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An association between both low and high birth weight and increased disorganized and negative symptom severity in schizophrenia and other psychoses

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ABSTRACT

Longitudinal cohort studies have implicated an association between both low and high birth weight and increased schizophrenia risk. In this study, we investigated the effect of birth weight on the symptom severity of psychotic disorders including schizophrenia in a Finnish schizophrenia family study sample. We used a multivariate GEE (General Estimating Equation) regression model to investigate the association of birth weight and symptom severity in 282 subjects with a primary psychotic disorder, 178 of whom had a diagnosis of schizophrenia. The Scales for the Assessment of Positive and Negative Symptoms (SAPS and SANS) were used as a measure of symptom severity. Sex, place of birth and year of birth were adjusted for in the model. Both low and high birth weight were associated with more severe symptoms with respect to bizarre behaviour, affective flattening and attentional impairment. In addition, low birth weight was associated with more severe symptoms with respect to positive formal thought. Our findings suggest that both low and high birth weight can influence the symptom severity of psychotic disorders. Our results implicate an association between both low and high birth weight and disorganized and negative symptoms.

1. Introduction

Longitudinal cohort studies have implicated an association between both low and high birth weight and increased schizophrenia susceptibility (Moilanen et al., 2010). To date most notably low birth weight (LBW) has been associated with increased schizophrenia susceptibility (Cannon et al., 2002; Abel et al., 2010). An association between high birth weight (HBW) and schizophrenia has also been described (Hultman et al., 1997; Gunnell et al., 2003; Bersani et al., 2007; Moilanen et al., 2010; Wegelius et al., 2011). Some studies have failed to find an association between birth weight and schizophrenia (Byrne et al., 2007).

It has been proposed that any adverse factor acting on the developing fetus will affect its growth (Rapoport et al., 2005). Birth weight has been suggested to depict an unspecific proxy variable reflecting the influence of the prenatal environment on the neurodevelopmental process (Cannon et al., 2002). Numerous biological factors are known to influence fetal growth the most evident being gestational diabetes and malnutrition, both of which have been associated with increased schizophrenia susceptibility (Cannon et al., 2002). LBW has been associated in the pathogenesis of a number of diseases including coronary heart disease, hypertension, type II diabetes, abnormalities in cholesterol metabolism and blood coagulation (Barker, 1995). HBW has been associated with an elevated risk of delivery complications, such as newborn asphyxia (Henriksen, 2008).

Although many schizophrenia-associated environmental risk factors have been characterized, the potential role of environmental factors in influencing the phenotypic variability of psychotic disorders including schizophrenia has gained less attention. It is not known whether specific environmental adversities, such as factors influencing fetal growth, could be associated with a specific symptomology. In the general population LBW has been associated with lower educational levels and decreased occupational functioning, as well as poorer cognitive performance (Tanskanen et al., 2011).

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In schizophrenia LBW has been associated with poor premorbid social adjustment and decreased cognitive functioning particularly among males (Rifkin et al., 1994; Hultman et al., 1999).

The dissection of the schizophrenia phenotype into symptom dimensions has been proposed to facilitate the interpretation and strengthen the power to detect associations between potential etiological factors and relevant phenotypic data (Derks et al., 2010). In a previous study we found an association between HBW (birth weight > 4000 g) and increased schizophrenia susceptibility in a Finnish schizophrenia family study sample (Wegelius et al., 2011). In the present study, we set out to investigate the association between birth weight and the clinical presentation of schizophrenia and other psychotic disorders in the same study sample. We postulated that both low and high birth weight may influence the severity of symptoms in psychotic disorders.

2. Materials and methods

2.1. Study sample

The Finnish schizophrenia family study sample has been collected based on the information obtained by the combination of three nationwide registers: the Hospital Discharge Register, the Pension Register and the Medication Reimbursement Register (Hovatta et al., 1997; Arajärvi et al., 2004). From these registers, we identified 33,731 individuals, born between 1940 and 1976, who had been hospitalized, had received disability pension or had been granted entitlement to free out-patient antipsychotic medication for the treatment of schizophrenia between 1969 and 1998. The parents and siblings of patients with schizophrenia were identified from the Population Register Center. Information regarding the psychiatric morbidity and diagnoses of relatives was obtained from the health care registers described above. Two samples assumed to have a high genetic risk of schizophrenia were drawn from the identified families. The first sample consisted of all nuclear families originating from an internal isolate region having at least one sibling with schizophrenia and at least two grandparents born in the isolate region (Arajärvi et al., 2004). The lifetime risk of developing schizophrenia in the isolate region is 3.2% (Hovatta et al., 1997). From the rest of Finland, families with at least two affected siblings were recruited (Ekelund et al., 2001; Paunio et al., 2001). The collection of these families was initiated in the early 1990s, as described in detail in Arajärvi et al. (2004). Since 1998, we have gained informed consent to collect birth records from all siblings participating in the study (Wegelius et al., 2011).

We obtained birth weight data of 1051 siblings from 315 families (Wegelius et al., 2011). Case records of all lifetime mental health treatments from in- and out-patient care were collected. 589 of the 1051 subjects with birth weight data were interviewed with the Structured Clinical Interview for DSM-IV Axis I Diagnosis (First et al., 1996), while the remaining subjects were diagnosed based on case record information only and were not included in the current analysis. Of these 589 subjects, 282 had a lifetime history of any primary psychotic disorder and were also assessed using the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983). Using information from case records and the interview, lifetime diagnoses were assigned by two, or in case of disagreement three, independent psychiatrists and/or psychiatric residents according to the DSM-IV criteria. The term 'primary psychotic disorder' was applied to subjects with a lifetime history of any psychotic disorder not caused by substance use or general medical condition (Wegelius et al., 2011).

The study was approved by the Ministry of Social Affairs and Health of Finland, the Ethics Committee of the National Public Health Institute of Finland (since January 1st 2009 National Institute for Health and Welfare), and the Ethics Committee of the Hospital District of Helsinki and Uusimaa. Probands were contacted by their treating physicians. Family members were contacted only if the respective proband gave permission. Written informed consent was obtained from each participant.

2.2. Psychometric measures

About 178 subjects (63.1%) had a diagnosis of schizophrenia (DSM-IV 295.10, 295.20, 295.30, 295.60, 295.90). About five had schizophreniform disorder (DSM-IV 295.40), 54 had schizoaffective disorder (DSM-IV 295.70), one had delusional disorder (DSM-IV 297.1), one had brief psychotic disorder (DSM-IV 298.8), 13 had major depressive disorder with psychotic features (DSM-IV 296.24, 296.34), 14 had bipolar I disorder with psychotic features (DSM-IV 296.04, 296.44, 296.54, 296.64) and 16 were assigned a diagnosis of psychotic disorder not otherwise specified (DSM-IV 298.9). The following global ratings from SAPS/SANS were used in the regression models: SAPS7=global rating of hallucinations, SAPS20=global rating of delusions, SAPS25=global rating of bizarre behaviour, SAPS34=global rating of formal thought disorder. SANS8=global rating of affective flattening, SANS13=global rating of alogia, SANS17=global rating of avolition–apathy , SANS22=global rating of anhedonia–asociality , SANS25=global rating of attention. Each of these was rated from 0=absent to 5=severe. SAPS and SANS are widely used, and their reliability and validity are thoroughly discussed elsewhere (Klimidis et al., 1993; Andreasen et al., 1995).

2.3. Statistical analysis

Subjects included in our data set could not be considered as being independent entities as family members are more likely to resemble one another in various aspects, including birth weight. We used a General Estimating Equation (GEE) model to investigate the association of birth weight and symptom dimensions. GEE is a quasi-likelihood-based method that produces population-averaged regression coefficients while adjusting for within-family correlations (Liang and Zeger, 1986). Birth weight and symptom dimension variables were all approximately normally distributed and were treated as continuous variables.

Obstetric practice in Finland evolved dramatically after World War II. In 1940, only 31.0% of deliveries in Finland took place in maternity hospitals, while in 1960, 92.5% of deliveries occurred in maternity hospitals (Hemminki, 1983). The internal isolate region represented a socio-economically disadvantaged area, in which the availability of prenatal, obstetric and neonatal care was more limited and infant mortality higher in comparison to the rest of the country (Palmgren, 1964). Therefore, place of birth (internal isolate vs. rest of Finland) and year of birth (born in or before 1960 vs. later) were adjusted for in the models. In addition, the models were adjusted for sex, as sex has been demonstrated to influence both schizophrenia susceptibility and birth weight.

Preliminary graphical examination suggested that the effect of birth weight on some symptom dimensions was not linear, see Supplementary Fig. 1. We used a quadratic polynomial regression model to test whether both low and high birth weight were associated with increased symptom severity by fitting a quadratic term in the model. Nested models with and without a quadratic effect were compared using Wald test to determine the best fitting model.

All analyses were performed using the R-program version 2.12.1 (R Development Core Team, 2010). A probability level of $p < 0.05$ was considered significant.

3. Results

Of the 1051 individuals with birth weight data, 282 subjects with primary psychotic disorder from 204 families had been assessed with the SAPS and SANS. The study group consisted of 103 females (37%) and 179 males (63%) with average birth weights of 3430 g and 3470 g, respectively (Table 1). The mean birth weight in the total sample was 3450 g, (SD 600 g). The median year of birth was 1956, and the median age at the time of interview was 44 yrs (range 25–59 yrs). Symptom severity was higher in the schizophrenia group in comparison to the primary psychotic disorder group with respect to all nine global SAPS/SANS measures investigated (Table 1).

3.1. The association between birth weight and symptom severity in primary psychotic disorders

Both low and high birth weight were associated with more severe symptoms of bizarre behaviour, as reflected by the statistically significant quadratic term ($\beta_{Linear} = -3.92$, SE=0.76, $p < 0.001$; $\beta_{Quadratic} = 0.57$, SE=0.12, $p < 0.001$) (Fig. 1). A statistically significant linear association between birth weight and formal thought disorder was observed ($\beta = -0.29$, SE=0.12, $p=0.02$), with lower birth weight correlating with greater symptom severity as indicated by the negative linear coefficient. A statistically significant association between birth weight and hallucinations ($\beta = -0.06$, SE=0.16, $p=0.70$) or delusions ($\beta = 0.07$, SE=0.14, $p=0.61$) was not observed.

Both high and low birth weight were associated with greater severity of affective flattening ($\beta_{Linear} = -1.87$, SE 0.67, $p=0.01$; $\beta_{Quadratic} = 0.26$, SE=0.10, $p=0.01$) and attentional deficits ($\beta_{Linear} = -2.72$, SE=0.90, $p < 0.001$; $\beta_{Quadratic} = 0.36$, SE=0.14, $p=0.01$), as indicated by the significant quadratic terms (Fig. 2). No statistically significant associations were observed between birth weight and alogia ($\beta = -0.17$, SE=0.16, $p=0.26$),