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Serum C-reactive protein in adolescence and risk of schizophrenia in adulthood: A prospective birth cohort study

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ABSTRACT

Objective: Meta-analyses of cross-sectional studies confirm an increase in circulating inflammatory markers during acute psychosis. Longitudinal studies are scarce but are needed to understand whether elevated inflammatory markers are a cause or consequence of illness. We report a longitudinal study of serum C-reactive protein (CRP) in adolescence and subsequent risk of schizophrenia and related psychoses in adulthood in the Northern Finland Birth Cohort 1986.

Method: Serum high-sensitivity CRP was measured at age 15/16 years in 6362 participants. ICD-10 diagnoses of schizophrenia and related psychoses were obtained from centralised hospital inpatient and outpatient registers up to age 27 years. Logistic regression calculated odds ratios (ORs) for psychotic outcomes associated with baseline CRP levels analysed as both continuous and categorical variables using American Heart Association criteria. Age, sex, body mass index, maternal education, smoking, and alcohol use were included as potential confounders.

Results: By age 27 years, 88 cases of non-affective psychosis (1.38%), of which 22 were schizophrenia (0.35%), were identified. Adolescent CRP was associated with subsequent schizophrenia. The adjusted OR for schizophrenia by age 27 years for each standard deviation (SD) increase in CRP levels at age 15/16 years was 1.25 (95% CI, 1.07–1.46), which was consistent with a linear, dose-response relationship (*P*-value for quadratic term 0.23). Using CRP as a categorical variable, those with high (>3 mg/L) compared with low (<1 mg/L) CRP levels at baseline were more likely to develop schizophrenia; adjusted OR 4.25 (95% CI, 1.30–13.93). There was some indication that higher CRP was associated with earlier onset of schizophrenia ($r_s = -0.40$; $P = 0.07$).

Conclusions: A longitudinal association between adolescent CRP levels and adult schizophrenia diagnosis indicates a potentially important role of inflammation in the pathogenesis of the illness, although the

Abbreviations: CRP, C-reactive protein; OR, odds ratio; IL, interleukin; TNFα, tumour necrosis factor alpha; ALSPAC, Avon Longitudinal Study of Parents and Children; NFBC, Northern Finland Birth Cohort; AHA, American Heart Association; CDC, Centers for Disease Control and Prevention; FHDR, Finnish Hospital Discharge Register; ICD-10, International Classification of Diseases, 10th revision; NAPLS, North American Prodrome Longitudinal Study.

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findings, based on a small number of cases, need to be interpreted with caution and require replication in other samples.

1. Introduction

A possible association between schizophrenia and the immune system was postulated over a century ago and is supported by epidemiological and genetic studies pointing to links with infection and with alteration in different components of the immune system; reviewed (Khandaker et al., 2015a; Khandaker and Dantzer, 2016). Schizophrenia is associated with increased prevalence of various infections, including the intracellular parasite *Toxoplasma gondii* (Torrey et al., 2007) and neurotropic viruses from the *Herpesviridae* family (Bartova et al., 1987; Delisi et al., 1986). Systematic reviews (Khandaker et al., 2012, 2013) of population-based studies suggest prenatal maternal infection (Brown et al., 2004a; Brown and Derkits, 2010; Buka et al., 2001a; Khandaker et al., 2013; Mortensen et al., 2007), raised inflammatory markers during pregnancy (Brown et al., 2004b; Buka et al., 2001b; Canetta et al., 2014), and childhood infections (Benros et al., 2011; Dalman et al., 2008; Khandaker et al., 2015b) are associated with psychotic disorders in adulthood and sub-clinical psychotic experiences (PEs) in adolescence. Similarly, infection/inflammation is associated with cognitive impairments in schizophrenia patients (Dickerson et al., 2012, 2008) and impaired neurodevelopment and behavioural problems in experimental animal models of prenatal immune activation (Meyer et al., 2008; Shi et al., 2009; Weir et al., 2015). Atopic disorder and autoimmunity, which reflect alterations in adaptive immune responses, are associated with adult schizophrenia (Eaton et al., 2006; Karlsson et al., 2012; Pedersen et al., 2012; Steiner et al., 2013) and adolescent PEs (Khandaker et al., 2014b).

There is convincing evidence that schizophrenia is associated with activation of the innate immune response (Di Nicola et al., 2013; Miller et al., 2011, 2013). Meta-analyses of a large number of cross-sectional studies confirm that both antipsychotic-naïve first-episode psychosis and acute psychotic relapse are associated with increased serum levels of acute phase proteins, such as C-reactive protein (CRP), and proinflammatory cytokines, such as interleukin 1 beta (IL-1β), IL-6, and tumour necrosis factor alpha (TNFα), and decreased serum levels of the anti-inflammatory cytokine IL-10, all of which tend to normalise after remission of symptoms with antipsychotic treatment (Goldsmith et al., 2016; Miller et al., 2011, 2013; Potvin et al., 2008; Upthegrove et al., 2014). However, it is difficult to ascertain the direction of association between inflammation and schizophrenia from cross-sectional data. Longitudinal studies of inflammatory markers and subsequent psychotic illness are scarce but are necessary to establish whether the increase in circulating inflammatory markers is a cause or consequence of illness.

Recently, a prospective study from the Avon Longitudinal Study of Parents and Children (ALSPAC), a general population birth cohort, has reported two-fold increased risk of PEs and psychotic disorder at age 18 years for higher serum levels of IL-6 at age 9 years (Khandaker et al., 2014a). Similarly, another population-based longitudinal study from Denmark has reported an increased risk of late- or very-late-onset schizophrenia in participants with higher serum CRP at baseline (Wium-Andersen et al., 2014). While these studies point towards an important role for systemic inflammation in the aetiology of psychosis, early- or late-onset cases may not be representative of all psychosis, the majority of which is incident in early adulthood. In order to examine the association between inflammation and schizophrenia, we have carried out a longitudinal study of serum CRP levels assessed at age 15/16 years and subsequent hospitalisation for schizophrenia and related psychosis until age 27 years in the Northern Finland Birth Cohort (NFBC) 1986. We hypothesised that higher CRP levels in adolescence would be associated with greater risk for schizophrenia in adulthood.

2. Method

2.1. Description of the cohort and sample

The NFBC 1986 is a general population-based longitudinal birth cohort study based on all pregnant women from the two northernmost provinces of Finland (Oulu and Lapland) with expected dates of delivery between July 1985 and June 1986 (http://kelo.oulu.fi/NFBC/). It consists of 9432 live births, which is 99% of all deliveries in the region during the study period. A wide variety of social and biological characteristics of the mother and family were recorded during pregnancy in antenatal clinics. Since birth, data have been collected by a number of means, including local midwives, three postal questionnaires (age 7, 8 and 16 years), and face-to-face assessment clinics, as well as from various hospital records and routine statistical registers. The current study is based on 6362 participants who had their serum CRP levels measured in blood samples collected during physical assessment at age 15/16 years. All participants and their parent(s) gave written informed consent.

The ethical committee of the Northern Ostrobothnia hospital district provided ethical approval for the NFBC 1986. Data protection is underpinned by the principles of the Finnish Ministry of Health and Social Affairs and has been scrutinized by the Privacy Protection Agency, Finland.

2.2. Measurement of CRP at age 15/16 years

Data on serum CRP levels measured in blood samples collected at age 15/16 years were available from the cohort, which were used for the current study. We could not include any other acute phase proteins or cytokines as these had not been measured. For CRP measurement blood samples were collected after overnight fasting during clinical assessment at age 15/16 years. Serum high-sensitivity CRP levels were measured by a quantitative, immunofluorometric method (Innotrac Aio!; Innotrac Diagnostics Ltd., Turku, Finland) (Hedberg et al., 2004). In the total sample, CRP values ranged from 0.01 to 48.23 mg/L. The minimum detection limit was 0.003 mg/L, which represents the lowest measureable analytic level for CRP that can be distinguished from zero. Those below detection limit were assigned a value of zero (n = 15; 0.23% of sample) and were also included in analysis.

In addition to analysing CRP as a continuous measure, a categorical variable for CRP was created based on the American Heart Association (AHA) and the Centers for Disease Control and Prevention (CDC), USA, guidelines on the use of high-sensitivity CRP levels in epidemiological studies (Pearson et al., 2003; Salazar et al., 2014; Yeh and Willerson, 2003). The sample was divided into three