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# A population-based study of atopic disorders and inflammatory markers in childhood before psychotic experiences in adolescence ☆

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ABSTRACT

*Objective:* Schizophrenia is associated with atopy and increased inflammatory markers. We report a population-based longitudinal study of the associations between childhood atopic disorders, subsequent serum inflammatory markers, interleukin 6 (IL-6) and C-reactive protein (CRP), and the risk of psychotic experiences (PEs).
*Method:* PEs were assessed at age 13 years (n = 6785). Presence of clinician-diagnosed atopic disorders (asthma and eczema) was determined from parent-completed questionnaires at age 10 years (n = 7814). Serum IL-6 and CRP were measured at age 9 years (n = 5076). Logistic regression examined the association between (1) atopy and PEs, (2) inflammatory markers and PEs, and (3) mediating effects of inflammatory markers on the atopy–PEs association. Linear regression examined the association between atopy and inflammatory markers. Age, gender, social class, ethnicity and body mass index were included as potential confounders.
*Results:* At age 10 years, about 14% of the sample was reported to have asthma, 12% eczema, and 7% both asthma and eczema. Compared with children with no atopy, risk of PEs at age 13 years was increased for all of these groups; adjusted odds ratios (95% CI) were, respectively, 1.39 (1.10–1.77), 1.33 (1.04–1.69), and 1.44 (1.06–1.94). Atopy was associated with increased serum IL-6 and CRP; however, this did not mediate association between atopy and PEs. Inflammatory markers were not associated with later PEs.
*Conclusion:* Childhood atopic disorders increase the risk of psychotic experiences in adolescence. Follow-up of these individuals will be useful to determine the effect of atopy and inflammation on different trajectories of early-life PEs.



## 1. Introduction

Several lines of evidence link adult psychotic illness with infection and abnormalities in various components of the immune system. Increased prevalence of antibodies to *Toxoplasma gondii* has been reported in schizophrenia (Torrey et al., 2012). Maternal infection (Buka et al., 2001a; Brown et al., 2004a, 2005; Mortensen et al., 2007; Brown and Derkits, 2010; Mortensen et al., 2010; Khandaker et al., 2012b), raised serum inflammatory markers during pregnancy (Buka et al., 2001b; Brown et al., 2004b), and childhood infection (Rantakallio et al., 1997; Dalman et al., 2008; Khandaker et al., 2012a) have been reported to be associated with the increased risk of schizophrenia in adult life. Studies of individuals with first episode psychosis or acute psychotic relapse suggest an increase in proinflammatory cytokines in serum (Miller et al., 2011), a marker of activation of the innate immune response (Weizman and Bessler, 1999). A recent meta-analysis has reported increased serum C-reactive protein (CRP) in schizophrenia (Miller et al., 2013). However, longitudinal studies of circulating markers of inflammation in childhood and subsequent risk of psychotic outcomes are lacking.

Increased autoantibodies against various brain regions and ion channels have been reported in adult psychotic illness (Rothermundt et al., 2001; Zandi et al., 2011), a marker of activation of the adaptive immune response. Epidemiological studies have also reported increased prevalence of autoimmune conditions in schizophrenia, and family members

*Abbreviations:* PEs, psychotic experiences; IL-6, interleukin 6; CRP, C-reactive protein; OR, odds ratio, 95%; CI, 95% confidence interval.



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of patients with schizophrenia (Eaton et al., 2006; Chen et al., 2012). Adaptive immune response elicited by non-infectious antigens underlies atopic disorders such as asthma, atopic dermatitis, urticaria and allergic rhinitis (Janeway et al., 2001). Therefore, it has been suggested that examination of possible links between immune responses and the development of schizophrenia should include atopic conditions as possible contributing factors (Rottem and Shoenfeld, 2003). The evidence base on this subject is growing. So far, two cross-sectional studies have reported increased prevalence of asthma in schizophrenia (Chen et al., 2009; Weber et al., 2009). Recently, a large population-based longitudinal study has reported increased risk of adult schizophrenia in individuals with atopic disorders (asthma, atopic dermatitis, urticaria and allergic rhinitis) earlier in life (Pedersen et al., 2012). Effects of inflammatory response on the developing brain have been proposed as one mechanism that may underlie this association (Pedersen et al., 2012); also, other epidemiological observations of associations between early life infection and adult schizophrenia (Brown and Derkits, 2010; Khandaker et al., 2012a, 2012b). However, empirical data on this topic involving human subjects is limited (Buka et al., 2001b; Brown et al., 2004b).

Population-based birth cohort studies have reported increased risk of adult psychotic illness among individuals reporting psychotic experiences (PEs) during childhood and adolescence (Poulton et al., 2000; Zammit et al., 2013). Early-life PEs also have been linked with a number of risk factors for schizophrenia (Horwood et al., 2008; Thomas et al., 2009; Zammit et al., 2009). Therefore, it has been suggested that studies of early-life PEs may be helpful to elucidate the pathophysiology of adult psychotic disorders (Kelleher and Cannon, 2011; Murray and Jones, 2012).

Using data from the population-based Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, we report associations between early-life atopic disorders, serum inflammatory markers (interleukin 6 or IL-6 and CRP) at age 9 years, and the risk of PEs at age 13 years. We predicted that atopic disorders will be associated with both increased levels of inflammatory markers and the risk of PEs. We also predicted that inflammatory markers will be associated with the risk of PEs, and finally, that they will mediate the association between atopic disorders and PEs. Fig. 1 illustrates the timing of data collection and the hypotheses tested.

## 2. Method

### 2.1. Sample

The ALSPAC birth cohort is based on all pregnant women residing in the county of Avon, a geographically defined region in the southwest of England, with expected dates of delivery between April 1991 and December 1992 (www.alspac.bris.ac.uk). The initial ALSPAC cohort consisted of 14,062 live births and 13,988 infants still alive at 12 months (Boyd et al., 2013; Fraser et al., 2013). Avon included both urban and rural areas, and the population was broadly representative of all children in the UK. The parents completed regular postal questionnaires about all aspects of their child's health and development since birth. Since the age of 7 years the children attended an annual assessment clinic during which they participated in a range of face-to-face interviews and physical tests. The current study is based on 6784 individuals who completed the Psychosis-like Symptoms interview (PLIKSi) at age 13 years.

Ethical approval for the study was obtained from ALSPAC Ethics and Law Committee and the Local Research Ethics Committees.

### 2.2. Assessment of psychotic experiences (PEs)

Psychotic experiences were assessed by the semi-structured Psychosis-like Symptoms interview (PLIKSi) at a mean age of 12.9 years (SD = 0.23). The interview instrument comprised 12 'core' questions derived from the Diagnostic Interview Schedule for Children–IV (DISC–IV) (Shaffer et al., 2000), and the Schedules for Clinical Assessment in Neuropsychiatry version 2.0 (SCAN 2.0) (WHO, 1994). It included twelve key symptoms covering the three main domains of positive psychotic symptoms: hallucinations (visual and auditory); delusions (delusions of being spied on, persecution, thoughts being read, reference, control, grandiose ability, and other unspecified delusions); and bizarre symptoms (thought broadcasting, insertion and withdrawal). Interviewees were asked about the presence of these symptoms and frequency of symptoms. We used the observer based rating for the presence or absence of any psychotic experiences in the past six months as the main outcome (i.e. a binary dependent variable). We also examined twelve specific PEs individually as outcomes. The group with PEs was compared with the rest of the cohort. We chose the binary definition of outcome rather than a dimensional approach based on symptom frequency in order to maximize power in multivariable regression analysis.

The interviews were carried out by 13 psychology graduates who were trained by two experienced clinicians and SCAN trainers (a child psychiatrist and a general adult psychiatrist) (Horwood et al., 2008). The interviewers were required to reach 95% agreement whilst scoring two 'gold standard' interview videotapes that were prepared by the trainers. Monthly booster training sessions and workshops were arranged to discuss scoring of complex cases and consolidate training. All interviews were audiotaped for each interviewer until they reached eight interviews containing several items rated 'positive' (i.e. PEs present). These tapes were independently rated by a second

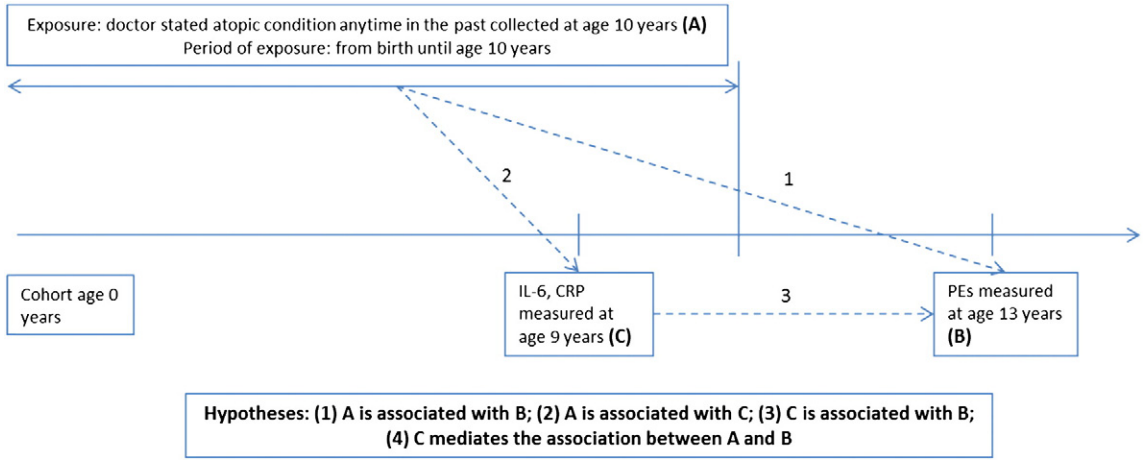


**Fig. 1.** Timing of data collection and hypotheses for the study of atopic disorders, inflammatory markers and risk of psychotic experiences (PEs) in ALSPAC.