Associations between childhood victimization, inflammatory biomarkers and psychotic phenomena in adolescence: A longitudinal cohort study

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ABSTRACT

Exposure to victimization in childhood has been linked to the development of psychosis. However, little is known about how childhood victimization is translated into biological risk for psychosis. One possibility is via increased inflammation. This study aimed to investigate the association between childhood victimization, psychotic experiences (PEs) in adolescence and inflammatory markers using data from a general population cohort. Participants were 1,419 British-born children followed from birth to age 18 years as part of the Environmental Risk Longitudinal Twin Study. Childhood victimization was measured prospectively using multiple sources from birth to age 12 years. PEs were assessed during private interviews with participants at age 18 years for the period since age 12. Plasma C-reactive protein (CRP), interleukin-6 (IL-6), and soluble urokinase plasminogen activator receptor (suPAR) levels were measured from plasma samples collected from participants at 18 years. Young people with both PEs and childhood victimization were more likely to belong to a group with elevated suPAR, CRP and IL-6 levels at 18 years of age (OR = 3.34, 95% CI 1.69–6.59, p = 0.001) than those with no childhood victimization and without PEs. However, this association was attenuated when adjusted for other risk factors for elevated inflammation at age 18 (OR = 1.94, 95% CI 0.94–4.04, p = 0.075). In contrast, presence of PEs without childhood victimization was not significantly associated with age-18 inflammatory markers and neither was childhood victimization without PEs (all p's greater than 0.05). The current study highlights that inflammatory dysregulation is mostly present in adolescents reporting PEs who also experienced childhood victimization, though this seemed to be largely due to concurrent inflammation-related risk factors.

1. Background

Childhood victimization, including physical, sexual or emotional abuse, neglect, bullying by peers, and exposure to domestic violence, can lead to long-term mental and physical health consequences across the life-course (Shonkoff and Garner, 2012; Takizawa et al., 2014). Children exposed to early life stressors show elevated rates of vascular diseases, diabetes, autoimmune disorders, and premature mortality

(Miller et al., 2011a), as well as higher rates of severe and disabling psychiatric disorders (Green et al., 2010). General population studies have suggested that childhood victimization may also be associated with the presence of psychotic symptoms in childhood and young adulthood (De Loore et al., 2007; Wolke et al., 2013; Arseneault et al., 2011). Such early psychotic symptoms represent a developmental risk for adult schizophrenia (Fisher et al., 2013; Poulton et al., 2000) and thus provide a framework for investigating aetiological factors for later psychosis

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(Kelleher et al., 2012a) as well as being potential targets for its prevention. Recent studies have shown that early biological changes are associated with psychotic disorders years later and may provide clues to the underlying pathophysiological mechanisms (English et al., 2018).

One potential biological mechanism is inflammation. The immune system is the body's first response against pathogenic organisms that represent a threat and it resolves once the threat has passed (Johnson et al., 2013). However, both human and animal studies suggest that childhood exposure to stress (such as victimization) can trigger a persistent inflammatory response, which could lead to the development of mental health problems through impacting on brain development, behavior and reactivity to later stressors (Danese and Baldwin, 2017). For example, studies conducted in humans have reported associations between childhood victimization and higher concentrations of systemic markers of inflammation, such as the cytokine interleukin-6 (IL-6) and the acute phase reactant C-reactive protein (CRP), in blood or saliva samples (Baldwin et al., 2018; Baumeister et al., 2016; Danese et al., 2007, 2011; Takizawa et al., 2015).

Furthermore, recent studies showed that cumulative exposure to childhood maltreatment was associated with significant elevation in soluble urokinase plasminogen activator receptor (suPAR) in young adults (Rasmussen et al., 2020) and mid-adulthood (Rasmussen et al., 2019). During immune and proinflammatory conditions, suPAR is released into the systemic circulation by the cleavage of the membrane-bound Urokinase receptor uPAR (Dekkers et al., 2000; Ostrowski et al., 2005) that is expressed on immune and endothelial cells and involved in several cellular processes, including adhesion, differentiation, proliferation, and migration (Blasi and Carmeliet, 2002). While CRP and IL-6 are markers which are affected by acute fluctuations in inflammation levels, for instance as a result of infections (Hunter and Jones, 2015; Rhodes et al., 2011), suPAR reflects a person's overall level of immune activity and has been shown to be predictive of low-grade chronic inflammation and organ damage (Desmedt et al., 2017; Lyngbæk et al., 2013), development and progression of disease, adverse clinical outcomes, and mortality (Eugen-Olsen et al., 2010; Rasmussen et al., 2016), and thus is a useful additional measure of enduring inflammatory response.

A significant aetiological role for immune-related processes and inflammation has been shown in the pathophysiology of psychosis (Sekar, 2016). Studies conducted mostly in animals have suggested that an increase in inflammatory biomarker levels may lead to decreased availability of serotonin, activation of the hypothalamic–pituitary-adrenal axis, and higher oxidative stress in the brain (Dantzer et al., 2008). There is limited evidence from cross-sectional human studies (Miller et al., 2011b, 2014) that increased IL-6 and CRP levels occur in psychosis, although most studies conducted on human samples did not control for potential confounding factors known to influence cytokine levels. These findings are supported by longitudinal studies using general population samples, including the Avon Longitudinal Study of Parents and Children birth cohort (ALSPAC). Specifically, higher levels of proinflammatory cytokines in childhood were found to be associated with increased risk for psychotic symptoms in adolescence and early adulthood (Khandaker et al., 2014; Metcalf et al., 2017) suggesting potential causal pathways between elevated inflammatory markers and psychosis. An abnormal biological response to stress persists at the onset of psychosis (Fraguas et al., 2019; Russell et al., 2015; Zajkowska and Mondelli, 2014), as well as predicting a poor treatment response (Mondelli et al., 2015, 2020; Nettis et al., 2019). Inflammation might represent a common underlying mechanism for a multitude of physical and mental health problems including depression, schizophrenia, cardiovascular diseases and diabetes that also are likely to co-occur with each other (Pradhan et al., 2001; Danesh et al., 2008; Khandaker et al., 2020; Metcalf et al., 2017). It is plausible that exposure to childhood victimization increases levels of circulating inflammatory biomarkers which in turn trigger the development of psychotic phenomena. Indeed, studies have suggested that the increase in pro-inflammatory cytokines

seen in psychosis may be attributable to the effects of child maltreatment (Corsi-Zuelli et al., 2019; Aas et al., 2017; Hepgul et al., 2012; Dennison et al., 2012), however findings are still inconsistent (Counotte et al., 2019).

The timing of the impact of childhood victimization on inflammation in individuals with psychotic symptoms also remains unclear, and specifically whether the association is present among youth experiencing early manifestations of psychosis. This is important to ascertain to guide prevention efforts. To address this research question, we investigated the association between childhood victimization, inflammatory biomarkers and pre-clinical psychotic experiences in a population-representative sample of children followed from birth to age 18. We hypothesized that higher levels of inflammatory biomarkers (CRP, IL-6 and suPAR) would be present among adolescents experiencing pre-clinical psychotic phenomena who had been victimized during childhood compared to those who had not been victimized and those without psychotic experiences.

2. Methods

2.1. Study cohort

Participants were members of the Environmental Risk (E-Risk) Longitudinal Twin Study, which tracks the development of a birth cohort of 2232 British children. The sample was drawn from a larger birth register of twins born in England and Wales in 1994–1995 (Trouton et al., 2002). Briefly, the E-Risk sample was constructed in 1999–2000, when 1116 families (93% of those eligible) with same-sex 5-year-old twins participated in home visit assessments (Moffitt and E-Risk Study Team, 2002). This sample comprised 56% monozygotic (MZ) and 44% dizygotic (DZ) twin pairs; sex was evenly distributed within zygosity (49% male). E-Risk participants are representative of UK households across the spectrum of neighborhood socioeconomic conditions: 27.0% of E-Risk participants lived in "wealthy achiever" neighborhoods compared to 25.4% of households nationwide, 7.2% vs 11.5% lived in "urban prosperity" neighborhoods, 26.8% vs 27.4% lived in "comfortably off" neighborhoods, 13.2% vs 13.8% lived in "moderate means" neighborhoods, and 25.8% vs 21.2% lived in "hard-pressed" neighborhoods (Odgers et al., 2012). E-Risk underrepresents urban prosperity neighborhoods because such households are likely to be childless.

Follow-up home visits were conducted when the children were aged 7 (98% participation), 10 (96%), 12 (96%), and 18 (93%) years. Home visits at ages 5, 7, 10, and 12 years included assessments with participants as well as their mother (or primary caretaker); the home visit at age 18 included structured interviews only with the participants. Each twin participant was assessed by a different interviewer. The average age of the twins at the time of the age-18 assessment was 18.4 years (*SD* = 0.36); all structured interviews were conducted after the 18th birthday. There were no differences in family socioeconomic status (SES) assessed when the cohort was initially defined ($\chi^2 = 0.86$, $p = 0.65$), age-5 IQ scores ($t = 0.98$, $p = 0.33$), or age-5 internalizing or externalizing behavior problems ($t = 0.40$, $p = 0.69$, and $t = 0.41$, $p = 0.68$, respectively), between those who did and did not take part at age 18.

The Joint South London and Maudsley and the Institute of Psychiatry Research Ethics Committee approved each phase of the study. Parents gave informed consent and twins gave assent between 5 and 12 years and then informed consent at age 18.

2.2. Materials

2.2.1. Childhood victimization

Exposure to several types of victimization was assessed prospectively when the children were 5, 7, 10, and 12 years of age (the age 5 assessment enquired about victimization since birth).

Dossiers were compiled for each child with cumulative information about exposure to domestic 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.

The dossiers comprised reports of victimization from caregivers, recorded narratives of the caregiver interviews, recorded debriefings with research workers who had coded any indication of abuse and neglect at any of the successive home visits, information from clinicians whenever the study team made a child-protection referral, and reports from the children themselves concerning bullying. The dossiers were reviewed by two independent researchers and rated for the presence and severity (none/mild/severe) of each type of victimization. Inter-rater agreement between the coders exceeded 85% among the victimized cases, and discrepantly coded cases were resolved by consensus review. In the present study, each type of prospectively-reported victimization was dichotomized to represent none/mild (0) versus severe (1) victimization. Additional details about the prospective measure of childhood victimization have been reported previously (Danese et al., 2016, Fisher et al., 2015) and are provided in Appendix A.

We created a composite of 'any victimization' by combining all forms of prospectively reported severe victimization experiences. A severe rating of domestic violence, bullying by peers, physical abuse, sexual abuse, physical neglect, and/or emotional abuse/neglect equated to a rating of 'any severe victimization'. Among children in this study, 1641 (73.5%) had no severe childhood victimization experiences, 591 (26.5%) had 1 or more severe victimization experiences by age 12.

2.2.2. Psychotic phenomena

When participants were aged 12, they were privately interviewed about seven psychotic symptoms pertaining to delusions and hallucinations, with items including "have other people ever read your thoughts?", "have you ever thought you were being followed or spied on?", and "have you ever heard voices that other people cannot hear?". Items and interviewer notes were assessed by a psychiatrist expert in schizophrenia, a psychologist expert in interviewing children, and a child and adolescent psychiatrist to verify the validity of the symptoms. The item choice was guided by the Dunedin Study's age-11 interview protocol (Poulton et al., 2000) and an instrument prepared for ALSPAC (Schreier et al., 2009). Interviewers coded each experience 0, 1, 2 indicating respectively "not a symptom", "probable symptom", and "definite symptom". A conservative approach was taken in designating a child's report as a symptom. First, the interviewer probed using standard prompts designed to discriminate between experiences that were plausible (e.g., "I was followed by a man after school") and potential symptoms (e.g., "I was followed by an angel who guards my spirit"), and wrote down the child's narrative description of the experience. Second, items and interviewer notes were assessed by a psychiatrist expert in schizophrenia, a psychologist expert in interviewing children, and a child and adolescent psychiatrist to verify the validity of the symptoms. Third, because children were twins, experiences limited to the twin relationship (e.g., "My twin and I often know what each other are thinking") were coded as "not a symptom". Children were only designated as experiencing psychotic symptoms if they reported at least one definite symptom. This structured interview and coding procedure has been described in detail previously (Polanczyk et al., 2010). At age 12, 125 (5.9%) children were designated as experiencing at least 1 definite psychotic symptom. This is similar to the prevalence of psychotic symptoms in other community samples of children and adolescents (Kelleher et al., 2012b; Horwood et al., 2008). We have previously shown that childhood psychotic symptoms in this cohort have good construct validity, sharing many of the genetic, social, neurodevelopmental, and behavioral risk factors and correlates as adult schizophrenia (Polanczyk et al., 2010).

Each E-Risk participant was also privately interviewed at age 18 about 13 psychotic *experiences* occurring between ages 12 and 18. Seven items pertained to hallucinations and delusions (see Polanczyk et al.,

2010) and 6 items pertained to unusual experiences which drew on item pools since formalized in prodromal psychosis instruments including the Structured Interview for Prodromal Syndromes (Miller et al., 2003) and the Prodromal Questionnaire (Loewy et al., 2011). These additional items included: "I have become more sensitive to lights or sounds"; "I feel as though I can't trust anyone"; "I worry that my food may be poisoned"; "People or places I know seem different"; "I believe I have special abilities or powers beyond my natural talents"; "My thinking is unusual or frightening". Interviewers coded each item 0, 1, 2 indicating respectively "not present", "probably present", and "definitely present". All 13 items were summed to create a psychotic *experiences* scale (range = 0–18, M = 1.19, SD = 2.58). Just over 30% of participants had at least one psychotic *experience* between ages 12 and 18 (coded 1; n = 623, 30.2%), whereas 69.8% reported no psychotic experiences (coded 0; n = 1440). This 30.2% prevalence is similar to the prevalence of self-reported psychotic experiences in other community samples of teenagers and young adults (Spauwen et al., 2004; Yung et al. 2009; Yoshizumi et al., 2004). These self-reported experiences capture a broader spectrum of more commonly occurring subthreshold psychotic phenomena than psychotic symptoms and have not been subject to clinical verification.

We additionally examined clinician-verified adolescent psychotic *symptoms* as a secondary outcome, using the same methodology as used at age 12 in this cohort (see above and Polanczyk et al., 2010). Responses to the 7 hallucination/delusion items were verified by a team of clinicians, including child and adolescent psychiatrists, to capture more clinically pertinent psychotic symptoms. Between ages 12 and 18, 2.9% (n = 59) of participants were designated as having experienced at least 1 definite psychotic *symptom*.

2.2.3. Inflammatory biomarkers

Venous blood was collected at age-18 follow-up from 1700 of the 2066 participants (82.3%) with EDTA tubes. Tubes were spun at 2500 g for 10 min and plasma samples obtained. Samples were stored at −80C. 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 (suPARnosticAUTOFlex ELISA, ViroGatesA/S) following the manufacturer's protocol. The coefficient of variation was 6%.

2.2.4. Covariates

To adjust for the potentially confounding effects of individual and family characteristics we included as covariates the study participants' biological sex and family SES. We have previously shown that childhood victimization is associated with elevated CRP levels in young women, independent of latent genetic influences and other key risk factors (Baldwin et al., 2018). Similarly, low family SES is associated with high CRP levels (Danese et al., 2009) and psychotic phenomena (Polanczyk et al., 2010). Family SES at the age of 5 years was defined through a standardized composite of parental income, education and occupation. The three SES indicators were highly correlated (r = 0.57–0.67) and loaded significantly onto one latent factor. The population-wide distribution of the resulting factor was divided in tertiles for analyses (Trzesniewski et al., 2006).

Secondly, we adjusted for factors that are commonly associated with elevated inflammation and thus might confound the associations with psychotic experiences and childhood victimization. Body fat mass is strongly correlated with markers of chronic inflammation (Festa et al., 2001) and a dose-dependent effect of childhood maltreatment on higher body mass index (BMI) and hs-CRP has been shown in individuals with schizophrenia (Aas et al., 2017). BMI (kg/m^2) was measured at age 18; overweight was defined as a BMI greater than or equal to 25 (n = 519,

25.6%). To account for the possible effect of unrecognized infectious and inflammatory disorders on inflammation levels (Danese et al., 2011), we adjusted for body temperature measured by trained research workers (via infrared digital ear thermometer Omron GT510) at the time of biomarker assessment at age 18. Daily cigarette smoking was assessed at age 18; current daily smokers (n = 461, 22.3%) were participants who endorsed daily smoking within the past year. Researchers also recorded, at age 18, participants' current illness and injury and use of anti-inflammatory medication (corticosteroids) within the past 2 weeks. The current illness or injury index is a count of 16 conditions present on the day of blood sample obtainment including: fever, swollen lymph glands, persistent cough, cold, influenza, asthma, repeated diarrhoea, eye pain/infection, bleeding gums, toothache, sore throat, tonsillitis, ear pain/infection, major bruising, major cuts (including tattoos), and sprains.

Furthermore, history of childhood victimization may contribute to the co-occurrence of depression and inflammation (Danese et al., 2009). As such, we controlled for the presence of depressive disorder over the previous 12 months assessed during the age-18 interview (n = 414, 20.1%) according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria (American Psychiatric Association, 1994). Individuals who develop post-traumatic stress disorder (PTSD) also show elevated inflammation levels (Passos et al., 2015) and we therefore adjusted for PTSD (n = 90, 4.4%) assessed at age 18 according to DSM-5 criteria (American Psychiatric Association, 2013).

Finally, to test whether victimization specifically occurring in childhood was associated with inflammation, we adjusted analyses for victimization exposure during adolescence. Severe adolescent experiences of victimization between the ages of 12 and 18 years were assessed at age 18 when the twins were interviewed using the Juvenile Victimization Questionnaire 2nd revision (JVQ-R2; Finkelhor et al., 2011; Hamby et al., 2004) adapted as a clinical interview (see Fisher et al., 2015 for full details). Exposure to seven different types of victimization (crime, peer or sibling violence, cyber-victimization, sexual abuse, maltreatment, family violence, and neglect) during adolescence were each coded on a 3-point scale (0 indicating no exposure, 1 indicating probable or less severe exposure, and 2 indicating definite or severe exposure). In this study, 1332 adolescents (64.6%) had no severe victimization experiences, and 730 (35.4%) were exposed to 1 or more types of severe victimization during adolescence.

2.3. Statistical analyses

Stata, version 15, was used for all analyses (StataCorp, 2017). Of the 2066 children who participated in the E-Risk Study assessments at age 18 years, 1447 had complete data for psychotic experiences (PEs), childhood victimization (CV), age-18 CRP, IL-6 and suPAR levels. Furthermore, as done previously (Rasmussen et al., 2020) 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 as they were likely to have acute trauma, infections, or pathology (Pearson et al., 2003), leaving a total of 1419 participants in the study sample. Participants with complete data did not differ from those with missing data with regard to age-5 family SES ($\chi^2(2)$ = 2.2, p = 0.326), but significant differences were present in terms of childhood victimization ($\chi^2(1)$ = 5.8, p = 0.016) and sex ($\chi^2(1)$ = 6.2, p = 0.013).

Both CRP and IL-6 levels were log-transformed to improve normality of their distributions, as previously done (Rasmussen et al, 2020). We calculated mean differences in age-18 CRP, IL-6 and suPAR across the following four groups and compared them using t-tests: 1) children with no severe victimization and without age-18 PEs (controls; n = 753), 2) children with no severe victimization and with age-18 PEs (PE only; n = 266), 3) children with any severe victimization and without age-18 PEs (CV only; n = 235), 4) children with any severe victimization and with age-18 PEs (CV + PE; n = 165).

We used ordinary least squares regression, reporting unstandardized

B and standardized β coefficients with 95% confidence intervals (CIs), to test for the association between PEs and continuous measures of CRP, IL-6 and suPAR levels in individuals presenting with and without severe childhood victimization.

In addition, we previously performed a latent class analysis (LCA) that combined ln(CRP), ln(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 (Rasmussen et al., 2020). This combined approach is important as high suPAR levels have been found to be positively correlated with CRP and IL-6 both in general and clinical populations (Rasmussen et al., 2019; Zimmermann et al., 2012), which may be due to unmeasured, latent influences. LCA is a person-centered technique that classifies individuals into groups based on a profile of variables, in this case each participant's level (i.e., elevated or low) of the 3 biomarkers. The advantages of LCA over other statistical models is that the optimal number of classes is decided using clear fit statistics, and people are assigned to classes using probabilistic routines, allowing hypothesis testing for different models and reducing the amount of subjectivity in model choice. Each person has a probability of membership in each subgroup, as opposed to an absolute assignment given by other methodologies. LCA-related techniques have been increasingly used in previous studies including childhood victimisation and inflammation (Lacey et al., 2020), as well as in different fields to investigate longitudinal trajectories of physical health functions (Schumacher & Kraft, 2007) and genome analysis (Norton et al., 2014).

For CRP we used the established clinical cut-off to identify participants with high CRP levels (3 mg/L [to convert to nanomoles per liter, multiplied by 9.524]); thus, high CRP level indicates a CRP level greater than 3 mg/L (n = 287; 20.6%). Clinical cut-offs for suPAR and IL-6 have not yet been established. To identify participants with high suPAR or high IL-6 levels, we chose a cut-off 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%). The latent class analysis was conducted in MPlus, version 7.4, accounting for clustering of twins within families and was reported in our previous paper on inflammation in this cohort (Rasmussen et al., 2020). In our study, 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 (Rasmussen et al., 2020). The LCA identified 3 inflammation groups of individuals: low levels of all 3 biomarkers, elevated CRP and IL-6 levels, and elevated CRP, IL-6, and suPAR levels (Supplementary Table B1). We used multinomial logistic regression, reporting ORs with 95% CIs, to test for the association between PEs and the 3 inflammation groups, in individuals presenting with and without severe childhood victimization.

All associations were adjusted for the non-independence of twin observations (Model 1) using the Huber-White variance estimator (Williams, 2000). We also checked whether these associations were robust after controlling for (i) sex and family SES (Model 2); (ii) plus from the age-18 assessment: being overweight, body temperature, daily smoking, current illness and injury, and use of anti-inflammatory medications over the past 2 weeks (Model 3); and (iii) all of the aforementioned covariates plus past-year depressive disorder and PTSD (Model 4).

We conducted a series of sensitivity analyses. Firstly, we replaced self-reported PEs with the presence/absence of any clinician-verified psychotic symptoms (PS) at age 18. Secondly, we used age-12 clinician-verified psychotic symptoms to explore longitudinal associations with age-18 inflammation. We tested in the whole sample whether the four groups of children with and without severe childhood victimization

and clinician-verified psychotic symptoms at age 12 (controls: n = 949; PS only: n = 37; CV only: n = 341; CV + PS: n = 51) differed in their CRP, IL-6 and suPAR levels and the combined inflammation groups at age 18. Thirdly, we included adolescent victimization in the main models to explore whether it accounted for associations between childhood victimization, psychotic phenomena and inflammatory makers (Model 5).

3. Results

3.1. Do adolescents with psychotic experiences (PEs) have elevated inflammation levels?

Of the 1419 individuals, a total of 431 reported one or more PEs between ages 12 and 18 (30.4%). Young adults with one or more PEs had higher BMI, lower family SES in childhood, were more likely to have been exposed to any severe victimization in childhood, smoke cigarettes, have a current illness or injury, and suffer from major depression and PTSD compared to participants without PEs (Table 1). There were no differences for biological sex, use of anti-inflammatory medications and body temperature between young adults with and without PEs.

Participants with PEs between ages 12 and 18 had higher mean levels of suPAR, but not CRP or IL-6 at 18 years of age compared to participants without PEs (Table 1). There was also a significantly higher prevalence of individuals with PEs within the elevated CRP, IL-6 and suPAR combined group. When the inflammatory biomarkers were analysed separately (Table 2, Model 1), there was a significant association between PEs and suPAR (B = 0.13, 95% CI 0.01–0.25, p = 0.035), though it became non-significant after adjusting for covariates (Table 2, Models 2–4). No associations were found for CRP or IL-6. Moreover, participants with PEs between ages 12 and 18 had two-fold greater odds of combined elevated levels of CRP, IL-6 and suPAR at age 18 compared with those without PEs (Table 2, Model 1), and this association remained significant after controlling for participants' sex and family SES (Table 2, Model 2). However, when body temperature, being overweight, daily smoking, current illness and injury, anti-inflammatory medication, depression and PTSD at age 18 were entered into the model the association was attenuated and became non-significant (Table 2, Models 3 and 4).

Similarly, in a sensitivity analysis when we restricted the analyses to clinician-verified psychotic symptoms at age 18, participants with these symptoms had three times greater odds of having combined elevated levels of CRP, IL-6 and suPAR at age 18 than those without these symptoms (Supplementary Table B2, Model 1). This association remained significant after adjusting for confounders (Table B2, Models 2–4).

In a second sensitivity analysis, psychotic symptoms at age 12 were significantly associated with high CRP and high IL-6 at age 18, both separately and combined (Table B3) and the associations were robust to confounders (Table B3, Models 2–4). No association was found between childhood psychotic symptoms and high suPAR at age 18 (Table B3, Models 1–4).

3.2. Do associations between PEs and inflammation at age 18 vary by exposure to childhood victimization?

Fig. 1 shows the mean levels of each inflammatory biomarker at age 18 stratified by the four study groups (controls, PE only, CV only, CV + PE). Mean levels of CRP at age 18, and to a very small extent levels of suPAR, appeared to be highest in the CV + PE group, whilst levels of IL-6 were highest in the CV only group (Fig. 1).

Table 3 shows the associations between the study groups and the age-18 inflammatory biomarker levels. Individuals with childhood victimization and adolescent PEs were more likely to have high suPAR levels (B = 0.33, 95% CI = 0.13–0.53, p = 0.001) than controls. The association remained significant after adjusting for sex and childhood SES (Table 3,

Table 1

Characteristics of the sample (n = 1419) and inflammatory biomarker levels at age 18 between those with and without adolescent psychotic experiences (PEs).

Variables	Total sample N = 1419	PEs absent n = 988	PEs present n = 431	Group differences	p value
Male, No. (%)	666 (46.9)	452 (45.8)	214 (49.7)	$\chi^2(1) = 1.8$	0.175
Low family socioeconomic status, No. (%)	480 (33.8)	300 (30.4)	180 (41.8)	$\chi^2(2) = 25.1$	**<0.001**
Any severe childhood victimization, No. (%)	400 (28.2)	235 (23.8)	165 (38.3)	$\chi^2(2) = 31.2$	**<0.001**
Overweight, No. (%)	343 (24.6)	224 (23.1)	119 (28.2)	$\chi^2(1) = 4.2$	**0.040**
Daily smoking, No./total No. (%)	330/1417 (23.3)	176/986 (17.9)	154/431 (35.7)	$\chi^2(1) = 53.7$	**<0.001**
Body temperature, mean (SE), °C	36.34 (0.02)	36.34 (0.02)	36.35 (0.03)	$t = 0.26$	0.793
Anti-inflammatory medication use, No./total No. (%)[a]	17/1419 (1.2)	14/988 (1.4)	3/431 (0.7)	$\chi^2(1) = 1.3$	0.251
Current illness or injury[b]	335 (23.6)	207 (21.0)	128 (29.7)	$\chi^2(1) = 12.7$	**<0.001**
Major depression, No. (%)	274 (19.3)	116 (11.8)	158 (36.7)	$\chi^2(1) = 119.9$	**<0.001**
PTSD, No. (%)	90 (4.37)	20 (1.4)	70 (11.3)	$\chi^2(1) = 101.7$	**<0.001**
Inflammatory biomarkers, mean (SE)					
suPAR level, ng/mL	3.23 (0.02)	3.19 (0.03)	3.32 (0.05)	$t = 2.44$	**0.015**
CRP level, mg/L[c]	2.34 (0.10)	2.25 (0.11)	2.55 (0.20)	$t = 1.39$	0.165
IL-6 level, pg/mL[c]	1.20 (0.03)	1.20 (0.04)	1.18 (0.05)	$t = 0.33$	0.742
Inflammation groups, No. (%)				$\chi^2(2) = 9.6$	**0.008**
Low Inflammation	1057 (76.0)	749 (77.2)	308 (73.3)		
Elevated CRP and IL-6	249 (17.9)	175 (18.0)	74 (17.6)		
Elevated CRP, IL-6 and suPAR	84 (6.0)	46 (4.7)	38 (9.1)		

Notes: Overweight = body mass index (BMI) greater than or equal to 25 (calculated as weight in kilograms divided by height in meters squared); CRP, C-reactive protein; IL-6, interleukin 6; PTSD, post-traumatic stress disorder; suPAR, soluble urokinase plasminogen activator receptor. Results from the log transformed data have been exponentiated. Statistically significant results (p < 0.05) are presented in bold text.

[a] Any use of anti-inflammatory medication (corticosteroids) in the past 2 weeks.

[b] The current illness or injury index is a count of 16 conditions present on the day of blood sample obtainment including: fever, swollen lymph glands, persistent cough, cold, influenza, asthma, repeated diarrhoea, eye pain/infection, bleeding gums, toothache, sore throat, tonsillitis, ear pain/infection, major bruising, major cuts (incl. tattoos), sprains.

[c] Log-transformed (natural logarithm).

Model 2), however the effect was attenuated and no longer significant after adjustment for potential covariates at age 18 (Table 3, Models 3 and 4). No significant associations were evident for the other inflammatory biomarkers.

Participants with childhood victimization only showed higher suPAR (B = 0.21, 95% CI = 0.05–0.36, p = 0.008) levels compared to the control group (Table 3, Model 1). The associations were non-significant when potential confounders were included in the model (Table 3,

Table 2
Association between levels of inflammatory biomarkers at age 18 and adolescent psychotic experiences (n = 1419).

Inflammation variables	Model 1[a]			Model 2[b]			Model 3[c]			Model 4[d]		
	B (95% CI)	β (95% CI)	p value	B (95% CI)	β (95% CI)	p value	B (95% CI)	β (95% CI)	p value	B (95% CI)	β (95% CI)	p value
Inflammatory markers												
suPAR	**0.13** (0.01; 0.25)	**0.14** (0.01; 0.27)	**0.035**	0.11 (−0.01; 0.22)	0.12 (−0.01; 0.24)	0.064	0.02 (−0.09; 0.12)	0.02 (−0.10; 0.13)	0.757	0.00 (−0.11; 0.11)	0.00 (−0.11; 0.12)	0.960
CRP	0.03 (−0.14; 0.20)	0.02 (−0.10; 0.14)	0.748	0.02 (−0.15; 0.19)	0.02 (−0.11; 0.14)	0.804	−0.05 (−0.22; 0.11)	−0.04 (−0.16; 0.08)	0.512	0.01 (−0.16; 0.18)	0.01 (−0.12; 0.13)	0.930
IL−6	0.00 (−0.07; 0.07)	0.00 (−0.12; 0.11)	0.962	−0.02 (−0.09; 0.05)	−0.03 (−0.14; 0.08)	0.626	−0.05 (−0.12; 0.02)	−0.07 (−0.18; 0.04)	0.202	0.02 (−0.10; 0.05)	0.04 (−0.15; 0.08)	0.543
Inflammation groups												
	OR (95% CI)	p value		OR (95% CI)	p value		OR (95% CI)	p value		OR (95% CI)	p value	
Low Inflammation	[reference]			[reference]			[reference]			[reference]		
Elevated CRP and IL-6	1.03 (0.75; 1.41)	0.861		1.00 (0.73; 1.38)	0.992		0.86 (0.62; 1.19)	0.373		0.98 (0.70; 1.38)	0.926	
Elevated CRP, IL-6, and suPAR	**2.01** (1.22; 3.30)	**0.006**		**1.89** (1.15; 3.12)	**0.012**		1.47 (0.88; 2.43)	0.138		1.46 (0.87; 2.48)	0.155	

Notes: B, unstandardized beta coefficient for ordinary least squares regression model, in which a 1-unit change in the variable (e.g., psychotic experiences) is associated with a corresponding change in B, holding all other variables constant; β, standardized beta coefficient; CI, confidence interval; CRP, C-reactive protein; IL-6, interleukin 6; OR, odds ratio derived using multinomial logistic regression; suPAR, soluble urokinase plasminogen activator receptor. The N within each model is restricted to participants with non-missing data on all variables included in the multivariate models. The comparison group is those who did not report any psychotic experiences at age 18. Statistically significant results ($p < 0.05$) are presented in bold text.

[a] Model 1: adjusted for the non-independence of twin observations.
[b] Model 2: adjusted for the non-independence of twin observations, sex and family socio-economic status.
[c] Model 3: adjusted for the non-independence of twin observations, sex, family socio-economic status, plus body temperature, overweight (body mass index greater than or equal to 25), daily smoking, current illness and injury, and anti-inflammatory medication measured at age 18.
[d] Model 4: adjusted for the non-independence of twin observations, sex and family socio-economic status, body temperature, overweight, daily smoking, current illness and injury, anti-inflammatory medication, plus major depression and post-traumatic stress disorder measured at age 18.

Models 2–4) even when further adjusting for adolescent victimization (Table B4). No significant associations were evident for the other inflammatory biomarkers. Individuals in the PE only group did not show a significant elevation in any of the inflammatory biomarkers (see Table 3).

When we repeated the analyses for the combined inflammation groups, those with childhood victimization and adolescent PEs had three times greater odds of having elevated levels of CRP, IL-6 and suPAR than individuals in the control group (Table 4, Model 1), however the association was reduced when adjusted for confounders at age 18 (Table 4, Models 2–4; and Table B4).

Longitudinal analyses of the association between study groups at age 12 and inflammatory biomarkers at age 18, showed that victimized-only children were more likely to have high suPAR levels compared to controls (Table B5, Models 1–2), but the association fell short of statistical significance after adjustment for body temperature, overweight, daily smoking, current illness, and anti-inflammatory medication (Table B5, Model 3). Participants with childhood psychotic symptoms who had additionally experienced childhood victimization had significantly higher IL-6 levels at age 18 compared to controls (no CV and no age-12 PS), also after adjustment for potential covariates and adolescent victimization (Table B5, Model 5). In terms of the combined inflammation groups, those with CV-only and those with CV + PS had significantly elevated levels of CRP, IL-6 and suPAR at age 18 compared to those with low inflammation levels (Table B5, Model 1). However, after adjustment for all covariates and adolescent victimization, only the children with CV + PS had significantly elevated levels of all three inflammatory biomarkers (Table B5, Model 5).

4. Discussion

In this longitudinal cohort study, we investigated associations between childhood victimization, psychotic phenomena, and inflammatory biomarkers in adolescence. First, our cross-sectional analyses showed that adolescents with PEs had higher mean levels of suPAR but not of CRP and IL-6 when compared to adolescents without PEs, however the association was not significant after adjustment for covariates. We also found that those with PEs were more likely to belong to a small group of participants (6% of the sample) with elevated levels of all three inflammatory markers when considered together than those without PEs. However, these associations were not robust to covariates, with associations becoming substantially attenuated after adjustment for concurrent inflammation-related risk factors. The longitudinal analyses showed that children presenting with clinician-verified psychotic symptoms at age 12 were more likely to belong to the group with both elevated CRP and IL-6 levels at age 18. Previous cross-sectional and longitudinal studies (Howren et al., 2009; Miller et al., 2014; Nielsen et al., 2015) have suggested that increased IL-6, CRP and suPAR levels might occur in adult psychosis. These results support the hypothesis that an inflammatory process might be involved in psychosis although it might be moderated by other risk factors for inflammation (Mondelli and Vernon, 2019; Sabherwal et al., 2016; Smyth and Lawrie, 2013). Interestingly, in contrast with previous findings, in our sample we did not find a specific association between CRP, IL-6 and psychotic phenomena in young adults when inflammatory biomarkers were analysed separately. It is possible that the null findings could be due to random measurement error due to diurnal variation of inflammation levels (Rudnicka et al., 2007) which might increase the likelihood of null findings.
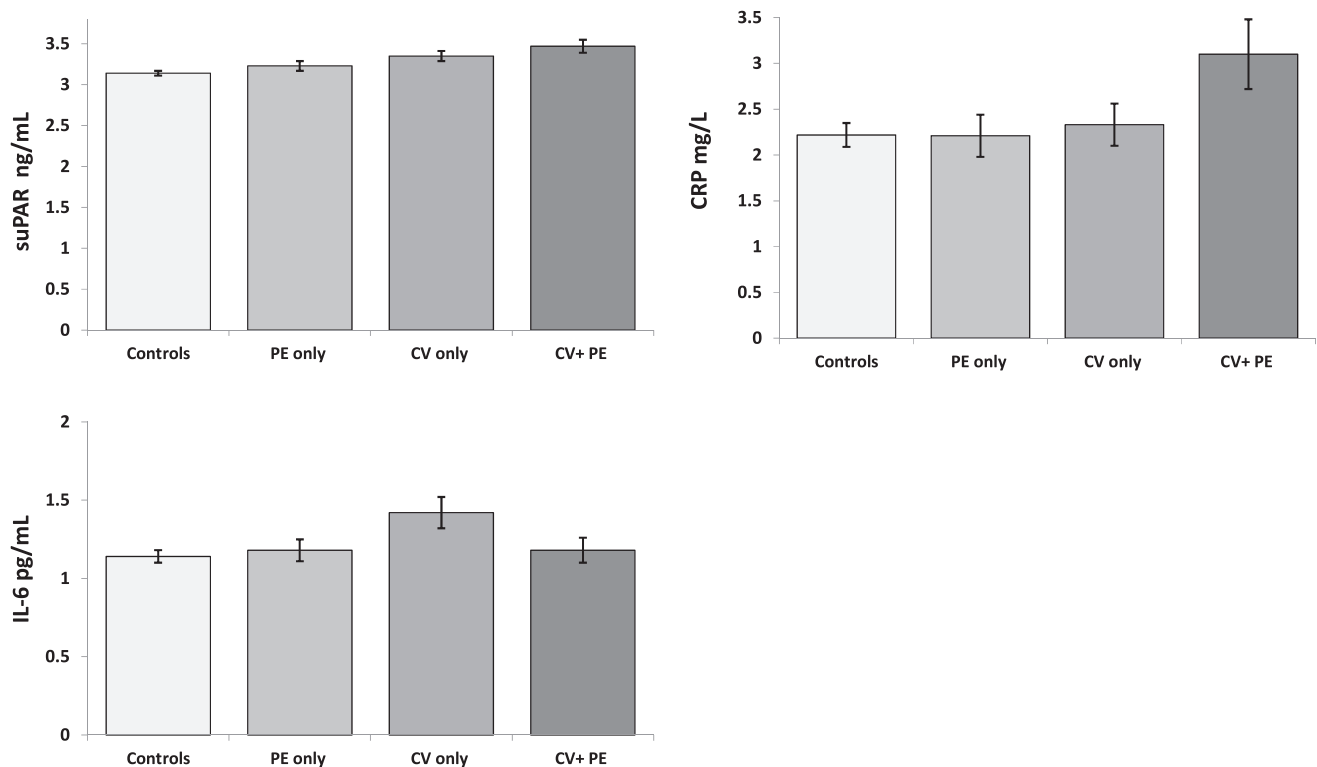
Notes: CRP, C-reactive protein; CV, childhood victimization; IL-6, interleukin-6; PE, psychotic experiences between ages 12-18 years; suPAR, soluble urokinase plasminogen activator receptor. Study groups: 1) children with no severe victimization and without adolescent psychotic experiences (controls; n=753); 2) children with no severe victimization and with adolescent psychotic experiences (PE only; n=266); 3) children with any severe victimization and without adolescent psychotic experiences (CV only; n=235); 4) children with any severe victimization and with adolescent psychotic experiences (CV + PE; n=165). Error bars indicate standard errors.

Fig. 1. Mean levels of inflammatory biomarkers at age 18 stratified by adolescent psychotic experiences and/or exposure to childhood victimization. Notes: CRP, C-reactive protein; CV, childhood victimization; IL-6, interleukin-6; PE, psychotic experiences between ages 12–18 years; suPAR, soluble urokinase plasminogen activator receptor. Study groups: 1) children with no severe victimization and without adolescent psychotic experiences (controls; n = 753); 2) children with no severe victimization and with adolescent psychotic experiences (PE only; n = 266); 3) children with any severe victimization and without adolescent psychotic experiences (CV only; n = 235); 4) children with any severe victimization and with adolescent psychotic experiences (CV + PE; n = 165). Error bars indicate standard errors.

Previous studies have shown that a history of childhood victimization is associated with elevated CRP levels (Danese et al., 2007; Copeland et al., 2014; Baumeister et al., 2016; Takizawa et al., 2015; Baldwin et al., 2018). However, we did not find associations between childhood victimization and CRP (or IL-6) in this study when the biomarkers were studied individually. CRP and IL-6 are traditionally utilised in research studies to capture levels of inflammation, but they may mix chronic and acute effects due to their sensitivity to short-term influences and involvement in the acute-phase response (Hunter and Jones, 2015; Rhodes et al., 2011), leading to variability in findings (Baumeister et al., 2016). The 6–12-year window in our study between exposure to victimization and assessment of inflammation may have resulted in us being unable to detect such acute fluctuations in the levels of these biomarkers. Indeed, associations between childhood victimization and the newer biomarker suPAR, the stability of which over time makes it a more reliable index of cumulative inflammation over the life course (Desmedt et al., 2017), were found in our study in the unadjusted models. suPAR has repeatedly been shown to be associated with adverse childhood experiences (Rasmussen et al., 2019, 2020) and adult stressful life events (Bourassa et al., 2021), while CRP and IL-6 were not consistently associated with these stressors. Furthermore, in relation to PEs, we found that associations between adolescent PEs and inflammatory biomarkers were present only in those who had also experienced childhood victimization. This tentatively suggests that a history of childhood victimization may have a significant role in explaining the co-occurrence of psychotic experiences and elevated inflammation in adolescence.

In this prospective cohort study, we observed the strongest associations between childhood victimization, adolescent psychotic experiences and inflammation at age 18 when combining biomarkers, however the association was reduced after adjusting for body temperature, being overweight, daily smoking, current illness and injury, anti-inflammatory medication, major depressive disorder and PTSD at age 18 and also victimization during adolescence. This might indicate that specific risk factors for inflammation can intervene in the association with childhood victimization and psychotic phenomena. Individuals with a history of childhood victimization are more likely to engage in risky health behaviors, such as smoking and use of medication, as well as be obese, which may explain the relationship between early victimization, inflammation, and psychotic phenomena (Danese and Baldwin, 2017; Ramiro et al, 2010). Recently, epidemiological studies have shown the presence of immunometabolic dysregulations in patients with depression (Lamers et al., 2020) and psychosis (Nettis et al., 2019). Stratification of patients according to immunometabolic markers may therefore help to identify subgroups of individuals more likely to respond to specific therapies (Milaneschi et al 2020). Future research is required to explore such stratification in general population samples and the potential for this to inform preventive interventions.

A recent *meta*-analysis also suggested that 24.2% of children exposed to a traumatic event meet the criteria for depression (Vibhakar et al., 2019) and that childhood maltreatment might lead to victimization by peers in adolescence (Benedini et al., 2016), thus also pointing to potential explanations for our findings. Nonetheless, our longitudinal associations between childhood psychotic symptoms and higher

Table 3

Association between childhood victimization, adolescent psychotic experiences and high levels of inflammatory markers at age 18.

Inflammation variables	PE only (n = 266)			CV only (n = 235)			CV + PE (n = 165)		
	B (95% CI)	β (95% CI)	p value	B (95% CI)	β (95% CI)	p value	B (95% CI)	β (95% CI)	p value
Inflammatory markers									
Model 1[a]									
suPAR	0.09 (−0.05; 0.23)	0.09 (−0.06; 0.25)	0.230	**0.21** (0.05; 0.36)	**0.22** (0.06; 0.39)	**0.008**	**0.33** (0.13; 0.53)	**0.35** (0.14; 0.57)	**0.001**
CRP	−0.04 (−0.24; 0.16)	−0.03 (−0.17; 0.11)	0.683	0.10 (−0.12; 0.33)	0.08 (−0.09; 0.24)	0.361	0.20 (−0.07; 0.48)	0.15 (−0.05; 0.35)	0.145
IL-6	0.02 (−0.06; 0.11)	0.04 (−0.10; 0.17)	0.578	0.11 (0.00; 0.23)	0.18 (0.00; 0.36)	0.053	0.03 (−0.09; 0.14)	0.04 (−0.13; 0.22)	0.638
Model 2[b]									
suPAR	0.05 (−0.08; 0.18)	0.05 (−0.09; 0.20)	0.457	0.14 (−0.01; 0.30)	0.15 (−0.01; 0.32)	0.066	**0.30** (0.11; 0.49)	**0.32** (0.12; 0.52)	**0.002**
CRP	−0.06 (−0.26; 0.14)	−0.04 (−0.19; 0.10)	0.566	0.08 (−0.15; 0.31)	0.06 (−0.11; 0.22)	0.485	0.21 (−0.07; 0.48)	0.15 (−0.05; 0.35)	0.138
IL-6	0.01 (−0.08; 0.09)	0.01 (−0.12; 0.15)	0.866	0.09 (−0.03; 0.21)	0.14 (−0.05; 0.33)	0.148	0.00 (−0.12; 0.12)	0.00 (−0.18; 0.19)	0.985
Model 3[c]									
suPAR	0.00 (−0.13; 0.13)	0.00 (−0.14; 0.14)	0.985	0.12 (−0.02; 0.27)	0.13 (−0.02; 0.29)	0.097	0.14 (−0.04; 0.32)	0.15 (−0.05; 0.34)	0.133
CRP	−0.08 (−0.27; 0.11)	−0.06 (−0.20; 0.08)	0.401	0.05 (−0.18; 0.27)	0.03 (−0.13; 0.20)	0.674	0.03 (−0.23; 0.30)	0.02 (−0.17; 0.22)	0.803
IL-6	0.00 (−0.09; 0.08)	−0.01 (−0.14; 0.13)	0.932	0.08 (−0.04; 0.20)	0.12 (−0.07; 0.31)	0.210	−0.07 (−0.18; 0.05)	−0.10 (−0.29; 0.08)	0.279
Model 4[d]									
suPAR	−0.01 (−0.14; 0.12)	−0.01 (−0.15; 0.13)	0.866	0.13 (0.02; 0.27)	0.14 (−0.02; 0.29)	0.085	0.13 (0.05; 0.32)	0.14 (−0.05; 0.34)	0.156
CRP	−0.03 (−0.23; 0.17)	−0.02 (−0.16; 0.13)	0.801	0.06 (−0.16; 0.29)	0.05 (−0.12; 0.21)	0.582	0.12 (−0.16; 0.41)	0.09 (−0.11; 0.29)	0.388
IL-6	0.02 (−0.07; 0.10)	0.02 (−0.11; 0.16)	0.727	0.08 (0.04; 0.21)	0.13 (0.06; 0.32)	0.175	−0.03 (−0.15; 0.09)	−0.05 (−0.24; 0.14)	0.621

Notes: B, unstandardized beta coefficient for ordinary least squares regression model, in which a 1-unit change in the variable (e.g., psychotic experiences) is associated with a corresponding change in B, holding all other variables constant; β, standardized beta coefficient; CI, confidence interval; CRP, C-reactive protein; CV, childhood victimization; IL-6, interleukin 6; PE, psychotic experiences between ages 12–18 years; suPAR, soluble urokinase plasminogen activator receptor. The N within each model is restricted to participants with non-missing data on all variables included in the multivariate models. PE only = children with no severe victimization and with adolescent PEs; CV only = children with any severe victimization and without adolescent PEs; CV + PE = children with any severe victimization and with adolescent PEs. The comparison group is those without childhood victimization and who did not report any psychotic experiences between 12 and 18 years of age. Statistically significant results ($p < 0.05$) are presented in bold text.

[a] Model 1: adjusted for the non-independence of twin observations.
[b] Model 2: adjusted for the non-independence of twin observations, sex and family socio-economic status.
[c] Model 3: adjusted for the non-independence of twin observations, sex, family socio-economic status, plus body temperature, overweight (body mass index greater than or equal to 25), daily smoking, current illness and injury, and anti-inflammatory medication measured at age 18.
[d] Model 4: adjusted for the non-independence of twin observations, sex, family socio-economic status, body temperature, overweight, daily smoking, current illness and injury, and anti-inflammatory medication, plus major depression and post-traumatic stress disorder measured at age 18.

inflammation levels at age 18 among children who had been victimized remained even after controlling for these potential covariates and mediators.

Our findings should be considered alongside some limitations. The cross-sectional nature of our inflammation data did not allow us to investigate whether inflammation mediated associations between childhood victimization and psychotic phenomena or to explore change in inflammatory biomarkers over time. Only 154 participants had CRP data at both ages 12 and 18, and thus we were underpowered to test for an association between childhood victimization, psychotic phenomena and longitudinal changes in CRP levels. Complete cross-sectional data were available for 1419 individuals in the E-Risk study, and there were differences in terms of gender and childhood victimization between participants with and without inflammatory biomarker data available that might have affected the results. Furthermore, the twin design might limit the generalizability of these results to singletons. Nevertheless, our results are in line with other studies, such as those found between childhood victimization and suPAR levels in the Dunedin Longitudinal Study cohort of singletons (Rasmussen et al., 2019). Moreover, the prevalence of childhood victimization and psychotic phenomena in this study are similar to the rates described in other studies of singletons

(Kelleher et al., 2012b; Lereya et al., 2015) and CRP levels are similar to levels described in other samples of youths (Copeland et al., 2014), suggesting that our sample is likely to be representative of the general population of a similar age. Finally, suPAR and IL-6 clinical thresholds have not yet been established as diagnostic biomarkers. However, the thresholds adopted in the current study are in line with previous literature that aimed to capture clinically relevant inflammatory states (Eugen-Olsen et al., 2010; Kofoed et al., 2008; Rasmussen et al., 2019).

It is also possible that genetic factors might influence inflammation levels in victimized children. Plasma CRP levels are moderately heritable (e.g., 40%; Pankow et al., 2001), and there is evidence of gene-environment correlation such that inflammatory genes might influence children's risk of experiencing victimization (Jaffee and Price, 2007; Danese and Baldwin, 2017). In a previous study from our research group, Baldwin et al. (2018) have shown that the heritability of CRP levels in the E-Risk sample was 40%, however childhood victimization was associated with elevated CRP levels independently of latent genetic influences. Addressing the question of the role of genetic factors in the association between childhood victimization, inflammatory biomarkers and psychotic phenomena was beyond the scope of the present study and requires further investigation.

Table 4

Association between childhood victimization, adolescent psychotic experiences and inflammation groups at age 18.

Inflammation variables	PE only (n = 266)		CV only (n = 235)		CV + PE (n = 165)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Inflammation groups						
Model 1						
Low Inflammation	1		1		1	
Elevated CRP and IL-6	1.11 (0.76; 1.61)	0.594	1.39 (0.93; 2.07)	0.108	1.13 (0.69;1.85)	0.629
Elevated CRP, IL-6, and suPAR	1.88 (0.98–3.61)	0.058	1.90 (0.98; 3.71)	0.059	**3.34 (1.69; 6.59)**	**0.001**
Model 2						
Low Inflammation	1		1		1	
Elevated CRP and IL-6	1.07 (0.73; 1.57)	0.739	1.34 (0.88; 2.03)	0.176	1.11 (0.67; 1.85)	0.682
Elevated CRP, IL-6, and suPAR	1.68 (0.88; 3.22)	0.115	1.61 (0.82; 3.16)	0.165	**3.16 (1.59; 6.30)**	**0.001**
Model 3						
Low Inflammation	1		1		1	
Elevated CRP and IL-6	1.00 (0.67; 1.47)	0.980	1.32 (0.86; 2.04)	0.202	0.81 (0.47; 1.38)	0.436
Elevated CRP, IL-6, and suPAR	1.44 (0.75; 2.77)	0.275	1.42 (0.69; 2.94)	0.345	1.94 (0.94; 4.04)	0.075
Model 4						
Low Inflammation	1		1		1	
Elevated CRP and IL-6	1.13 (0.76; 1.68)	0.540	1.34 (0.87; 2.07)	0.187	0.96 (0.56;1.65)	0.884
Elevated CRP, IL-6, and suPAR	1.40 (0.71–2.74)	0.332	1.45 (0.70; 3.01)	0.316	**2.13 (1.01; 4.48)**	**0.047**

Notes: CI, confidence interval; CRP, C-reactive protein; CV, childhood victimization; IL-6, interleukin 6; OR, odds ratio derived using multinomial logistic regression; PE, psychotic experiences between ages 12–18 years; suPAR, soluble urokinase plasminogen activator receptor. The N within each model is restricted to participants with non-missing data on all variables included in the multivariate models. PE only = children with no severe victimization and with adolescent PEs; CV only = children with any severe victimization and without adolescent PEs; CV + PE = children with any severe victimization and with adolescent PEs. The comparison group is those without childhood victimization and who did not report any psychotic experiences between 12 and 18 years of age. Statistically significant results ($p < 0.05$) are presented in bold text.

[a]Model 1: adjusted for the non-independence of twin observations.

[b]Model 2: adjusted for the non-independence of twin observations, sex and family socio-economic status.

[c]Model 3: adjusted for the non-independence of twin observations, sex, family socio-economic status, plus body temperature, overweight (body mass index greater than or equal to 25), daily smoking, current illness and injury, and anti-inflammatory medication measured at age 18.

[d]Model 4: adjusted for the non-independence of twin observations, sex, family socio-economic status, body temperature, overweight, daily smoking, current illness and injury, and anti-inflammatory medication, plus major depression and post-traumatic stress disorder measured at age 18.

Furthermore, the measure of psychotic experiences used in our main analyses was not subject to clinical verification. Reliance on self-report may lead to an over-estimation of the prevalence of psychotic experiences, because participants may misinterpret questions (Kendler et al., 1996). However, there is evidence that self-report measures show a good correlation with interviewer-rated psychotic phenomena (Kelleher et al., 2011; Konings et al., 2006; Liraud et al., 2004). Moreover, in the first step of our analyses, we found comparable associations with inflammatory biomarkers in our sensitivity analyses utilizing clinician-verified psychotic symptoms.

Taken together, our findings shed light on the association between early psychotic phenomena and inflammatory dysregulation and suggest that the association is stronger in those exposed to early victimization. Early victimization might act on complementary pathways by altering the psycho-biological development of the individual. Exposure to victimization early in life could impact on the child's psychological development by creating negative representations of the self, others and the world, a state of hypervigilance to threatening stimuli and general sense of mistrust, which have also been suggested to fuel psychotic phenomena (Freeman, 2007). In turn, or in parallel, this might trigger a biological dysregulation with enduring changes in the immune response (Danese and McEwen, 2012). Longitudinal analyses are required to disentangle the temporal ordering of these associated factors. Nonetheless, information about experiences of childhood victimization may help to identify individuals with psychotic experiences who also have elevated inflammation levels and has the potential to lead to new targeted psychological and pharmacological treatments for this specific population.

Declaration of Competing Interest

Valeria Mondelli has received research funding from Johnson & Johnson, a pharmaceutical company interested in the development of anti-inflammatory strategies for depression, but the research described in this paper is unrelated to this funding. No other disclosures were reported.

and Dr Fisher had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2021.08.209.

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