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The association of fetal and childhood growth with risk of schizophrenia. Cohort study of 720,000 Swedish men and women

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Abstract

Previous investigations of the association of schizophrenia with patterns of pre- and post-natal growth have been based on small numbers of cases or have not taken account of the effects of prematurity on birthweight. We investigated the association of fetal growth with schizophrenia in a large cohort of Swedish males and females. We linked data from the Swedish Medical Birth Register (1973–1980), Inpatient and Discharge Register (1988–2002), Military Service Conscription Register (1990–1997), and the Population and Housing Censuses (1970 and 1990). Altogether 719,476 males and females were followed up from the age of 16 for a mean of 9.9 years. There were 736 incident cases of schizophrenia. Even in models that did not control for gestational age there was little evidence of an association between birthweight and schizophrenia (hazard ratio per kg increase in birthweight: 0.90 (95% CI 0.78 to 1.03); the hazard ratio in babies weighing <2.5 kg compared to 3.5–4.0 kg was 1.29 (95% CI 0.85 to 1.96). There was an inverse association of birth length with schizophrenia across the range of birth lengths. Short babies were at an increased risk (hazard ratio per 10 cm increase in birth length: 0.53, 95% CI 0.31 to 0.89 (fully adjusted model)). All associations were little changed when analyses were restricted to term (>36 week gestation) babies. In males, low body mass index and short height at age 18 were associated with increased risk. There is some evidence that patterns of risk in relation to fetal growth differ depending on post-natal growth patterns: the increased risk associated with low body mass index was restricted to long babies who became light adults. The exposures underlying these associations and the biological mechanisms mediating them require clarification.

Keywords: Schizophrenia; Psychosis; Cohort study; Birth weight; Birth length

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1. Introduction

Current models of schizophrenia describe it as a complex neurodevelopmental disorder arising as a consequence of an interplay of genes and the environment (Tsuang et al., 2001; Cannon et al., 2002). Despite growing evidence that patterns of pre- and post-natal growth are associated with schizophrenia, a number of issues remain unresolved. Firstly, it is unclear whether the increased risk of schizophrenia in low birth weight babies reported in some studies is due to the effect of pre-maturity on risk. Pre-maturity is associated with increased risk in some studies (Ichiki et al., 2000) but this may be because pre-mature babies have low birth weights and are more susceptible to hypoxia and traumatic brain injury during delivery. Some studies of birthweight–psychosis associations have not controlled for gestational age (Wahlbeck et al., 2001). Those studies that have investigated the effect of controlling for gestational age on birthweight associations report that the inverse association with birthweight persist (Dalman et al., 2001; Hultman et al., 1999; Gunnell et al., 2003) whilst others find that associations are attenuated (Jones et al., 1998; Ichiki et al., 2000). Secondly, a few studies have reported associations between high birth weight and risk of psychosis (Gunnell et al., 2003; Moilanen et al., 2002; Hultman et al., 1997), but findings are inconsistent (Wahlbeck et al., 2001). Clarification of this issue may yield clues concerning biological mechanisms, such as maternal diabetes, which may underlie the development of some cases of schizophrenia (Gunnell et al., 2003). Lastly, birth weight is a crude measure of fetal growth retardation. A fuller picture of patterns of fetal growth can be obtained by examining associations with birth length, birthweight in relation to length (Hultman et al., 1999, 1997; Dalman et al., 1999) and birth anthropometry in relation to final adult size (Gunnell et al., 2003).

In a previous paper, we reported a reverse J-shaped association of birth weight with schizophrenia amongst Swedish males born in 1973–1980 and followed-up to 1997 (Gunnell et al., 2003). Here we assess associations of schizophrenia with fetal growth in females as well as males after a further 5-years of follow-up of this cohort up to 2002.

2. Methods

2.1. Dataset examined

The cohort comprises 719,476 singleton males and females, born in Sweden between 1973 and 1980, who were still alive and resident in Sweden at the age of 16 years. The characteristics of study members have been described in previous papers (Harrison et al., 2003; Sipos et al., 2004). Subjects were excluded if they had been admitted to hospital with a diagnosis of psychosis prior to 16 years of age or if data for variables of interest were incomplete or implausible (see below). Information on the study sample was obtained from linkage between Sweden's Medical Birth Registry, its Population and Housing census of 1990, its Inpatient Discharge Register (up to 31 December 2002), and its cause of death and emigration registers (up to 31 December 2001). For males only we obtained data on height and weight at around 18 years of age from the Military Service Conscription Register (up to 31 December 1997).

2.2. Disease outcomes

Our analysis was based on records of people admitted to hospital between 1989–2002 with a diagnosis of schizophrenia (international classification of diseases, 10th revision, ICD-10: F20; 9th revision, ICD-9, Swedish version: all 295 except 295 F and 295 H).

2.3. Risk factors investigated

We investigated associations with three markers of fetal growth: (i) birthweight, (ii) ponderal index (birth weight (kg)/ birth length (m^3)) and (iii) birth length. We also assessed associations with gestational age at birth as this is strongly associated with birth size.

We investigated the effect on associations of controlling for the following possible confounding factors: sex, year of birth, gestational age (five categories), birthweight (six categories: <2.5, 2.5–2.9,3.0–3.4,3.5–3.9,4.0–4.4 and ≥4.5 kg), birth length (<49, 49, 50, 51, 52 and ≥53 cm), operative (caesarean) delivery, uterine atony, mothers parity, paternal age, Apgar score at 5 min (binary variable ≤6 and >6), place of birth (three categories: rural,