	.10
Cold	155 (11.2)	0.18 (0.13; 0.24)	<b>&lt;.001</b>		0.14 (0.07; 0.21)	<b>&lt;.001</b>		0.01 (-0.04; 0.06)	.57
Influenza <sup>d</sup>	4 (0.3)	0.09 (0.07; 0.11)	<b>&lt;.001</b>		0.10 (0.05; 0.16)	<b>&lt;.001</b>		0.01 (-0.01; 0.04)	.39
Asthma <sup>c</sup>	30 (2.2)	0.03 (-0.02; 0.08)	.22		0.04 (-0.02; 0.10)	.23		0.04 (-0.03; 0.10)	.24
Repeated diarrhea	3 (0.2)	-0.002 (-0.03; 0.02)	.88		0.01 (-0.04; 0.05)	.79		0.06 (-0.03; 0.14)	.19
Eye pain/infection	12 (0.9)	0.04 (-0.02; 0.09)	.19		0.01 (-0.03; 0.05)	.66		0.04 (-0.004; 0.09)	.07
Bleeding gums	15 (1.1)	-0.04 (-0.08; 0.003)	.07		0.001 (-0.05; 0.05)	.96		-0.01 (-0.07; 0.05)	.83
Toothache <sup>c</sup>	25 (1.8)	-0.03 (-0.08; 0.02)	.19		0.01 (-0.06; 0.08)	.85		-0.05 (-0.10; -0.0003)	<b>0.049</b>
Sore throat	91 (6.6)	0.16 (0.11; 0.21)	<b>&lt;.001</b>		0.15 (0.08; 0.21)	<b>&lt;.001</b>		0.02 (-0.02; 0.07)	.27
Tonsilitis	7 (0.5)	0.08 (0.04; 0.12)	<b>&lt;.001</b>		0.04 (-0.01; 0.08)	.11		0.02 (-0.06; 0.10)	.59
Ear pain/infection	28 (2.0)	0.08 (0.03; 0.13)	<b>&lt;.001</b>		0.07 (0.004; 0.13)	<b>.036</b>		0.01 (-0.04; 0.06)	.71
Major bruising	10 (0.7)	0.06 (0.01; 0.11)	<b>.013</b>		0.01 (-0.03; 0.06)	.55		0.04 (-0.03; 0.10)	.28
Major cuts (incl. tattoos)	5 (0.4)	0.05 (-0.004; 0.10)	.07		0.07 (-0.001; 0.15)	.053		0.06 (0.01; 0.11)	<b>.015</b>
Sprains	9 (0.7)	0.02 (-0.04; 0.07)	.54		0.03 (-0.01; 0.07)	.11		0.03 (-0.03; 0.10)	.29
Abbreviations: CI, confidence interval; CRP, C-reactive protein; IL-6, interleukin-6; suPAR, soluble urokinase plasminogen activator receptor.									
<sup>a</sup> Log-transformed (natural logarithm)									
<sup>b</sup> Standardized estimated regression coefficients; all correlations are adjusted for sex, and P values are adjusted for clustering within families.									
<sup>c</sup> n=1,389									
<sup>d</sup> n=1,388									

<b>eTable 2. Results of a Latent Class Analysis Using Data About Inflammation Measured With CRP, IL-6, and suPAR (n = 1390)<sup>a</sup></b>						
<b>No. groups</b>	<b>Loglikelihood</b>	<b>AIC</b>	<b>BIC</b>	<b>Entropy</b>	<b>LMR-adjusted LRT</b>	<b>P Value</b>
2	-5362.641	10745.282	10797.653	0.860	420.215	0.0002
3	-5269.287	10566.574	10639.893	0.774	180.473	0.0006
4	-5234.261	10504.523	10598.790	0.750	67.713	0.0197
5	-5217.430	10478.861	10594.076	0.727	32.538	0.6556
6	-5198.254	10448.508	10584.671	0.730	37.068	0.0602
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CRP, C-reactive protein; IL-6, interleukin-6; LMR-adjusted LRT Test, Lo-Mendell-Rubin adjusted likelihood ratio test; suPAR, soluble urokinase plasminogen activator receptor. <sup>a</sup> We examined fit statistics for 2 to 6 groups. The best solution appeared to be either a 3- or 4-class solution, with the entropy test favoring the 3-class solution and the chi-square difference test favoring the 4-class solution. The difference between the solutions is that the 4-class solution divided the final 3-class solution group into participants with 'high' and 'very high' values on all three inflammation biomarkers. One participant with extreme values was excluded from the Latent Class Analysis.						

eTable 3. Levels of CRP, IL-6, and suPAR in the 3 Inflammation Groups Identified by Latent Class Analysis (n = 1390)									
		CRP			IL-6			suPAR	
Latent class inflammation groups	n	Median (IQR)	Z-score mean (95% CI)		Median (IQR)	Z-score mean (95% CI)		Median (IQR)	Z-score mean (95% CI)
1: Low inflammation	1,057	0.56 (0.27; 1.19)	-0.36 (-0.40; -0.31)		0.79 (0.59; 1.07)	-0.31 (-0.35; -0.26)		2.91 (2.50; 3.39)	-0.27 (-0.31; -0.23)
2: Elevated CRP and IL-6	249	5.55 (3.01; 10.68)	1.25 (1.17; 1.34)		1.82 (1.35; 2.58)	1.14 (1.03; 1.26)		3.40 (3.01; 4.00)	0.26 (0.17; 0.36)
3: Elevated CRP, IL-6, and suPAR	84	2.84 (1.13; 7.56)	0.76 (0.56; 0.96)		1.30 (0.94; 1.93)	0.60 (0.40; 0.81)		5.57 (5.04; 6.05)	2.61 (2.44; 2.77)
Abbreviations: CI, confidence interval; CRP, C-reactive protein; IL-6, interleukin-6; IQR, interquartile range; suPAR, soluble urokinase plasminogen activator receptor.									



**eTable 4. Correlations Between Different Types of Adverse Experiences and CRP, IL-6, and suPAR at Age 18 Years in the E-Risk Study**

		CRP <sup>a</sup>			IL-6 <sup>a</sup>			suPAR	
Variable		n (%)	r <sup>b</sup> (95% CI)	P	r <sup>b</sup> (95% CI)	P		r <sup>b</sup> (95% CI)	P
<b>Age 12 years:</b>									
Emotional abuse/neglect		45 (3.2)	0.03 (-0.03; 0.08)	.37	0.01 (-0.03; 0.05)	.59		0.02 (-0.02; 0.07)	.30
Foster/non-parental care		18 (1.3)	-0.02 (-0.08; 0.04)	.54	0.01 (-0.03; 0.05)	.54		0.03 (-0.02; 0.07)	.28
Physical abuse		75 (5.4)	0.01 (-0.05; 0.07)	.70	0.05 (-0.003; 0.10)	.06		0.08 (0.01; 0.14)	<b>.016</b>
Physical neglect		24 (1.7)	0.03 (-0.03; 0.08)	.36	0.06 (0.001; 0.13)	<b>.045</b>		0.05 (-0.02; 0.13)	.17
Sexual abuse		11 (0.8)	0.001 (-0.06; 0.06)	.98	0.04 (-0.03; 0.12)	.25		0.03 (-0.01; 0.07)	.13
<b>Age 18 years:</b>									
Crime victimization		265 (19.1)	0.02 (-0.04; 0.07)	.55	0.06 (-0.003; 0.11)	.06		0.11 (0.05; 0.16)	<b>&lt;.001</b>
Maltreatment		43 (3.1)	-0.002 (-0.06; 0.06)	.93	0.007 (-0.05; 0.06)	.80		0.04 (-0.01; 0.10)	.13
Peer victimization		226 (16.2)	0.05 (-0.003; 0.11)	.06	0.01 (-0.04; 0.07)	.58		0.05 (-0.01; 0.11)	.08
Sexual victimization (n=1,390)		39 (2.8)	0.02 (-0.02; 0.06)	.37	0.04 (-0.01; 0.10)	.14		0.07 (0.01; 0.13)	<b>.015</b>
Family victimization		182 (13.1)	0.04 (-0.02; 0.09)	.16	-0.008 (-0.07; 0.05)	.77		0.07 (0.02; 0.12)	<b>.0098</b>
Cyber victimization		93 (6.7)	0.02 (-0.03; 0.07)	.46	0.04 (-0.01; 0.09)	.14		0.01 (-0.05; 0.07)	.73
Neglect		29 (2.1)	0.02 (-0.03; 0.06)	.49	-0.02 (-0.06; 0.03)	.40		0.02 (-0.03; 0.06)	.47

Abbreviations: CI, confidence interval; CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; suPAR, soluble urokinase plasminogen activator receptor.

<sup>a</sup>Log-transformed (natural logarithm).

<sup>b</sup>Standardized estimated regression coefficients; all correlations are adjusted for sex, with confidence intervals and P values adjusted for clustering within families.

**eTable 5. Associations of Childhood Adversities With Plasma suPAR at Age 18 Years in the E-Risk Study After Adjustment for Sex and Indicated Correlates**

	Adjusted for sex and:									
	Cleanliness of home (n=1,342)		Childhood SES (n=1,391)		CRP <sup>a</sup> (n=1,391)		IL-6 <sup>a</sup> (n=1,391)		CRP <sup>a</sup> and IL-6 <sup>a</sup> (n=1,391)	
Victimization measures	B (95% CI) <sup>b</sup>	β (95% CI) <sup>c</sup>	B (95% CI) <sup>b</sup>	β (95% CI) <sup>c</sup>	B (95% CI) <sup>b</sup>	β (95% CI) <sup>c</sup>	B (95% CI) <sup>b</sup>	β (95% CI) <sup>c</sup>	B (95% CI) <sup>b</sup>	β (95% CI) <sup>c</sup>
Adverse childhood experiences	0.05 (0.02 to 0.07)	0.13 (0.06 to 0.20)	0.04 (0.01 to 0.06)	0.10 (0.03 to 0.18)	0.05 (0.03 to 0.07)	0.15 (0.09 to 0.21)	0.05 (0.03 to 0.07)	0.14 (0.08 to 0.20)	0.05 (0.03 to 0.07)	0.14 (0.08 to 0.19)
Severe childhood experience of stress or violence	0.13 (0.05 to 0.22)	0.10 (0.03 to 0.16)	0.13 (0.05 to 0.22)	0.10 (0.03 to 0.16)	0.16 (0.08 to 0.24)	0.12 (0.06 to 0.17)	0.15 (0.06 to 0.23)	0.10 (0.05 to 0.16)	0.14 (0.06 to 0.22)	0.10 (0.05 to 0.16)
Severe adolescent experience of stress or violence	0.09 (0.03 to 0.16)	0.09 (0.03 to 0.16)	0.09 (0.03 to 0.15)	0.09 (0.03 to 0.15)	0.10 (0.04 to 0.16)	0.10 (0.04 to 0.16)	0.10 (0.04 to 0.16)	0.10 (0.04 to 0.16)	0.10 (0.04 to 0.16)	0.10 (0.04 to 0.15)
Groups of cumulative stress and violence experiences (birth to age 18) identified in latent class analysis:										
Exposure to parental intimate-Partner violence in childhood <sup>d</sup>	0.31 (0.15 to 0.48)	0.34 (0.16 to 0.51)	0.28 (0.12 to 0.44)	0.31 (0.13 to 0.48)	0.33 (0.18 to 0.48)	0.36 (0.19 to 0.52)	0.33 (0.18 to 0.49)	0.36 (0.19 to 0.52)	0.32 (0.17 to 0.47)	0.35 (0.19 to 0.51)
Exposure to peer and street-crime victimization throughout childhood and adolescence <sup>d</sup>	0.13 (0.01 to 0.25)	0.14 (0.01 to 0.27)	0.12 (-0.003 to 0.24)	0.13 (-0.003 to 0.26)	0.12 (-0.003 to 0.24)	0.13 (-0.003 to 0.25)	0.13 (0.01 to 0.26)	0.14 (0.01 to 0.28)	0.12 (-0.001 to 0.24)	0.13 (-0.001 to 0.26)
Exposure to multiple types of violence in both childhood and adolescence <sup>d</sup>	0.39 (0.18 to 0.59)	0.42 (0.20 to 0.64)	0.37 (0.16 to 0.57)	0.40 (0.17 to 0.62)	0.43 (0.24 to 0.62)	0.47 (0.26 to 0.67)	0.43 (0.25 to 0.62)	0.47 (0.27 to 0.67)	0.42 (0.24 to 0.61)	0.45 (0.25 to 0.65)

Abbreviations: CI, confidence interval; CRP, C-reactive protein; IL-6, interleukin-6; SES, socioeconomic status; suPAR, soluble urokinase plasminogen activator receptor.

<sup>a</sup>Log-transformed (natural logarithm).

<sup>b</sup>Unstandardized B coefficient for Ordinary Least Squares regression model, where a 1-unit change in the predictor (e.g., adverse childhood experiences) is associated with a corresponding change in B, holding all other variables constant.

<sup>c</sup>Standardized regression coefficients.

<sup>a</sup>Estimates represent standardized mean differences from the “No victimization” group.

**eTable 6. Associations Between Adverse Experiences and Inflammation Groups at Age 18 Years<sup>a</sup>**

Adverse childhood experiences (ACEs)						
	OR (95% CI)	P			OR (95% CI)	P
Low CRP, low suPAR	1			Low IL-6, low suPAR	1	
High CRP, low suPAR	1.03 (0.87–1.23)	.71		High IL-6, low suPAR	1.12 (0.96–1.31)	0.14
Low CRP, high suPAR	1.22 (1.03–1.43)	<b>.019</b>		Low IL-6, high suPAR	1.26 (1.07–1.49)	<b>0.0069</b>
High CRP, high suPAR	1.41 (1.16–1.71)	<b>&lt;.001</b>		High IL-6, high suPAR	1.39 (1.13–1.71)	<b>0.0020</b>
Severe childhood experience of stress or violence						
	OR (95% CI)	P			OR (95% CI)	P
Low CRP, low suPAR	1			Low IL-6, low suPAR	1	
High CRP, low suPAR	1.09 (0.92–1.30)	.32		High IL-6, low suPAR	1.18 (1.01–1.38)	<b>.036</b>
Low CRP, high suPAR	1.15 (0.98–1.36)	.088		Low IL-6, high suPAR	1.18 (1.01–1.38)	<b>.040</b>
High CRP, high suPAR	1.33 (1.12–1.57)	<b>.0010</b>		High IL-6, high suPAR	1.34 (1.11–1.63)	<b>.0027</b>
Severe adolescent experience of stress or violence						
	OR (95% CI)	P			OR (95% CI)	P
Low CRP, low suPAR	1			Low IL-6, low suPAR	1	
High CRP, low suPAR	1.15 (0.99–1.35)	.071		High IL-6, low suPAR	1.08 (0.92–1.28)	.36
Low CRP, high suPAR	1.33 (1.14–1.55)	<b>&lt;.001</b>		Low IL-6, high suPAR	1.27 (1.09–1.48)	<b>.0025</b>
High CRP, high suPAR	1.28 (1.05–1.56)	<b>.015</b>		High IL-6, high suPAR	1.35 (1.12–1.64)	<b>.0022</b>
Cumulative stress or violence experiences: Multiple types of violence						
	OR (95% CI)	P			OR (95% CI)	P
Low CRP, low suPAR	1			Low IL-6, low suPAR	1	
High CRP, low suPAR	1.37 (0.75–2.48)	.31		High IL-6, low suPAR	1.13 (0.62–2.04)	.70
Low CRP, high suPAR	2.45 (1.39–4.30)	<b>.0020</b>		Low IL-6, high suPAR	2.04 (1.13–3.71)	<b>.019</b>
High CRP, high suPAR	2.51 (1.27–4.97)	<b>.0080</b>		High IL-6, high suPAR	3.04 (1.61–5.73)	<b>&lt;.001</b>

Abbreviations: CI, confidence interval; CRP, C-reactive protein; IL-6, interleukin-6; OR, odds ratio; suPAR, soluble urokinase plasminogen activator receptor.

<sup>a</sup>Standardized odds ratios with confidence intervals and P values adjusted for clustering within families.

<b>eTable 7. Associations Between Adverse Experiences and Latent Class Inflammation Groups at Age 18 Years<sup>a</sup></b>		
<b>Adverse childhood experiences (ACEs)</b>		
<b>Latent class inflammation groups</b>	<b>OR (95% CI)</b>	<b>P</b>
1: Low inflammation	1	
2: Elevated CRP and IL-6	1.12 (0.97–1.28)	.12
3: Elevated CRP, IL-6, and suPAR	1.38 (1.11–1.72)	<b>.0036</b>
<b>Severe childhood experience of stress or violence</b>		
<b>Latent class inflammation groups</b>	<b>OR (95% CI)</b>	<b>P</b>
1: Low inflammation	1	
2: Elevated CRP and IL-6	1.13 (0.97–1.30)	.11
3: Elevated CRP, IL-6, and suPAR	1.30 (1.06–1.60)	<b>.011</b>
<b>Severe adolescent experience of stress or violence</b>		
<b>Latent class inflammation groups</b>	<b>OR (95% CI)</b>	<b>P</b>
1: Low inflammation	1	
2: Elevated CRP and IL-6	1.12 (0.97–1.29)	.14
3: Elevated CRP, IL-6, and suPAR	1.34 (1.08–1.67)	<b>.0089</b>
<b>Cumulative stress or violence experiences: Multiple types of violence</b>		
<b>Latent class inflammation groups</b>	<b>OR (95% CI)</b>	<b>P</b>
1: Low inflammation	1	
2: Elevated CRP and IL-6	1.10 (0.63–1.93)	.74
3: Elevated CRP, IL-6, and suPAR	4.07 (2.10–7.90)	<b>&lt;.001</b>
Abbreviations: CI, confidence interval; CRP, C-reactive protein; IL-6, interleukin-6; OR, odds ratio; suPAR, soluble urokinase plasminogen activator receptor.		
<sup>a</sup> Standardized odds ratios with confidence intervals and P values adjusted for clustering within families.		

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