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Associations between plasma inflammatory markers and psychotic disorder, depressive disorder and generalised anxiety disorder in early adulthood: A nested case-control study

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ABSTRACT

Background: Low-grade inflammation may occur in association with several mental disorders of early adulthood, though associations with markers of chronic inflammation such as soluble urokinase plasminogen activator receptor (suPAR) are less well-established. We aimed to examine associations between acute and chronic inflammatory markers and mental disorders, as well as psychiatric co-morbidity, in young adults aged 24 years in the Avon Longitudinal Study of Parents and Children.

Methods: Included were 781 participants (of 4019 who attended at age 24 years) who completed psychiatric assessments and provided plasma samples. Of these, 377 met criteria for psychotic disorder, depressive disorder or generalised anxiety disorder and 404 did not. Plasma concentrations of IFN-γ, IL-6, IL-8, IL-10, TNF-α, CRP, sVCAM1, sICAM1, suPAR and alpha-2-macroglobulin were measured using immunoassays. Logistic regression compared standardised inflammatory marker levels in cases and controls. Negative binomial regression evaluated associations between inflammatory markers and co-morbidity (number of mental disorders). Models were adjusted for sex, body mass index, cigarette smoking, cannabis use and employment status, then additionally for childhood trauma.

Results: For psychotic disorder, there was evidence for associations with IL-6 (odds ratio[OR] 1.68, 95 %CI 1.20–2.34) and suPAR (OR 1.74, 95 %CI 1.17–2.58). There was weaker evidence for an association between suPAR and depressive disorder (OR 1.31, 95 %CI 1.05–1.62). There was little evidence for associations between inflammatory markers and generalised anxiety disorder. There was weak evidence for an association between suPAR and co-morbidity (β 0.10, 95 %CI 0.01–0.19). There was little evidence for additional confounding by childhood trauma.

Conclusions: There was evidence that 24-year-olds with psychotic disorder had raised plasma IL-6 and suPAR concentrations compared to controls. These findings have implications regarding the role of inflammation in mental disorders in early adulthood.

1. Introduction

Mental disorders such as depressive disorder, anxiety disorders, schizophrenia and bipolar disorder are among the leading causes of disability in young people (Erskine et al., 2015). These conditions often have their onset in adolescence or early adulthood (Solmi et al., 2021) and can be associated with long-term functional impairment (Gibb, Fergusson, & Horwood, 2010; Iorfino et al., 2018). This has spurred investigations to better characterise the biological and psychosocial characteristics of mental disorders in young people (Colizzi, Lasalvia, &

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Ruggeri, 2020; McGorry, Hartmann, Spooner, & Nelson, 2018; Nelson, McGorry, Wichers, Wigman, & Hartmann, 2017), with growing interest in the potential role of inflammation.

Multiple studies of blood-based inflammatory markers, including cytokines such as C-reactive protein (CRP) and interleukin(IL)-6, support an association between inflammation and several mental disorders. A *meta*-analysis reported cross-sectional evidence of higher levels of CRP, IL-3, IL-6, IL-12, IL-18, soluble IL-2 receptor (sIL-2R) and tumour necrosis factor-α (TNF-α) in people with depression compared to controls (Osimo et al., 2020a). For CRP and IL-6, a further *meta*-analysis reported longitudinal associations with future depressive symptoms (Mac Giollabhui et al., 2020). In young populations specifically, there is *meta*-analytic evidence of increased CRP and IL-6 in children and adolescents with concurrent depression compared to controls (Colasanto, Madigan, & Korczak, 2020). There are fewer studies of inflammatory markers in anxiety disorders, although there is *meta*-analytic evidence for increased CRP in patients with generalised anxiety disorder compared to controls (Costello, Gould, Abrol, & Howard, 2019).

Regarding psychotic disorders, higher peripheral levels of IL-6, TNF-α, IL-1β IL-12 and transforming growth factor-β (TGF-β) have been consistently reported in people with schizophrenia compared to controls (Momtazmanesh, Zare-Shahabadi, & Rezaei, 2019). Levels of certain cytokines (including IL-6, IL-8, IFN-γ and IL-2) fluctuate in response to treatment, suggesting a role as possible state markers (Miller, Buckley, Seabolt, Mellor, & Kirkpatrick, 2011; Momtazmanesh et al., 2019). However, some may also represent trait markers given evidence for raised levels in early psychosis phenotypes. Meta-analyses of studies comparing first episode antipsychotic-naïve patients to controls provide evidence of higher levels of several pro-inflammatory cytokines including IL-1β, sIL-2R, IL-6, and TNF-α (Pillinger, D'Ambrosio, McCutcheon, & Howes, 2019; Upthegrove, Manzanares-Teson, & Barnes, 2014). Individuals at clinical high-risk of psychosis have higher blood levels of IL-6 compared to healthy controls (Park & Miller, 2020). A *meta*-analysis of prospective studies reported a statistically significant longitudinal association between high (>3mg/L) vs low (≤3 mg/L) CRP and subsequent psychosis, though not when CRP was used as a continuous variable (Osimo et al., 2021). Analyses examining the broader proteome have previously evidenced dysregulation of the complement system prior to the onset of psychosis in those at clinical high-risk (Heurich, Föcking, Mongan, Cagney, & Cotter, 2021; Mongan et al., 2020). Among the topmost proteomic predictors of development of psychosis was lower levels of alpha-2-macroglobulin (A2M), a protease inhibitor with diverse functions including inhibition of multiple pro-inflammatory cytokines (Borth, 1992). A2M concentrations have also been found to be reduced in patients with depression and bipolar disorder compared to controls (Comes et al., 2018).

To date, much of the existing literature has focused on markers of acute inflammation that may only reliably measure inflammatory status in the short-term. Soluble plasminogen urokinase activator receptor (suPAR) is a relatively novel biomarker thought to be a more stable marker of long-term immune activity (Haupt et al., 2019) and hence a better index of chronic inflammation (Rasmussen et al., 2021a; Rasmussen et al., 2021b). suPAR is formed when uPAR is cleaved from immune cell membranes under inflammatory conditions (Montuori & Ragno, 2009). Previous studies have associated higher levels of suPAR with smoking (Haupt et al., 2019), accelerated ageing (Rasmussen et al., 2021a) and mortality (Haupt et al., 2019) although associations with psychiatric outcomes, particularly in youth, have been relatively understudied.

There remain several unresolved questions regarding the relationship between inflammatory markers and mental disorders in early adulthood. The degree to which inflammation is independent of factors such as smoking, body mass index (BMI) and socioeconomic status remains unclear (Mørch et al., 2019; Nielsen et al., 2015; Perry et al., 2019). Furthermore, psychological trauma in childhood or adolescence has been associated with increased risk of adult mental disorders (McKay et al., 2021) as well as higher levels of inflammatory markers (Baumeister et al., 2016a) including suPAR (Line Jee Hartmann Rasmussen et al., 2020), although inconsistent findings have also been reported (Carpenter, Gawuga, Tyrka, & Price, 2012). Finally, although co-morbidity between mental disorders is common (McGrath et al., 2020), the relationship between inflammatory markers and psychiatric co-morbidity in young adults is not well-established.

In this study, we aimed to measure plasma inflammatory markers in a young adult general population sample. We measured a panel of cytokines as markers of acute inflammation; A2M, a key regulator of cytokine and inflammatory activity; and suPAR, as a marker of chronic inflammation. Our primary analyses aimed to compare levels of these markers in individuals with and without psychotic disorder, depressive disorder and generalised anxiety disorder while adjusting for several key confounders. We specifically examined whether additional adjustment for childhood trauma exposure affected these associations. In secondary analyses, we aimed to investigate whether levels of these markers were associated with degree of psychiatric co-morbidity.

2. Methods

2.1. Study design

The current investigation comprised a nested case-control study in the Avon Longitudinal Study of Parents and Children (ALSPAC), a general population birth cohort (Boyd et al., 2013; Fraser et al., 2013; Northstone et al., 2019). The study website details available data through a data dictionary and search tool (http://www.bristol.ac.uk/alspac/researchers/access). Pregnant women in Avon, United Kingdom with expected delivery dates between 1st April 1991–31st December 1992 were invited to participate. 14,541 pregnancies were enrolled with 13,988 children alive at 1 year of age. When the oldest children were approximately 7 years old, an attempt was made to bolster the initial sample with eligible cases who did not join originally. The total sample size from age 7 years is 15,454 pregnancies with 14,901 children alive at 1 year of age. Data were collected and managed using REDCap data capture tools (Harris et al., 2019; Harris et al., 2009).

2.2. Participants

When approximately 24 years old, ALSPAC participants were invited to attend a clinic where anthropometric measurements, questionnaires, interviews and blood sample collection were completed. Of 9958 participants invited, 4019 (40.4%) attended. Of these, 3966 (98.7%) completed at least one psychiatric assessment and 3288 (81.8%) provided an ethylenediaminetetraacetic acid (EDTA) plasma sample. The current study was based on a subsample of participants ($n = 781$) who attended the age 24 clinic, completed assessments for mental disorders, and provided a plasma sample.

2.2.1. Cases

Cases were participants who met criteria for the outcomes of psychotic disorder, depressive disorder or generalised anxiety disorder (GAD) at age 24 years according to the outcome definitions below.

2.2.2. Controls

Participants were eligible to be selected as controls if they provided a plasma sample at ages 11, 17 and 24 years; completed assessments and did not have suspected or definite psychotic experiences, psychotic disorder, depressive disorder (mild, moderate or severe) or GAD at age 24; and had data available on BMI (a key confounder). The sample size for controls was chosen such that controls were sampled in an approximately 2:1 ratio compared to the largest case outcome group.

2.3. Outcomes

Three non-mutually exclusive outcomes were examined.

Psychotic disorder: At the age 24 clinic, participants completed the semi-structured Psychosis-Like Symptoms Interview (PLIKSi) to assess for psychotic experiences (Horwood et al., 2008). The PLIKSi asks 12 core questions regarding psychotic experiences comprising hallucinations, delusions and experiences of thought interference. Participants who answered 'yes' or 'maybe' were cross-questioned to establish whether the experiences were psychotic, and these were coded according to the Schedules for Clinical Assessment in Neuropsychiatry (Organisation, 1994). Trained interviewers rated symptoms as 'not present', 'suspected' or 'definite' and coded whether the experience was attributable to sleep or fever.

In line with previous studies (Sullivan et al., 2020; Zammit et al., 2013), psychotic disorder was defined as having at least one definite psychotic experience not attributable to sleep or fever which recurred at least once per month over the previous six months, and was associated with severe distress, marked impairment of the participant's social or occupational functioning, or led them to seek help from a professional source.

Depressive disorder: Participants completed the self-administered computerised version of the Clinical Interview Schedule Revised (CIS-R)(Lewis, 1994). The CIS-R includes questions about the occurrence and severity of depressive symptoms in the past two weeks, providing diagnoses of mild, moderate or severe depressive disorder according to International Classification of Diseases version 10 (ICD-10) criteria (World Health, 2004). In the current study, this outcome was defined as meeting ICD-10 criteria for moderate or severe depressive disorder.

Generalised anxiety disorder (GAD): The CIS-R also contains questions pertaining to anxiety symptoms in the past two weeks to determine diagnosis of GAD according to ICD-10 criteria (World Health, 2004). In the current study, this outcome was defined as meeting ICD-10 criteria for GAD.

2.4. Plasma inflammatory markers

Participants were requested to fast for at least six hours prior to clinic attendance. Peripheral blood samples were collected according to a standardised protocol. Samples were obtained between 8am and 2 pm in > 99% of cases at both clinics. Following collection, samples were centrifuged within 90 min and plasma was stored at −80 °C. All samples underwent one freeze–thaw cycle for aliquoting prior to analysis.

Multiplex analytes: Twelve markers were quantified using multiplex enzyme-linked immunosorbent assays (ELISA). Plasma concentrations of IFN-γ, TNF-α, IL1-β, IL2, IL4, IL6, IL8, IL10 and IL13 were measured using V-Plex Pro-Inflammatory Panel 1 Human kit (Meso Scale Diagnostics). CRP, sICAM1 and sVCAM1 were measured using V-Plex Vascular Injury Panel 2 Human kit (Meso Scale Diagnostics). A Sector Imager 2400 microplate reader (Meso Scale Diagnostics) was used to measure optical densities. A standard curve was generated for each plate and plasma concentrations were interpolated using Meso Scale Discovery Workbench software. Standards and participant samples were measured in duplicate and the mean value calculated to determine concentration.

Soluble urokinase plasminogen activator receptor (suPAR): Plasma concentrations of suPAR were measured using suPARnostic ELISA kit (Virogates) according to manufacturer's instructions. A SpectraMax M3 microplate reader was used to measure optical densities. A standard curve was generated for each plate and plasma concentrations were interpolated using Virogates' custom results calculation tool (https://www.virogates.com/support). Standards were measured in duplicate and participant samples in singlet.

Alpha-2-macroglobulin (A2M): Plasma concentrations of A2M were measured using Human Alpha-2-Macroglobulin ELISA kit (Abcam) according to manufacturer's instructions. A SpectraMax M3 microplate reader was used to measure optical densities. A standard curve was generated for each plate and plasma concentrations interpolated using GraphPad Prism 8 software with four-parameter logistic curve-fit. Standards were measured in duplicate and participant samples in singlet.

The lower limits of detection (LOD) for each assay are provided in Supplementary Table 1.

2.5. Confounders

Based on previous literature and recommendations regarding effects of biobehavioural factors on inflammatory markers (O'Connor et al., 2009) the following covariates were included as confounders in the primary analyses: sex (female/male); BMI (kg/m^2); average number of cigarettes per day in preceding 30 days; regular cannabis use (yes/no); and whether the participant was not engaged in employment, education or training (NEET) (yes/no).

The degree to which childhood trauma confounds associations between inflammation and mental disorders is debated (Brown, Worrell, & Pariante, 2021). To assess this, models were additionally adjusted for trauma exposure (physical abuse, sexual abuse, emotional abuse, emotional neglect, domestic violence, or bullying) from birth to 17 years (yes/no) using variables derived from 121 questions regarding traumatic events in assessments completed by parents or self-reported by participants, as previously described (Croft et al., 2019).

Data were also available on alcohol intake (AUDIT-C score) and medication use (participants were asked if they took medication for delusions, hallucinations or another mental health problem). These could be considered as potential confounders, but due to the relatively small size of the smallest case group ($n = 35$ for psychotic disorder), we also wished to limit the number of parameters in models. Guided by evidence from previous literature, these variables were not included in favour of those described above. Further details on confounders are included in Supplementary Methods.

2.6. Statistical methods

Statistical analyses were performed in Stata 16 (StataCorp).

2.6.1. Descriptive analyses

Cases ($n = 377$) and controls ($n = 404$) were compared on key characteristics including age, sex, ethnicity, BMI, smoking, alcohol intake, cannabis use, medication use, NEET status and childhood trauma exposure. Continuous variables were summarised using the mean and standard deviation or median and interquartile range and compared using two-tailed *t*-tests (with unequal variances specified where Levene's test $p < 0.05$) or Mann-Whitney *U* tests as appropriate. Categorical variables were summarised using proportions and compared using chi-squared tests.

2.6.2. Plasma inflammatory markers

Multiplex analytes: Multiplex analytes were taken forward for analysis if < 20% of plasma concentration values were below LOD and < 20% of values had coefficient of variation (CV) > 20%. Based on these criteria, eight markers were taken forward: IFN-γ, IL-6, IL-8, IL-10, TNF-α, CRP, sICAM1 and sVCAM1. Values below the LOD (*n* varied from < 5 to 21 depending on the specific marker) were replaced with LOD divided by $\sqrt{2}$. Samples where the CV of duplicates was > 20% were excluded. Mean concentration values were log-transformed, converted to z-scores and winsorised within ± 4z.

suPAR: For suPAR, plasma concentration values (ng/ml) were converted to z-scores and winsorised within ± 4z. No values were below LOD.

A2M: For A2M, plasma concentration values (μg/ml) were log-transformed, converted to z-scores and winsorised within ± 4z. No values were below LOD.

Distributions of multiplex analytes, suPAR and A2M are provided in Supplementary Fig. 1.

2.6.3. Multiple imputation

Missing data for inflammatory markers and confounders (Supplementary Figure 2) were imputed using multiple imputation with chained equations. In addition to the markers, outcomes and confounders above, 29 auxiliary variables were included in the imputation model (see Supplementary Methods). Twenty imputed datasets were created and estimates combined using Rubin's rules (Rubin).

2.6.4. Associations between inflammatory markers and mental disorders

The primary analyses examined associations between inflammatory markers and mental disorders (psychotic disorder, depressive disorder and GAD) using logistic regression, with the dependent variable indicating case/control status (1/0). Firstly, unadjusted associations were examined (series 1). Secondly, models were adjusted for sex, BMI, cigarette smoking, regular cannabis use and NEET status (series 2). Thirdly, models were additionally adjusted for childhood trauma (series 3).

2.6.5. Associations between inflammatory markers and psychiatric co-morbidity

In secondary analyses we examined associations between inflammatory markers and co-morbidity using negative binomial regression. The dependent variable was number of mental disorders (none; one; two; or three). Unadjusted (series 1) and adjusted (series 2) models were examined using the same covariates as above, with additional adjustment for childhood trauma (series 3).

2.6.6. Sensitivity analyses

Firstly, all analyses were repeated using a complete-case approach to compare results using imputed and non-imputed data. Secondly, these analyses were repeated but participants with CRP $>$ 10 mg/l were excluded. Several studies have previously applied this criterion on the basis that the individual may have been acutely unwell. However, there has been criticism that this practice is not clearly justified and may risk excluding legitimate values (N. Mac Giollabhui et al., 2020). Statistical processes such as winsorisation have been advanced as alternative strategies (N. Mac Giollabhui et al., 2020). Thus, the primary analyses included participants with CRP $>$ 10 mg/l ($n = 42$), with winsorisation performed within $\pm$ 4z.

2.6.7. Interpretation

Results were interpreted based primarily on effect estimates and 95% confidence intervals (CI). *P*-values are reported for information but an arbitrary threshold for statistical significance was not assigned. For the primary analyses, we additionally report *p*-values adjusted for multiple comparisons using a false discovery rate of 5% (Benjamini & Hochberg, 1995). Given the exploratory nature of our secondary analyses, p-values for those analyses were not similarly adjusted.

2.7. Ethical approval and consent

Approval for ALSPAC was obtained from ALSPAC Ethics and Law Committee and local research ethics committees. Consent for biological samples was collected in accordance with the Human Tissue Act (2004). Informed consent for use of questionnaire and clinic data was obtained following recommendations of the ALSPAC Ethics and Law Committee at the time. Ethical approval for the present analyses was granted by the Royal College of Surgeons in Ireland (REC1240bb).

3. Results

3.1. Sample characteristics

The study sample comprised 377 case participants who met criteria for at least one outcome (psychotic disorder, $n = 35$; depressive disorder, $n = 202$; or GAD, $n = 268$) and 404 control participants. Compared to controls, there was evidence that cases had slightly higher mean BMI, as well as higher proportions for female sex, daily tobacco smoking, regular cannabis use, medication use, NEET status and childhood trauma (Table 1).

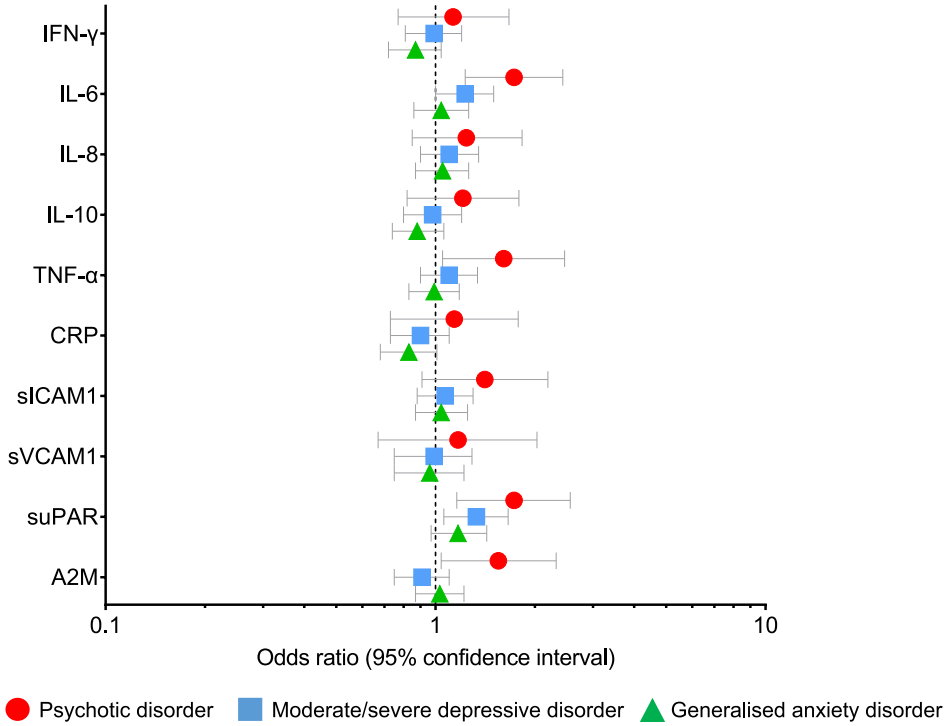

Fig. 1. Associations between plasma inflammatory markers and mental disorders (cases compared to controls).

Table 1
Characteristics of cases and controls in the study sample.

	Cases, *n* = 377	Controls, *n* = 404	*p*	Missing data, n (%)
Age in years on attendance at age 24 clinic, mean (SD)	24.1 (0.8)	24.0 (24.0)	0.238	<5 (<0.7%)*
Sex, *n* (%)	283 female (75.1%) 94 male (24.9%)	213 female (52.7%) 191 male (47.3%)	<0.001	<5 (<0.7%)*
Ethnicity, *n* (%)	13 non-white (3.9%) 322 white (96.1%)	11 non-white (2.9%) 367 white (97.1%)	0.473	68 (8.7%)
BMI in kg/m^2 at age 24 years, mean (SD)	25.3 (6.0)	24.1 (4.2)	<0.001	9 (1.2%)
Daily smoker at age 24 years, n (%)	79 yes (21.0%) 297 no (79.0%)	26 yes (6.4%) 378 no (93.6%)	<0.001	<5 (<0.7%)*
Average number of cigarettes smoked per day in preceding 30 days if daily smoker, median (IQR)	10 (7)	7 (9)	0.183	<5 (<0.7%)*
AUDIT-C score at age 24 years, median (IQR)	5 (4)	5 (3)	0.024	10 (1.3%)
Regular cannabis use[a] at age 24 years, *n* (%)	42 yes (11.1%) 335 no (88.9%)	13 yes (3.2%) 391 no (96.8%)	<0.001	<5 (<0.7%)*
In employment, education or training at age 24 years, *n* (%)	313 yes (85.5%) 53 no (14.5%)	372 yes (92.8%) 29 no (7.2%)	0.001	14 (1.8%)
Takes medication for delusions, hallucinations or other mental health problem at age 24 years, *n* (%)	290 no (78.6%) 79 yes (21.4%)	>399 no (>98.8%) <5 yes (<1.2%)	<0.001	8 (1.0%)
Trauma exposure from birth to age 17 years, *n* (%)	244 yes (70.1%) 104 no (29.9%)	216 yes (55.4%) 174 no (44.6%)	<0.001	43 (5.5%)

* Data suppressed due to small cell counts for missing data; may include 0.
AUDIT-C: Alcohol Use Disorders Identification Test – Concise; BMI: body mass index; IQR: interquartile range; SD: standard deviation.
[a] Regular cannabis use was defined as using cannabis at least weekly or daily over the past year.

3.2. Plasma inflammatory markers

The mean, standard deviation and number of values below detection limits for each marker are provided in Supplementary Table 2. CV data are provided in Supplementary Table 3. Intra-assay CV ranged from 2.5% for sVCAM-1 to 16.0% for IFN-γ. Inter-assay CV ranged from 3.0% for IL-10 to 19.2% for A2M.

3.3. Associations between inflammatory markers and mental disorders

Results of logistic regression analyses examining associations between inflammatory markers and mental disorders are provided in Table 2 and shown in Fig. 1. Supplementary Table 4 provides the average relative increase for each logistic regression model. This describes the relative increase (averaged over all coefficients) in variance of the estimates due to missing values, which was small (≤0.03).

3.3.1. Psychotic disorder

There was evidence of an association between levels of IL-6 and psychotic disorder in unadjusted analyses (series 1 odds ratio [OR] 1.74, 95 %CI 1.30–2.32, $p < 0.001$) and following adjustment for sex, BMI, cigarette smoking, regular cannabis use and NEET status (series 2 odds ratio [OR] 1.68, 95 %CI 1.20–2.34, $p = 0.002$). There was weaker evidence of an association with TNF-α (series 2 OR 1.58, 95 %CI 1.04–2.40, $p = 0.031$). There was little evidence for associations with the remaining multiplex analytes. There was evidence of an association between suPAR and psychotic disorder in both unadjusted (series 1 OR 2.13, 95 %CI 1.53–2.99, $p < 0.001$) and adjusted analyses (series 2 OR 1.74, 95 %CI 1.17–2.58, $p = 0.006$). Adjusted analyses provided weak evidence for an association with A2M (series 2 OR 1.50, 95 %CI 1.00–2.24, $p = 0.048$).

3.3.2. Depressive disorder

There was evidence of an association between IL and 6 and depressive disorder in unadjusted analyses (series 1 OR 1.41, 95 %CI 1.18–1.68, $p < 0.001$) which attenuated on adjustment (series 2 OR 1.21, 95 %CI 0.99–1.48, $p = 0.062$). There was little evidence for associations with the remaining multiplex analytes. There was evidence of an association with suPAR in unadjusted analyses (series 1 OR 1.70, 95 %CI 1.40–2.05, $p < 0.001$) which weakened on adjustment (series 2 OR 1.31, 95 %CI 1.05–1.62, $p = 0.015$). There was little evidence for an association with A2M (series 2 OR 0.89, 95 %CI 0.73–1.07, $p = 0.208$).

3.3.3. Generalised anxiety disorder

Unadjusted analyses suggested weak evidence for an association between IL and 6 and GAD (series 1 OR 1.21, 95 %CI 1.03–1.43, $p = 0.024$) but this attenuated on adjustment for confounders (series 2 OR 1.03, 95 %CI 0.85–1.25, $p = 0.748$). There was little evidence for associations with the remaining multiplex analytes. While unadjusted analyses suggested an association with suPAR (series 1 OR 1.54, 95 %CI 1.30–1.83, $p < 0.001$), this attenuated on adjustment (series 2 OR 1.16, 95 %CI 0.96–1.41, $p = 0.122$). There was little evidence for an association with A2M (series 2 OR 1.02, 95 %CI 0.86–1.20, $p = 0.849$).

3.3.4. Additional adjustment for childhood trauma exposure

Effect estimates for associations between inflammatory markers and mental disorders were broadly similar when models were further adjusted for childhood trauma exposure (series 3 in Table 2), suggesting little evidence of additional confounding by this variable.

Inflammatory markers are standardised such that odds ratios may be interpreted per standard deviation increase in inflammatory marker. Error bars are 95% confidence intervals. Odds ratios are derived from models adjusted for sex, body mass index, cigarette smoking (average number of cigarettes smoked in preceding 30 days), regular cannabis use (weekly or daily use over the past year), NEET (not in education, employment or training) status and childhood trauma exposure.

IFN-γ: Interferon-gamma; IL-6: Interleukin-6; IL-8: Interleukin-8; IL-10: Interleukin-10; TNF-α: tumour necrosis factor alpha; CRP: C-reactive protein; sICAM1: soluble intercellular adhesion molecule 1; sVCAM1: soluble vascular cell adhesion molecule 1; suPAR: soluble urokinase plasminogen activator receptor; A2M: Alpha-2-macroglobulin.

3.4. Associations between inflammatory markers and psychiatric co-morbidity

772 participants completed assessments for all three mental disorders. Of these, 257 participants met criteria for one disorder, 95 met criteria for two disorders, and 16 met criteria for all three disorders. Results of negative binomial regression analyses examining associations between inflammatory markers and number of mental disorders are provided in Table 3.

Unadjusted analyses provided evidence for an association between IL and 6 and number of mental disorders (series 1 β 0.16, 95 %CI 0.08–0.25, $p < 0.001$) but this attenuated on adjustment for confounders

Table 2
Associations between plasma inflammatory markers and mental disorders using logistic regression.

Outcome	Marker	Series 1: Unadjusted models					Series 2: Adjusted for sex, BMI, smoking, cannabis use, NEET status					Series 3: Additionally adjusted for childhood trauma exposure				
		Odds ratio	SE	95% confidence interval	*p*	Adj *p* (FDR 5%)	Odds ratio	SE	95% confidence interval	*p*	Adj *p* (FDR 5%)	Odds ratio	SE	95% confidence interval	*p*	Adj *p* (FDR 5%)
Psychotic disorder	IFN-γ	1.09	0.20	0.76–1.55	0.651	0.723	1.11	0.22	0.76–1.63	0.585	0.680	1.13	0.22	0.77–1.67	0.521	0.575
	IL-6	1.74	0.26	1.30–2.32	<0.001	<0.005	1.68	0.29	1.20–2.34	0.002	0.020	1.73	0.30	1.23–2.43	0.002	0.020
	IL-8	1.24	0.21	0.88–1.74	0.222	0.317	1.27	0.24	0.87–1.85	0.218	0.363	1.24	0.24	0.85–1.83	0.267	0.445
	IL-10	1.19	0.22	0.83–1.69	0.342	0.428	1.17	0.22	0.80–1.71	0.409	0.584	1.21	0.24	0.82–1.79	0.339	0.484
	TNF-α	1.50	0.28	1.03–2.17	0.033	0.072	1.58	0.34	1.04–2.40	0.031	0.103	1.61	0.35	1.05–2.46	0.029	0.083
	CRP	1.48	0.28	1.03–2.13	0.036	0.072	1.11	0.25	0.72–1.72	0.644	0.680	1.14	0.26	0.73–1.78	0.556	0.575
	sICAM1	1.64	0.35	1.08–2.48	0.020	0.067	1.37	0.31	0.89–2.13	0.152	0.152	1.41	0.32	0.91–2.19	0.122	0.244
	sVCAM1	1.01	0.26	0.61–1.67	0.959	0.959	1.12	0.31	0.65–1.94	0.680	0.680	1.17	0.33	0.67–2.03	0.575	0.575
	suPAR	2.13	0.37	1.53–2.99	<0.001	<0.005	1.74	0.35	1.17–2.58	0.006	0.030	1.73	0.35	1.16–2.56	0.007	0.035
	A2M	1.45	0.27	1.00–2.10	0.047	0.078	1.50	0.31	1.00–2.24	0.048	0.120	1.55	0.32	1.04–2.32	0.033	0.083
Moderate/ severe depressive disorder	IFN-γ	1.03	0.09	0.86–1.22	0.778	0.864	0.97	0.09	0.80–1.17	0.756	0.771	0.99	0.10	0.81–1.20	0.897	0.920
	IL-6	1.41	0.13	1.18–1.68	<0.001	<0.005	1.21	0.12	0.99–1.48	0.062	0.310	1.23	0.13	1.00–1.50	0.050	0.250
	IL-8	1.06	0.10	0.89–1.27	0.519	0.649	1.11	0.11	0.91–1.35	0.307	0.577	1.10	0.11	0.90–1.35	0.346	0.582
	IL-10	0.99	0.09	0.83–1.19	0.919	0.919	0.97	0.10	0.80–1.18	0.748	0.771	0.98	0.10	0.80–1.20	0.851	0.920
	TNF-α	1.10	0.10	0.93–1.31	0.271	0.452	1.10	0.11	0.90–1.34	0.346	0.577	1.10	0.11	0.90–1.34	0.349	0.582
	CRP	1.17	0.10	0.98–1.38	0.076	0.220	0.88	0.09	0.72–1.08	0.224	0.560	0.90	0.09	0.73–1.10	0.301	0.582
	sICAM1	1.17	0.11	0.98–1.39	0.088	0.220	1.06	0.10	0.87–1.29	0.549	0.771	1.07	0.11	0.88–1.30	0.495	0.707
	sVCAM1	0.86	0.10	0.68–1.09	0.212	0.424	0.96	0.13	0.74–1.25	0.771	0.771	0.99	0.13	0.75–1.29	0.920	0.920
	suPAR	1.70	0.16	1.40–2.05	<0.001	<0.005	1.31	0.14	1.05–1.62	0.015	0.150	1.33	0.15	1.06–1.66	0.012	0.120
	A2M	0.94	0.08	0.80–1.12	0.503	0.649	0.89	0.08	0.73–1.07	0.208	0.560	0.91	0.09	0.75–1.10	0.307	0.582
Generalised anxiety disorder	IFN-γ	0.89	0.08	0.75–1.05	0.168	0.300	0.85	0.08	0.71–1.03	0.092	0.407	0.87	0.08	0.72–1.04	0.129	0.430
	IL-6	1.21	0.10	1.03–1.43	0.024	0.120	1.03	0.10	0.85–1.25	0.748	0.858	1.04	0.10	0.86–1.26	0.693	0.802
	IL-8	1.01	0.09	0.85–1.19	0.932	0.932	1.06	0.10	0.88–1.28	0.528	0.858	1.05	0.10	0.87–1.26	0.620	0.802
	IL-10	0.89	0.08	0.75–1.05	0.156	0.300	0.88	0.08	0.74–1.05	0.164	0.410	0.88	0.08	0.74–1.06	0.176	0.430
	TNF-α	0.99	0.08	0.85–1.16	0.928	0.932	0.98	0.09	0.83–1.17	0.858	0.858	0.99	0.09	0.83–1.18	0.877	0.877
	CRP	1.09	0.09	0.93–1.28	0.296	0.423	0.82	0.08	0.67–1.00	0.050	0.407	0.83	0.08	0.68–1.01	0.061	0.430
	sICAM1	1.15	0.09	0.98–1.35	0.083	0.277	1.03	0.09	0.86–1.23	0.735	0.858	1.04	0.10	0.87–1.25	0.633	0.802
	sVCAM1	0.86	0.10	0.69–1.07	0.180	0.300	0.93	0.12	0.73–1.19	0.565	0.858	0.96	0.12	0.75–1.22	0.722	0.802
	suPAR	1.54	0.13	1.30–1.83	<0.001	<0.010	1.16	0.11	0.96–1.41	0.122	0.407	1.17	0.12	0.97–1.43	0.107	0.430
	A2M	1.04	0.08	0.89–1.22	0.594	0.743	1.02	0.09	0.86–1.20	0.849	0.858	1.03	0.09	0.87–1.22	0.710	0.802

Odds ratios compare cases to controls. Inflammatory markers are standardised such that odds ratios may be interpreted per standard deviation increase in inflammatory marker. Models in series 2 included the following covariates: sex; body mass index; number of cigarettes smoked in preceding 30 days; regular cannabis use (weekly or daily use over the past year); employment, education or training status. Models in series 3 included these covariates as well as exposure to any childhood trauma from birth to age 17 years.

SE: Standard Errror; Adj *p*: Adjusted p-value; FDR: false discovery rate; NEET: not in employment, education or training; IFN-γ: Interferon-gamma; IL-6: Interleukin-6; IL-8: Interleukin-8; IL-10: Interleukin-10; TNF-α: tumour necrosis factor alpha; CRP: C-reactive protein; sICAM1: soluble intercellular adhesion molecule 1; sVCAM1: soluble vascular cell adhesion molecule 1; suPAR: soluble urokinase plasminogen activator receptor; A2M: Alpha-2-macroglobulin.

Table 3
Associations between plasma inflammatory markers and psychiatric co-morbidity (number of mental disorders) using negative binomial regression.

Marker	Series 1: Unadjusted models				Series 2: Adjusted for sex, BMI, smoking, cannabis use, NEET status				Series 3: Additionally adjusted for childhood trauma exposure			
	Co-efficient	Standard error	95% confidence interval	*p*	Co-efficient	Standard error	95% confidence interval	*p*	Co-efficient	Standard error	95% confidence interval	*p*
IFN-γ	−0.04	0.05	−0.14–0.06	0.422	−0.06	0.05	−0.16–0.04	0.244	−0.05	0.05	−0.15–0.05	0.332
IL-6	0.16	0.04	0.08–0.25	<0.001	0.08	0.05	−0.02–0.18	0.115	0.08	0.05	−0.02–0.18	0.111
IL-8	0.02	0.05	−0.07–0.11	0.682	0.03	0.05	−0.06–0.13	0.510	0.02	0.05	−0.07–0.12	0.615
IL-10	−0.04	0.05	−0.13–0.06	0.448	−0.04	0.05	−0.14–0.05	0.375	−0.04	0.05	−0.13–0.05	0.408
TNF-α	0.05	0.05	−0.04–0.14	0.242	0.03	0.05	−0.06–0.13	0.495	0.03	0.05	−0.06–0.13	0.503
CRP	0.07	0.05	−0.02–0.16	0.125	−0.08	0.05	−0.18–0.02	0.128	−0.07	0.05	−0.17–0.03	0.167
sICAM1	0.10	0.05	0.01–0.19	0.028	0.03	0.05	−0.06–0.12	0.461	0.04	0.05	−0.05–0.13	0.376
sVCAM1	−0.06	0.06	−0.18–0.07	0.354	−0.01	0.06	−0.13–0.12	0.923	0.01	0.06	−0.11–0.14	0.855
suPAR	0.25	0.04	0.18–0.33	<0.001	0.10	0.05	0.01–0.19	0.029	0.10	0.05	0.01–0.19	0.026
A2M	−0.01	0.05	−0.10–0.08	0.895	−0.03	0.05	−0.12–0.06	0.500	−0.02	0.05	−0.11–0.07	0.640

Inflammatory markers are standardised such that coefficients may be interpreted per standard deviation increase in inflammatory marker. Models in series 2 included the following covariates: sex; body mass index; number of cigarettes smoked in preceding 30 days; regular cannabis use (weekly or daily use over the past year); employment, education or training status. Models in series 3 included these covariates as well as exposure to any childhood trauma from birth to age 17 years.
NEET: not in employment, education or training; IFN-γ: Interferon-gamma; IL-6: Interleukin-6; IL-8: Interleukin-8; IL-10: Interleukin-10; TNF-α: tumour necrosis factor alpha; CRP: C-reactive protein; sICAM1: soluble intercellular adhesion molecule 1; sVCAM1: soluble vascular cell adhesion molecule 1; suPAR: soluble urokinase plasminogen activator receptor; A2M: Alpha-2-macroglobulin.

(series 2 β 0.08, 95 %CI 0.02–0.18, $p = 0.115$). There was little evidence for associations with the remaining multiplex analytes. Unadjusted analyses showed strong evidence for an association with suPAR (series 1 β 0.25, 95 %CI 0.18–0.33, $p < 0.001$) though this weakened on adjustment for confounders (series 2 β 0.10, 95% CI 0.01–0.19, $p = 0.029$). There was little evidence for an association with A2M (series 2 β −0.03, 95 %CI −0.12–0.06, $p = 0.500$).

3.4.1. Additional adjustment for childhood trauma exposure

Effect estimates for associations between inflammatory markers and psychiatric co-morbidity were broadly similar when models were further adjusted for childhood trauma exposure (series 3 in Table 3), suggesting little evidence of additional confounding by this variable.

3.5. Sensitivity analyses

Results were generally similar, though with less precise effect estimates due to the reduced sample size, when a complete-case approach was used (Supplementary Tables 5 and 6). For example, in relation to psychotic disorder, there was consistent evidence for associations with respect to IL-6 (series 2 OR 1.73, 95% CI 1.24–2.42, $p = 0.001$) and suPAR (series 2 OR 1.73, 95% CI 1.11–2.72, $p = 0.016$). In keeping with reduced power, evidence for an association between suPAR and co-morbidity was weaker (series 2 β 0.08, 95% CI −0.02–0.19, $p = 0.107$).

Effect estimates were also similar when participants with CRP > 10 mg/l were excluded, though less precisely estimated given the reduced sample size (Supplementary Tables 7 and 8). For example, in relation to psychotic disorder, consistent evidence remained for associations with respect to IL-6 (series 2 OR 1.68, 95% CI 1.17–2.42, $p = 0.005$) and suPAR (series 2 OR 1.70, 95% CI 1.12–2.59, $p = 0.013$). Again, evidence weakened for an association between suPAR and co-morbidity (series 2 β 0.08, 95% CI −0.02–0.17, $p = 0.109$).

4. Discussion

We measured multiple plasma inflammatory markers in 24-year-old individuals with psychotic disorder, moderate/severe depressive disorder and generalised anxiety disorder (GAD) compared to controls. When adjusting for several confounding factors, there was strong evidence that individuals with psychotic disorder had higher plasma concentrations of IL-6 and suPAR compared to controls. There was comparatively little evidence for associations between inflammatory markers and depressive disorder or GAD compared to controls. There was weak evidence that higher levels of suPAR were associated with psychiatric co-morbidity. Adjusting for childhood trauma exposure did not substantially change these results.

Previous studies have evidenced higher levels of inflammatory markers in schizophrenia (Miller et al., 2011), first episode psychosis (Upthegrove et al., 2014) and individuals at clinical high-risk (Park & Miller, 2020) compared to controls. Among multiplex analytes in the current study, the strongest association was for IL-6, which has been found to be consistently raised in acute exacerbation of schizophrenia (Miller et al., 2011) and first-episode psychosis (Upthegrove et al., 2014). Previous ALSPAC studies have found that higher blood levels of IL-6 at age 9 years were associated longitudinally with increased risk of psychotic experiences at age 18 years (Khandaker, Pearson, Zammit, Lewis, & Jones, 2014) and psychotic disorder at age 24 years (Perry et al., 2021b), suggesting early dysregulation of IL-6 may occur well before the onset of psychosis. This possibly reflects a pro-inflammatory genetic predisposition in association with psychosis (Ripke et al., 2014). Mendelian randomisation analyses do not support a relationship between genetic liability to schizophrenia and CRP (Lin et al., 2019), though such studies have evidenced that genetically-predicted IL-6 (Perry et al., 2021) and soluble IL-6 receptor levels (Hartwig, Borges, Horta, Bowden, & Davey Smith, 2017) are associated with schizophrenia risk. It is likely that perinatal (Davies et al., 2020) and early life (Sideli et al., 2020) risk factors interact with genetic risk to increase propensity towards an inflammatory phenotype in those at risk of psychosis.

IL-6 has context-dependent functions, decreasing inflammation through classic signalling via membrane-bound receptors and increasing inflammation through *trans*-signalling via soluble receptors (Scheller, Chalaris, Schmidt-Arras, & Rose-John, 2011). IL-6 plays a prominent role in the initial acute inflammatory response, when it can exert anti-inflammatory effects by regulating pro-inflammatory cytokines (Borovcanin et al., 2017; Gabay, 2006; Xing et al., 1998). However, if IL-6 production persists unchecked, it can contribute to development of chronic inflammation, for example via promotion of monocyte accumulation (Gabay, 2006). Sustained high levels of IL-6 with increased *trans*-signalling have been hypothesised to contribute to T regulatory cell dysfunction in psychosis (Corsi-Zuelli et al., 2021).

The current finding of increased IL-6 in association with psychotic disorder in early adulthood could reflect previous findings that it is a state marker in psychosis (Miller et al., 2011) since the participants met criteria for disorder at time of sampling. Alternatively, chronic inflammation may already be in process in psychosis in early adulthood. This

view is strengthened by the complementary finding of increased plasma levels of suPAR, thought to be a superior marker of chronic inflammation (Rasmussen et al., 2021a; Line Jee Hartmann Rasmussen et al., 2020). Consistent with the present findings, a previous study found patients with schizophrenia had higher suPAR levels compared to controls (Nielsen et al., 2015). A further study of male patients with acute exacerbation of schizophrenia compared to controls reported no significant difference in suPAR (Genc et al., 2016). One possible explanation for the discrepancy between this study and the current findings relates to sex differences. The present subsample was predominantly female, and sex was included as a confounder in adjusted analyses. In common with several other markers of inflammation, higher levels of suPAR have been reported in females compared to males, which may be at least in part related to differences in visceral adiposity (Mehta et al., 2020). However, a further explanation is that the previous study was also conducted in an older sample with an average duration of illness of approximately 9 years. It is possible this reflects temporal changes in patterns of inflammation in psychosis. Notably, a study of British adolescents found higher levels of suPAR at age 18 in those reporting psychotic experiences between age 12 to 18 years compared to those who did not, although associations attenuated on adjustment for confounders (Trotta et al., 2021). In the current study the association between suPAR and psychotic disorder persisted after adjustment, suggesting this relationship is not entirely explained by traditional inflammatory risk factors such as BMI and smoking. However, this will require confirmation in larger samples.

There was weak evidence for increased plasma A2M levels in psychotic disorder. In longitudinal studies, decreased levels of A2M have been associated with later development of psychotic experiences (English et al., 2018) and transition to psychotic disorder in individuals at clinical high-risk (Mongan et al., 2020). Cross-sectional studies provide inconsistent findings regarding A2M in psychotic disorders, with no clear pattern of up- or down-regulation compared to controls (Comes et al., 2018; Heurich et al., 2021). One potential explanation may be that the pattern of expression varies temporally, with low levels of A2M preceding the first episode of psychosis, followed by more heterogeneous patterns of expression. However, this will need to be clarified in longitudinal studies with repeated measures of A2M.

Regarding depressive disorder, a *meta*-analysis reported increased levels of several cytokines in patients with depression compared to controls even when adjusting for confounding factors (Osimo et al., 2020a). Several studies have reported downregulation of A2M in depressive disorder (Comes et al., 2018), although conflicting results have also been reported (Rothermundt et al., 2001). We found little evidence for robust associations between the examined inflammatory cytokines and depressive disorder. There was some evidence for an association between suPAR and depressive disorder, though this was weaker than for psychotic disorder. It is possible these findings reflect the non-clinical population from which participants were sampled. A further explanation is the relatively young age of study participants compared to most of the existing literature. However, a *meta*-analysis reported findings of increased CRP and IL-6 both concurrent with and preceding depressive disorder in young people (Colasanto et al., 2020). Furthermore, while levels of inflammatory markers vary over time, the present analyses were cross-sectional and hence unable to describe associations between trajectories of inflammatory markers and risk of depression. Notably, a previous ALSPAC study using serial CRP measurements found that a subgroup of individuals whose CRP levels increased between age 9 and age 18 had a higher risk of depression at age 18 compared to those with persistently low CRP (Osimo et al., 2020b). Regarding GAD, the current study provides little evidence for associations with the examined inflammatory markers. There is *meta*-analytic evidence for increased CRP concentrations in patients with GAD compared to controls (Costello et al., 2019). However, consistent with the present results, a recent *meta*-analysis reported little evidence for raised inflammatory markers in young people with anxiety disorders (Parsons, Roberts, & Mills, 2021).

This study adds to the literature regarding associations between suPAR and psychiatric outcomes (Haastrup et al., 2014; Latham et al., 2022; Nielsen et al., 2015; Ventorp, Gustafsson, Träskman-Bendz, Westrin, & Ljunggren, 2015). suPAR levels have previously found to be higher in adults with depression (Gustafsson et al., 2017) and in people who have attempted suicide compared to controls (Ventorp et al., 2015). Depression risk in youth has been associated longitudinally with suPAR levels later in life (Latham et al., 2022). Our secondary analyses provide preliminary evidence that suPAR levels may be weakly associated with degree of psychiatric co-morbidity. This may reflect an association with severity of psychopathology more generally, though it is not possible to infer the direction of this association. Psychosocial factors such as childhood adversity and exposure to violence have been longitudinally associated with higher suPAR levels in later life (Line Jee Hartmann Rasmussen et al., 2020).Thus, suPAR may reflect cumulative exposure to biological, psychological and social transdiagnostic risk factors for mental disorders.

Notably, the current findings were not substantially altered when models were additionally adjusted for childhood trauma. Childhood adversity has been longitudinally associated with raised inflammatory markers including CRP (D. Baumeister et al., 2016) and suPAR (Line Jee Hartmann Rasmussen et al., 2020; L. J. H. Rasmussen et al., 2019), although results of individual studies are inconsistent (Brown et al., 2021; Iob, Lacey, Giunchiglia, & Steptoe, 2022). Associations between trauma and inflammation may be mediated through factors such as BMI (Slopen, Kubzansky, McLaughlin, & Koenen, 2013) and social disadvantage (Olvera Alvarez, Kubzansky, Campen, & Slavich, 2018). It is possible the other confounders included in the current analyses may have captured a proportion of the associated variance. However, trauma was not the focus of this investigation. Childhood trauma likely has differential effects depending on type, age of exposure, frequency, severity and functional impact (D. Baumeister et al., 2016; Brown et al., 2021) which were not captured by the broad variable used in the present study. Further analyses are required to investigate the influence of such factors.

This study has several limitations. Given its cross-sectional nature, it is not possible to infer causal relationships. Serial measurements over time, particularly of IL-6 and suPAR, would be helpful to investigate associations between longitudinal trajectories of inflammatory markers in childhood and adolescence and mental disorders in early adulthood. Residual confounding is possible. For example, data regarding physical activity and current medical conditions were not available. Furthermore, we were unable to adjust for potential effects of medication use (see Supplementary Methods for further details). Several previous studies have reported effects of antidepressant and antipsychotic treatment on certain inflammatory markers (Tourjman et al., 2013; Więdłocha et al., 2018), although evidence across markers is inconsistent. Effects likely depend on the specific marker and medication, as well as dose and duration (Baumeister et al., 2016b). Participants self-reported whether they took medication for delusions, hallucinations or another mental health problem, but were not asked regarding type, dose or duration of treatment. Future studies in larger populations could investigate linkage with prescription records to further elucidate the role of medication on the examined markers in young people. The cohort is mostly Caucasian and based in a relatively affluent area of the United Kingdom, which may limit generalisability. Due to low sample volumes, we were unable to perform duplicate measurements of suPAR and A2M. While this study focused on individuals meeting clinical thresholds for mental disorders, we plan in future work to extend these analyses to consider associations between inflammatory markers and counts or severity of symptoms. The PLIKSi does not provide ICD-10-defined diagnosis, but most individuals who fulfilled the outcome criteria for psychotic disorder would also likely meet ICD criteria given they were experiencing regular psychotic symptoms with severe distress or impairment. Finally, our secondary analyses used number of disorders as

an index of psychiatric co-morbidity, which could be considered a relatively crude measure. More sophisticated methods, such as latent variable models, have been used to derive a unidimensional general psychopathology factor known as *p* (Caspi et al., 2014), although other analyses have indicated that the sum of diagnoses is in some situations statistically almost identical to *p* (Fried, Greene, & Eaton, 2021).

5. Conclusions

We report associations between plasma levels of IL-6 and suPAR with psychotic disorder in young adults aged 24 years compared to controls. There was weaker evidence for an association between suPAR and depressive disorder, but little evidence for associations with GAD. Secondary analyses provided preliminary evidence that suPAR was weakly associated with psychiatric co-morbidity. The results suggest that, among these mental disorders of early adulthood, peripheral inflammatory burden is greatest in psychotic disorder. Further investigation is required to confirm these findings and to elucidate the utility of suPAR as a marker of severity of psychopathology in early adulthood.

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Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Requests for access to ALSPAC data may be submitted to the ALSPAC executive committee as detailed on the study website: http://www.bristol.ac.uk/alspac/researchers/access/

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Appendix A. Supplementary data

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