Socioenvironmental Adversity and Adolescent Psychotic Experiences: Exploring Potential Mechanisms in a UK Longitudinal Cohort

Joanne B. Newbury1,2, Louise Arseneault1, Terrie E. Moffitt1,3,4,5, Candice L. Odgers6,7, Laura D. Howe2, Ioannis Bakolis8,9, Aaron Reuben3,5,6, Andrea Danese10,11, Karen Sugden1, Benjamin Williams3, Line J. H. Rasmussen3,12, Antonella Trotta1,13, Antony P. Ambler1,10, and Helen L. Fisher1,14,*

1King’s College London, Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, London, UK; 2Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK; 3Department of Psychiatry and Neurosciences, Duke University, Durham, NC, USA; 4Department of Psychology and Behavioural Sciences, Duke University, Durham, NC, USA; 5Centre for Genomic and Computational Biology, Duke University, Durham, NC, USA; 6Social Science Research Institute, Duke University, Durham, NC, USA; 7Department of Psychological Science, School of Social Ecology, University of California, Irvine, Irvine, CA, USA; 8King’s College London, Centre for Implementation Science, Department of Health Service and Population Research, Institute of Psychiatry, Psychology and Neuroscience, London, UK; 9King’s College London, Department of Biostatistics and Health Informatics, Institute of Psychiatry, Psychology and Neuroscience, London, UK; 10King’s College London, Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, London, UK; 11National and Specialist CAMHS Clinic for Trauma, Anxiety, and Depression, South London and Maudsley NHS Foundation Trust, London, UK; 12Department of Clinical Research, Copenhagen University Hospital Amager and Hvidovre, Hvidovre, Denmark; 13School of Health and Social Care, University of Essex, Colchester, UK; 14ESRC Centre for Society and Mental Health, King’s College London, London, UK

*To whom correspondence should be addressed; Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, 16 De Crespigny Park, London SE5 8AF, UK; tel: +44- (0)208-7848-5430, fax: +44- (0)208-7848-0866, e-mail: helen.2.fisher@kcl.ac.uk

Background and Hypothesis: Children exposed to socioenvironmental adversities (eg, urbanicity, pollution, neighborhood deprivation, crime, and family disadvantage) are more likely to subsequently develop subclinical psychotic experiences during adolescence (eg, hearing voices, paranoia). However, the pathways through which this occurs have not been previously investigated. We hypothesized that cognitive ability and inflammation would partly explain this association. Study Design: Data were utilized from the Environmental-Risk Longitudinal Twin Study, a cohort of 2232 children born in 1994–1995 in England and Wales and followed to age 18. Socioenvironmental adversities were measured from birth to age 10 and classified into physical risk (defined by high urbanicity and air pollution) and socioeconomic risk (defined by high neighborhood deprivation, neighborhood disorder, and family disadvantage). Cognitive abilities (overall, crystallized, fluid, and working memory) were assessed at age 12; and inflammatory markers (C-reactive protein, interleukin-6, soluble urokinase plasminogen activator receptor) were measured at age 18 from blood samples. Participants were interviewed at age 18 regarding psychotic experiences. Study Results: Higher physical risk and socioeconomic risk were associated with increased odds of psychotic experiences in adolescence. The largest mediation pathways were from socioeconomic risk via overall cognitive ability and crystallized ability, which accounted for ~11% and ~19% of the association with psychotic experiences, respectively. No statistically significant pathways were found via inflammatory markers in exploratory (partially cross-sectional) analyses. Conclusions: Cognitive ability, especially crystallized ability, may partly explain the association between childhood socioenvironmental adversity and adolescent psychotic experiences. Interventions to support cognitive development among children living in disadvantaged settings could buffer them against developing subclinical psychotic phenomena.

Key words: disadvantage/intelligence/mediation/neighborhood/psychosis/urban

Introduction

Psychotic disorders such as schizophrenia have a lifetime prevalence of around 3%1 and place a large burden on the individuals affected and society more broadly.2 Subclinical psychotic experiences (eg, hearing voices and paranoia) are considered to lie on a continuum with psychotic disorders and affect a greater proportion of the general population.3 These experiences are especially...
prevalent earlier in development, affecting up to a third of children and adolescents.\textsuperscript{4,6} As they are common and associate familially\textsuperscript{7} and longitudinally\textsuperscript{8,9} with psychotic disorders (with approximately a 7- to 16-fold increased risk of schizophreniform disorders in adulthood\textsuperscript{8,9}), they provide an important and useful framework for investigating early-life risk factors for clinical psychosis. They also associate with a wide range of other current and subsequent mental health problems such as conduct disorder,\textsuperscript{10} self-harm and suicide attempts,\textsuperscript{11} depression,\textsuperscript{12} and PTSD,\textsuperscript{8} making them an important early marker of vulnerability for psychopathology more broadly. Moreover, early psychotic phenomena have also been associated with functional difficulties, risky behaviors, and poor quality of life in young adulthood.\textsuperscript{11} Therefore, understanding how subclinical psychotic experiences emerge is crucial to inform the development and testing of targeted preventive interventions in the general population.

Various socioenvironmental adversities appear to contribute to the development of psychotic disorders. These include urbanicity,\textsuperscript{13} and a milieu of correlated exposures such as air pollution,\textsuperscript{14} neighborhood\textsuperscript{15} and family deprivation,\textsuperscript{16} and other neighborhood problems like crime and disorganization.\textsuperscript{17,18} Similar associations are seen for early psychotic experiences,\textsuperscript{6,19-22} indicating that the association between socioenvironmental adversities and psychosis has early-life origins (although causality has not been proven).

Given their pervasiveness, adversities such as high urbanicity, deprivation, and air pollution could be prime targets for interventions to potentially reduce the population burden of psychotic phenomena. However, little is known about the mechanism(s) linking these adversities to psychosis. Identifying pathways could open new avenues for preventive interventions. We are aware of only one such mechanistic study by Lewis et al.,\textsuperscript{23} which investigated a mediating role of IQ in the association of population density and neighborhood deprivation at birth with schizophrenia in Swedish men. To the best of our knowledge, there have been no such studies focusing on subclinical psychotic experiences thus highlighting an important gap in the existing literature.

In considering potential mechanisms, cognition, and inflammation are useful starting points because they provide insight into processes in the brain and body. Cognitive ability tests, such as the Wechsler Intelligence Scales, measure neurocognitive strengths, and weaknesses, thereby providing standardized estimates of knowledge acquisition and, arguably, noninvasive proxies of brain development and functioning.\textsuperscript{24,25} Additionally, inflammatory markers obtained from blood samples provide insight into systemic inflammation, high levels of which may signify chronic stress and underlying disease processes\textsuperscript{26} and can adversely affect multiple organs including the brain.\textsuperscript{27}

Figure 1 illustrates hypothesized pathways that could lead from socioenvironmental adversities, via cognitive ability and inflammation, to psychotic experiences. Briefly, physical toxins enriched in the urban environment, such as air pollutants, could promote oxidative stress and damage brain tissue by directly entering the brain.\textsuperscript{28-30} Exposures such as neighborhood deprivation and neighborhood disorder could also promote psychological stress and dysregulate neurobiological pathways linked to psychosis such as the hypothalamic–pituitary–adrenal axis\textsuperscript{28} and dopaminergic system.\textsuperscript{31} These processes could each have downstream effects on cognition and inflammation,\textsuperscript{32,34} both of which, based on longitudinal\textsuperscript{35-38} and mendelian randomization\textsuperscript{39,40} evidence, appear to have causal roles in psychosis.

It is likely that infants and children are most vulnerable to socioenvironmental adversities because their brains and immune systems are still developing.\textsuperscript{43} Therefore, in a longitudinal birth cohort followed to early adulthood, we conducted the first study to examine the roles of cognitive abilities and inflammation in the associations of socioenvironmental adversities in childhood with psychotic experiences in adolescence. We examined overall cognitive ability (IQ), and 3 subdomains (crystallized ability, fluid ability, and working memory) to explore potential specific neurocognitive pathways. Likewise, we examined 3 specific inflammatory biomarkers (C-reactive protein [CRP], interleukin-6 [IL-6], and soluble urokinase plasminogen activator receptor [suPAR]). Socioenvironmental adversities included urbanicity, air pollution, neighborhood deprivation, neighborhood disorder, and family disadvantage, and were selected a priori based on previous evidence in this cohort.\textsuperscript{6,19-22} However, analyses were guided by the exposome literature, which highlights the interdependent nature of associations between environmental exposures and mental disorders,\textsuperscript{44} and we, therefore, applied exploratory factor analysis to these socioenvironmental adversities. We hypothesized that cognitive ability and inflammation would partly mediate the association between socioenvironmental adversities and psychotic experiences.

Methods
Study Cohort
Participants were members of the Environmental Risk (E-Risk) Longitudinal Twin Study, which tracks the development of a nationally representative birth cohort of 2232 twin children born in 1994–1995 across England and Wales and initially assessed at age 5. Follow-up home visits were conducted when participants were aged 7, 10, 12, and 18 years (participation rates were 98%, 96%, 96%, and 93%, respectively). At 18 years of age, the E-Risk sample included 2066 participants, comprising 56.2% monozygotic twin pairs and 47.5% males. There were no differences between those who did and did not take part at age 18 in terms of age-5 socioeconomic status (SES).
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...age-5 IQ scores ($P = .33$), or age-5 internalizing or externalizing behavioral problems ($P = .69$ and $P = .68$, respectively). E-Risk families are representative of UK households across the spectrum of neighborhood socioeconomic conditions (supplementary figure 1). 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 participants gave written assent at ages 5–12 and written informed consent at age 18. Further details are reported elsewhere, and in supplementary material. Table 1 displays characteristics of the age-18 cohort.

Measures
Socioenvironmental variables are described below, with more detail in supplementary material.

Urbanicity. This was derived from classifications from 2011 census data, linked to home postcodes at ages 5, 7, and 10, and averaged across ages 5–10. A 3-level urbanicity variable was used representing rural (19.8%, $N = 405$), intermediate (47.8%, $N = 980$), and urban settings (32.4%, $N = 665$).

Air Pollution. This exposure was measured using a coupled regional chemical transport model and street-scale dispersion model. Performance statistics are shown in supplementary table 1. Based on our previous findings, the present study focuses on nitrogen dioxide ($NO_2$). Annualized estimates of ambient $NO_2$ were linked to home postcodes at the age of 10 ($M = 25.9\, \mu g/m^3$, $SD = 10.2$).

Neighborhood Deprivation. This was based on a geodemographic discriminator that used over 400 census variables for Great Britain (CACI Information Services; http://www.caci.co.uk/). Classifications were linked to home postcodes at ages 5, 7, and 10, and then averaged across ages 5–10. Classifications ranged from 1 = “Wealthy Achiever” (19.9%, $N = 410$) to 5 = “Hard Pressed” (25.9%, $N = 532$) neighborhoods.

Neighborhood Disorder. This was measured at age 5 via interviews with the children’s mothers. Mothers were asked whether 13 problems affected their neighborhood (eg, noisy neighbors, vandalism, burglaries, etc.). Items (coded 0–2) were summed for each mother ($M = 3.95$, $SD = 3.82$).

Family Disadvantage. This was measured at the age of 5 as a composite of household social class (1 = unemployed/unskilled, 0 = part skilled, skilled manual, skilled non-manual, managerial/technical, professional); total
CRP and IL-6 are involved in the acute-phase response but may also reflect chronic inflammation. In contrast, suPAR is thought to provide a more stable indication of historic/chronic immune system activation.  

Covariates. The selection of confounders was informed using a directed acyclic graph (figure 2). To account for potential confounding due to the selection of at-risk families into disadvantaged environments, we controlled for family psychiatric history, parental education, participants’ polygenic risk scores for schizophrenia, participants’ polygenic risk scores for educational attainment, and participants’ polygenic risk scores for cognitive performance. Additional covariates included biological sex and, for the inflammation analyses, body temperature at age 18. All covariates are described in supplementary material.

Statistical Analyses. The analysis plan was preregistered (https://sites.duke.edu/moffittcaspiprojects/files/2021/07/Newbury_2021a.pdf). Analyses were conducted in Stata v17.0. To recognize the exposome literature as well as to reduce data, we applied exploratory factor analysis to the socioenvironmental variables prior to the main analyses. Factor analysis was performed on the polychoric correlation matrix (principal factors with varimax rotation). This suggested a two-factor solution: correlations, variances, and factor loadings are shown in supplementary tables 2–4, and a scree plot is shown in supplementary figure 2. We extracted analysis variables directly from the two-factor solution, using the “predict” command in Stata. The first factor, conceptualized as “physical risk,” had the highest loadings from urbanicity and air pollution, as well as smaller loadings from the other three variables (M = 1.80, SD = 0.63, range = 0.74–2.73). The second factor, conceptualized as “socioeconomic risk,” had the highest loadings from neighborhood deprivation, neighborhood disorder, and family disadvantage, as well as smaller loadings from the other 2 variables (M = 1.66, SD = 0.60, range = 0.69–2.88). The correlation between the two factors was r = 0.08 (P < .001). For the main analyses, we first conducted regression analysis to examine the associations of socioenvironmental adversities with psychotic experiences (ordinal logistic regression) and with cognitive ability and inflammation (linear regression). Second, ordinal logistic regression was used to examine the longitudinal association of cognitive ability with adolescent psychotic experiences and the cross-sectional association of inflammation with adolescent psychotic experiences. Third, generalized structural equation modeling (gsem) was used to partition the total effect of socioenvironmental adversities on psychotic experiences into the direct effect (not mediated via putative mediators) and the indirect (mediated) effects via cognitive
### Table 1. Sample Characteristics and Missing Data for the Cohort at Age 18 (N = 2066)

<table>
<thead>
<tr>
<th>Sample characteristics</th>
<th>M/N</th>
<th>SD/%</th>
<th>Range</th>
<th>Missing N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychotic experiences</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1440</td>
<td>69.80%</td>
<td>—</td>
<td>3 (0.15)</td>
</tr>
<tr>
<td>1–2</td>
<td>319</td>
<td>15.46%</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>3–5</td>
<td>166</td>
<td>8.05%</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>6 or more</td>
<td>138</td>
<td>6.69%</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Overall cognitive ability</td>
<td>100.15</td>
<td>15.00</td>
<td>46.52–147.45</td>
<td>56 (2.71)</td>
</tr>
<tr>
<td>Crystallized ability</td>
<td>9.26</td>
<td>3.21</td>
<td>1–19</td>
<td>56 (2.71)</td>
</tr>
<tr>
<td>Fluid ability</td>
<td>9.50</td>
<td>2.80</td>
<td>1–19</td>
<td>57 (2.76)</td>
</tr>
<tr>
<td>Working memory</td>
<td>10.65</td>
<td>3.34</td>
<td>1–19</td>
<td>57 (2.76)</td>
</tr>
<tr>
<td>ln(CRP)</td>
<td>−0.08</td>
<td>1.39</td>
<td>−4.42–3.16</td>
<td>636 (30.78)</td>
</tr>
<tr>
<td>ln(IL-6)</td>
<td>−0.03</td>
<td>0.64</td>
<td>−5.00–2.66</td>
<td>626 (30.30)</td>
</tr>
<tr>
<td>suPAR</td>
<td>3.23</td>
<td>0.93</td>
<td>1.15–7.30</td>
<td>622 (30.11)</td>
</tr>
<tr>
<td>Physical risk factor score</td>
<td>1.80</td>
<td>0.63</td>
<td>0.74–2.73</td>
<td>87 (4.21)</td>
</tr>
<tr>
<td>Socioeconomic risk factor score</td>
<td>1.66</td>
<td>0.60</td>
<td>0.69–2.88</td>
<td>87 (4.21)</td>
</tr>
<tr>
<td>Separate socioenvironmental adversities:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urbanicity (ages 5–10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>405</td>
<td>19.76%</td>
<td>—</td>
<td>16 (0.77)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>980</td>
<td>47.80%</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>665</td>
<td>32.44%</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Air pollution* (age 10)</td>
<td>25.94</td>
<td>10.17</td>
<td>2.59–57.87</td>
<td>75 (3.63)</td>
</tr>
<tr>
<td>Neighborhood deprivation (ages 5–10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wealthy achiever</td>
<td>414</td>
<td>20.12%</td>
<td>—</td>
<td>8 (0.39)</td>
</tr>
<tr>
<td>Urban prosperity</td>
<td>223</td>
<td>10.84%</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Comfortably off</td>
<td>535</td>
<td>26.00%</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Moderate means</td>
<td>376</td>
<td>18.27%</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Hard pressed</td>
<td>510</td>
<td>24.78%</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Neighborhood disorder (age 5)</td>
<td>3.95</td>
<td>3.82</td>
<td>0–22</td>
<td>6 (0.29)</td>
</tr>
<tr>
<td>Family disadvantage (ages 0–5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1011</td>
<td>48.94%</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>350</td>
<td>16.94%</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>246</td>
<td>11.91%</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>201</td>
<td>9.73%</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>178</td>
<td>8.62%</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>5 forms of disadvantage</td>
<td>80</td>
<td>3.87%</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Covariates:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>981</td>
<td>47.48%</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Female</td>
<td>1085</td>
<td>52.52%</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Family psychiatric history</td>
<td>0.37</td>
<td>0.27</td>
<td>0–1</td>
<td>56 (2.71)</td>
</tr>
<tr>
<td>Parental education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least CSE grade 0–5</td>
<td>1799</td>
<td>87.08%</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>None</td>
<td>267</td>
<td>12.92%</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>PRS for schizophrenia</td>
<td>−0.02</td>
<td>1.00</td>
<td>−3.75–3.53</td>
<td>203 (9.83)</td>
</tr>
<tr>
<td>PRS for educational attainment</td>
<td>0.01</td>
<td>1.00</td>
<td>−3.70–3.31</td>
<td>232 (11.23)</td>
</tr>
<tr>
<td>PRS for cognitive performance</td>
<td>0.01</td>
<td>1.00</td>
<td>−2.93–2.80</td>
<td>232 (11.23)</td>
</tr>
<tr>
<td>Body temperature at age 18</td>
<td>36.34</td>
<td>0.58</td>
<td>34–38.2</td>
<td>13 (0.63)</td>
</tr>
</tbody>
</table>

Note: CRP, C-reactive protein; CSE, certificate of secondary education (school-leaving qualification); IL-6, interleukin-6; ln, natural logarithm; M, mean; N, number; PRS, polygenic risk score; SD, standard deviation; suPAR, soluble urokinase plasminogen activator receptor; *air pollution was nitrogen dioxide.

Mediation pathways are shown in figure 2. Overall cognitive ability was analyzed as a separate mediator. Cognitive ability subdomains were analyzed as mediators simultaneously to account for potentially correlated pathways. We then conducted a supplementary mediation analysis of inflammation instead of cognitive ability, with inflammatory biomarkers analyzed simultaneously. This was considered exploratory because inflammation was measured contemporaneously to psychotic experiences at age 18 and therefore did not achieve the appropriate temporal sequencing usually required for mediation. Main analyses focused on the physical and socioeconomic risk factor scores. We conducted supplementary analyses for the separate socioenvironmental variables that comprised the factor scores. Finally, we calculated e-values where evidence of mediation was strongest. E-values indicate the strength of unmeasured confounding required to nullify
associations and are recommended for observational research because unmeasured confounding is inevitable.62 All analyses (including mediation models) controlled for the non-independence of twin observations using the “cluster” command. This procedure is derived from the Huber-White variance estimator, and provides robust standard errors adjusted for within cluster (ie, within the family) correlated data.63 To handle potential issues arising from missing data, all analyses were conducted following multiple imputations by chained equations, described in supplementary material. We also conducted complete case analyses for main models.

Results
Sample Characteristics
Distributions for the main variables and covariates are described in table 1. At age 18, just under a third of adolescents (N = 626; 30.2%) reported having at least one psychotic experience after the age of 12.

Are Socioenvironmental Adversities Associated With Psychotic Experiences?
Higher physical risk (adjusted odds ratio [adjOR] = 1.35, 95% CI = 1.13–1.61, P = .001) and socioeconomic risk (adjOR = 1.72, 95% CI = 1.42–2.08, P < .001) in childhood were associated with increased odds for psychotic experiences in adolescence.

Are Socioenvironmental Adversities Associated With Cognitive Ability and Inflammation?
Higher socioeconomic risk up to the age of 10 was associated with lower overall cognitive ability, crystallized ability, fluid ability, and working memory at the age of 12, before and after covariate adjustment (supplementary table 5). For instance, each unit increase in the socioeconomic risk factor score was associated with a 5.92-IQ-points decrease in overall cognitive ability (adjusted beta [adjB] = −5.92, 95% CI = −7.20–−4.64). Effect sizes were smaller and CIs included the null for associations between physical risk and cognitive abilities (figure 3 [Panel A] and supplementary table 5).

Higher socioeconomic risk up to the age of 10 was also associated with higher IL-6 and suPAR levels at age 18. For instance, increases in the socioeconomic risk factor score were associated with 0.20ng/ml higher suPAR levels (adjB = 0.20, 95% CI = 0.10–0.31). Unexpectedly, the higher physical risk was associated with lower CRP and suPAR levels. For instance, increases in the physical risk factor score were associated with 0.09ng/ml lower suPAR levels (adjB = −0.09, 95% CI = −0.18–0.00) (figure 3 [Panel A] and supplementary table 5).
Are Cognitive Ability and Inflammation Associated With Psychotic Experiences?

Higher scores for each of the cognitive abilities were associated with lower odds for adolescent psychotic experiences, though confidence intervals crossed the null for fluid ability following covariate adjustment (figure 3 [Panel B] and supplementary table 6). For instance, each unit increase in crystallized ability was associated with 9% lower odds for psychotic experiences (adjOR = 0.92, 95% CI = 0.89–0.96).

Associations between inflammation and psychotic experiences in this cohort have been reported previously, but we report associations again for the present analytic sample. Each unit increase in suPAR was associated with 18% greater odds for psychotic experiences (adjOR = 1.18, 95% CI = 1.02–1.36) (figure 3 [Panel B] and supplementary table 6). Neither CRP nor IL-6 was associated with psychotic experiences.

Does Cognitive Ability Mediate the Association of Socioenvironmental Adversity With Psychotic Experiences?

Figure 4 shows the adjusted total effects of the physical and socioeconomic risk factor scores on adolescent psychotic experiences, the direct effect (unmediated by cognitive abilities), the indirect effects mediated via cognitive abilities, as well as mediation percentages. Supplementary table 7 additionally shows unadjusted results.

Overall cognitive ability mediated ~11% (indirect adjOR = 1.06, 95% CI = 1.01–1.11) and crystallized ability ~19% (indirect adjOR = 1.09, 95% CI = 1.03–1.16) of the total effect of socioeconomic risk on psychotic experiences. In contrast, the only slight signal of mediation from physical risk was via crystallized ability, and this effect was small (~5%) and confidence intervals crossed the null. Furthermore, there was no evidence of mediation via fluid ability or working memory.
Notably, direct effects remained strong after considering mediation pathways, indicating that a large proportion of the association between socioenvironmental adversity and psychotic experiences was not explained by cognitive ability.

Supplementary Analyses
We conducted an exploratory partially cross-sectional mediation analysis using inflammatory biomarkers. The only slight signal of mediation was from socioeconomic risk via suPAR, and this effect was small (~5%).
and confidence intervals crossed the null (supplementary table 7). There was no evidence of mediation via CRP or IL-6.

In keeping with the main findings, all separate socioenvironmental adversities were associated with lower cognitive ability scores, particularly overall cognitive ability and crystallized ability (supplementary tables 8–12). Higher neighborhood deprivation, neighborhood disorder, and family disadvantage were also associated with higher suPAR levels. Unexpectedly (though in keeping with the main findings) urbanicity and air pollution were associated with lower CRP and suPAR levels (supplementary tables 8–12). However, there was evidence of mediation only via overall cognitive ability, which mediated the effects of deprivation, disorder, and disadvantage; and crystallized ability, which additionally mediated the effect of urbanicity (supplementary tables 13–22).

E-values

E-values were calculated for the socioeconomic risk—crystallized ability—psychotic experience mediation model and are shown in supplementary table 23 alongside the associations of covariates with exposure, mediator, and outcome. E-values for the total (OR = 2.61, lower CI = 1.90) and direct effects (OR = 2.34, lower CI = 1.64) were relatively large, and usually close to or greater than the magnitude of associations of included covariates with exposure, mediator, and outcome. The e-value for the indirect effect was smaller (OR = 1.40, lower CI = 1.21), though still greater than the effect sizes for most covariates. This suggests that any unmeasured confounder(s) would require a stronger confounding influence than most of the included covariates to nullify associations.

Results from complete case analyses were similar to those from imputed data (supplementary tables 24–26).

Discussion

This study assessed the mechanisms linking socioenvironmental adversities to psychotic experiences. Children exposed to more socioenvironmental adversity (both physical and socioeconomic) had greater odds of psychotic experiences in adolescence. Additionally, physical and socioeconomic risk were associated with several cognitive abilities and inflammatory markers; some of which, in turn, were associated with psychotic experiences. However, we found robust evidence only for overall cognitive ability and crystallized ability as mediators, which explained, respectively, ~11% and ~19% of the association between socioeconomic risk and psychotic experiences.

Our findings are partly consistent with those from Lewis et al., who reported that IQ at age 18 explained 23% of the association between neighborhood deprivation at birth and schizophrenia in adulthood; though it did not mediate the association between urbanicity and schizophrenia. In our study, as well as mediating the socioeconomic risk-psychotic experience association, crystallized ability also explained a small proportion of the association of urbanicity with psychotic experiences, which could suggest a particular role of this subdomain of cognition.

A mediation pathway via cognitive ability, especially crystallized ability, is plausible and aligns with the neurodevelopmental model of psychosis, which describes the importance of early-life vulnerabilities and adversities for increasing neural abnormalities that later result in psychotic disorders. Though the nature of crystallized ability remains equivocal, it represents information stores acquired through learning and experience. Thus, of the domains we examined, crystallized ability is arguably subject to the most influence from socioenvironmental adversities. Notably, deficits in crystallized ability are associated with reduced cortical thickness which is itself associated with psychosis.

Our findings are consistent with a process whereby socioenvironmental adversities impact neurodevelopment during childhood, leading to reduced crystallized ability and an increased propensity for psychotic experiences in adolescence. However, a non-mutually exclusive psychosocial mechanism could also underlie these findings, whereby children growing up in disadvantaged environments face barriers to learning at school; and later, with reduced opportunities during the transition to adulthood, encounter more psychological stress which precipitates the emergence of psychotic experiences. For both suggested mechanisms, interventions to support cognitive development among children could help to weaken the effect of socioenvironmental adversity on psychotic experiences. Notably, this accords with research into cognitive remediation in psychosis which suggests that cognitive training improves functioning and reduces clinical transition among adolescents and young adults at ultrahigh risk for psychosis.

Unexpectedly, there was a dissociation in effects for inflammation. Socioeconomic risk was associated with higher IL-6 and suPAR levels, whereas, physical risk was associated with lower CRP and suPAR levels; a pattern reflected by the separate socioenvironmental variables. This finding brought to mind recent mendelian randomization evidence suggesting a negative causal relationship between CRP and schizophrenia, whereby high levels appeared protective. Together, these findings could suggest a complex interplay between socioenvironmental adversities, inflammation, and psychosis; with dysregulation, rather than increase, being the hallmark of associations. Further mendelian randomization research could shed light on these dissociated patterns.
Strengths and Limitations

Our study had several strengths, including a longitudinal design, use of comprehensive data on several socioenvironmental adversities across childhood, and exploration of subcomponents of cognitive ability and inflammation. Moreover, E-Risk families are representative of the UK population in terms of urbanicity and socioeconomics.31

We also highlight some limitations. Inflammation was measured at age 18, meaning that we could not achieve the appropriate temporal sequence to properly explore inflammation as a mediator, and these results (null or weak mediation) are thus interpreted with caution. A powerful approach would be to measure biomarkers at multiple time points across development to obtain a longer-term picture of systemic inflammation. However, we used the novel biomarker suPAR, which may better capture the longer-term inflammatory consequences of socioenvironmental adversity, as shown previously for other types of childhood adversity.14 It was interesting that there was (weak) evidence of mediation only for this biomarker. Additionally, mediation models assume there is no unmeasured confounding. Though we identified potential confounders via a directed acyclic graph, residual confounding is inevitable. However, the reasonably large e-values increased our confidence in the findings. Additionally, we examined only two potential mechanisms, and the mediation pathway via the strongest mediator (crystallized ability) was still relatively modest, suggesting that a large proportion of the association between the socioenvironmental adversity and psychotic experiences is explained by different mechanisms. Future studies should explore other potential pathways between socioenvironmental adversity and psychotic experiences, such as childhood maltreatment and bullying; as well as processes upstream of cognitive abilities and inflammation, such as glucocorticoid levels. Furthermore, it is likely that some participants first had psychotic experiences after age 18, potentially in the context of schizophrenia, and were therefore missed by our study. Relatedly, it is unclear whether these findings would generalize to psychotic disorder, although they do align with Lewis et al.’s23 findings on schizophrenia. Finally, the causality of the association between socioenvironmental adversity and psychosis remains equivocal, with evidence that it could partly be driven by the selection of individuals with higher genetic risk into deprived35 and urban36 settings. However, we have previously shown in this cohort that these associations persist after controlling for numerous measures of genetic risk.22

Conclusions

Our study builds on emerging evidence that cognitive ability occupies a pathway between socioenvironmental adversities and psychosis. We extend this evidence to early psychotic experiences and specific cognitive abilities. If replicated, these findings suggest that interventions to enhance cognitive development during childhood could increase resilience to psychotic experiences and potentially later psychopathology among children raised in disadvantaged circumstances.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

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Conflict of Interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

References


