Growth trajectory during early life and risk of adult schizophrenia

Megan A. Perrin, MPH, **Henian Chen, MD, PhD**, **David E. Sandberg, PhD**, **Dolores Malaspina, MD, MSciPH**, and **Alan S. Brown, MD**

Cognitive Neurophysiology Laboratory, Nathan S. Kline Institute for Psychiatric Research, Orangeburg, New York

Departments of Biostatistics and Epidemiology, New York State Psychiatric Institute, New York

Division of Child Behavioral Health, Department of Pediatrics, University of Michigan, Ann Arbor, Michigan

Department of Psychiatry, New York University School of Medicine, New York

Joseph Mailman School of Public Health, Columbia University and Department of Psychiatry, College of Physicians and Surgeons of Columbia University, New York State Psychiatric Institute, New York, USA

Abstract

Background—Growth abnormalities have been suggested as a precursor to schizophrenia, but previous studies have not assessed growth patterns using repeated measures.

Aims—To assess the association between early life/later childhood growth patterns and risk of schizophrenia.

Methods—Using prospectively collected data from a birth cohort (born 1959–1967), measurements of height, weight and body mass index (BMI) were analysed to compare growth patterns during early life and later childhood between 70 individuals with schizophrenia-spectrum disorder (SSD) and 7710 without.

Results—For women, growth in the SSD group was approximately 1 cm/year slower during early life (*P*<0.01); no association was observed for men. Later childhood growth was not associated with SSD. Weight patterns were not associated with SSD, whereas slower change in BMI was observed among the SSD group during later childhood.

Conclusions—The association between slower growth in early life and schizophrenia in women suggests that factors responsible for regulating growth might be important in the pathogenesis of the disorder.

Several lines of evidence suggest that abnormal growth during development is associated with an increased risk of adult schizophrenia. A small high-risk sample showed that slower growth in childhood is associated with early-onset schizophrenia (Fish, 1959). However, results are inconsistent in other studies and most are limited by reliance on isolated (rather than serial) measurements of height. Large cohort studies extrapolating growth patterns from measures of birth weight, birth length and adult weight and height suggest that atypical

Correspondence: Megan A. Perrin, The Cognitive Neurophysiology Laboratory, Nathan S. Kline Institute for Psychiatric Research, 140 Old Orangeburg Road, Orangeburg, New York 10962, USA. Tel: +1 845 398 6547; fax: + 1 845 398 6545; mperrin@nki.rfmh.org.

Declaration of interest None.

growth is associated with adult psychosis (Gunnell *et al*, 2003, 2005a). Such associations suggest that factors responsible for abnormal growth might influence the pathogenesis of schizophrenia. We compared patterns of growth using serial measurements between individuals with schizophrenia and healthy participants from a large and well-characterised birth cohort (Susser *et al*, 2000). We predicted that adults who went on to develop schizophrenia would exhibit a slower rate of growth during early life and later childhood, and that the effect would be modified by gender.

Method

The cohort comprised offspring of women participating in the Kaiser Foundation Health Plan (KFHP) who received obstetric care and were delivered in Alameda County, California, between 1959 and 1967, and who agreed to participate in the Child Health and Development Study (CHDS) (*n*=19 044). The KFHP was one of the first and largest health insurance plans in the USA, and nearly all pregnant women who were members participated in the CHDS. A comparison of these participants' demographic data with US census data demonstrated that although both income extremes were underrepresented, members were demographically similar with respect to ethnicity, occupation and educational attainment (Krieger, 1992).

The study reported here is restricted to a cohort referred to as the Prenatal Determinants of Schizophrenia (PDS) study cohort, which is a subsample of the offspring of those participating in the CHDS. The design for the PDS study cohort has been previously described in full (Susser *et al*, 2000); thus, only a summary is provided here. The PDS study cohort was designed to follow up and assess participants for the presence of schizophrenia-spectrum disorders in order to evaluate developmental determinants of schizophrenia. It included offspring of mothers from the CHDS cohort who were members of KFHP from 1 January 1981 to 31 December 1997 (*n*=12 094). These dates correspond to the period of case ascertainment, which commenced when KFHP began using computerised records, making it feasible to identify all members who had accessed mental health services. Participants in the PDS cohort are comparable with the CHDS sample, with two exceptions: mothers of African American ethnicity were more likely to be included in the PDS cohort (CHDS 16%, PDS 28%) and offspring of low-income unmarried mothers were somewhat less likely to be included (CHDS 26, PDS 20%).

Height measurements

Height in inches to the nearest sixteenth of an inch (1.6 mm) was measured and recorded during regular paediatric visits from birth to age 13 years. These measurements were systematically abstracted from medical records by trained CHDS abstractors. The present analyses were restricted to data from birth to age 9 years, since reliable data on the pubertal stage of development were not available. The average number of height measurements between birth and age 2½ years was 9 for both the schizophrenia-spectrum disorder (SSD) group and the non-SSD group ranging from 3 to 15 measurements for the former and 1 to 31 for the latter. Between ages 2½ years and 9 years the average number of height measurements was 6 for both groups, ranging from 1 to 19 measurements for the SSD group and 1 to 41 for the non-SSD group. To identify outliers, height was standardised by computing gender- and age-adjusted means using the least mean squares (LMS) method (Cole, 1990). This method is advantageous for standardising height because it uses a series of calculations to reduce asymmetry in skewed data. Height measurements that were greater than 4 standard deviations above or below the mean were considered to be outliers and were excluded from the analyses; 1.0% of all measurements were excluded.

Assessment of potential confounders

Potential confounding factors were determined *a priori* based on characteristics that have been shown to be associated with both height and schizophrenia. These included gender, maternal race and education, standardised maternal height, pre-pregnancy body mass index (BMI), gestational age at birth and birth weight. (It is unnecessary to control for birth length in the adjusted analysis because it is used to estimate growth patterns.) Demographic measures were assessed through maternal interview, which was completed during the first prenatal visit.

Maternal race was categorised as White, Black or other. Maternal education was rated on a seven-point scale reflecting the highest level of education achieved. Because not all levels of education were represented among the SSD sample, the categories were collapsed as follows: less than high-school diploma, high-school graduate with or without trade school, high-school graduate plus 1–3 years of college, and college graduate.

Maternal height was measured during the maternal interview. Because paternal height was based on maternal report and we had insufficient data on paternal height, standardised maternal height was used as a proxy for the child's genetic growth potential. Standardisation of maternal height was accomplished using the LMS method. Because adult height is not typically achieved until 20 years of age, *z*-score transformations of height for mothers aged 15–19 years were calculated separately at 1-year intervals. Mothers aged 20 years or over were assumed to have attained their adult height and were standardised as one group irrespective of age. Maternal pre-pregnancy BMI was calculated using self-reported weight prior to pregnancy and was classified based on categories used in a previous study assessing the association between maternal BMI and schizophrenia-spectrum disorders in this cohort: low, ≤ 19.9 kg/m^2; average, 20.0–26.9 kg/m^2; greater than average, 27.0–29.9 kg/m^2; high, ≥ 30.0 kg/m^2) (Schaefer *et al*, 2000). Maternal prepregnancy BMI data were missing in a proportion of the sample (8 SSD and 1166 non-SSD). To preserve sample size, the average maternal BMI value was substituted for missing data in the adjusted analyses. Gestational age at birth was calculated as the number of days between the last reported menstrual period and birth.

Ascertainment and diagnosis

We identified potential cases of schizophrenia-spectrum disorder through the KFHP computerised records of in-patient, out-patient and pharmacy registries. With regard to the hospitalisation registry, potential cases were first identified if the individual had received ICD–9 diagnosis codes of 295, 296, 297, 298 or 299 (World Health Organization, 1978) or were not given a specific diagnosis. A review of psychiatric and medical records by a psychiatrist was conducted to determine whether individuals screened positive for evidence of a psychotic disorder. Individuals from the out-patient registry were considered to be screen-positive for SSD if they had diagnosis codes of 295, 297, 298 or 299. For the pharmacy registry, cases screened positive if the individual had received treatment with antipsychotic medication.

We identified 183 participants for further diagnostic assessment. Of those identified, 13 had died. Of the 170 remaining, 146 (86%) were successfully contacted and 107 (58% of those originally identified) completed the Diagnostic Interview for Genetic Studies (DIGS; Nurnberger *et al*, 1994) administered by a trained research clinician. For the remaining 76 (42%) individuals who were not interviewed, a diagnosis was made based on review of the medical records by trained clinicians. All individuals provided written informed consent for participation prior to the diagnostic interview. Informed consent was approved by the institutional review boards of the New York State Psychiatric Institute and the Kaiser

Permanente Division of Research. Diagnoses were made by consensus of three diagnosticians who independently reviewed all relevant material for each case. In total, 71 cases were identified (43 schizophrenia, 17 schizoaffective disorder, 5 schizotypal disorder, 1 delusional disorder and 5 other schizophrenia-spectrum psychosis). Forty-four individuals completed the DIGS and 27 were diagnosed by chart review.

Analytical data-set

The PDS cohort comprised 12 094 individuals – 71 SSD and 12 023 non-SSD. Because our analysis required information obtained through maternal interview during enrolment, people who had not completed the interview were excluded ($n=$ 2412), reducing the sample size to 9682. Since siblings represent non-independent observations, only one sibling per family was included in the analysis and siblings of offspring with schizophrenia-spectrum disorder were excluded ($n=1886$). Two people in the SSD group were siblings, so one of them was randomly selected and the data excluded from the analysis. The final cohort consisted of 7795 persons. Please see Susser *et al* (2000) for a further description of the method for deriving the analytic sample. From this cohort only 15 individuals (all from the non-SSD group) were excluded because they did not have at least one valid height measurement; thus, the analytic sample comprised 7780 persons (SSD $n=70$; non-SSD $n=7710$). A summary of the exclusion criteria for the analytical data-set is provided in Fig. 1.

Statistical analyses

The relationship between growth and adult schizophrenia was examined using multilevel growth models (McArdle & Aber, 2000; Cohen *et al*, 2003; Chen & Cohen, 2006). The PROC MIXED function in the SAS statistical package (Littell *et al*, 1996) was used to estimate the growth pattern of height. In these multilevel growth models, longitudinal data on individuals are considered the basic 'random' data, similar to a cross-sectional study where single individual variables are the basic units of analyses (Cohen *et al*, 2003).

The first step in the analyses was to determine the best model fit for the relationship between growth and age from birth to 2½ years, which is referred to as the basic growth model. We first examined the mean level model, which is the between-participant differences in mean level of height (i.e. height=β_0+error). The results suggested that between participants differences were found for height; the estimated variance of the mean height was 2.06 (s.e.=0.28, $P<0.001$). To determine the best model for predicting growth, we compared three additional models: linear change in height (height=β_1+age+error), quadratic change in height (height=β_2+ age+age^2+error) and cubic change in height (height=β_3+age +age^2+age^3+error), where random variation was permitted for each age term. To estimate model fit, we calculated the chi-squared value by subtracting the −2 log likelihood estimates from the subsequent models (i.e. mean level *v.* linear, linear *v.* quadratic, and quadratic *v.* cubic). Compared with the mean level model, the addition of the linear term significantly improved model fit ($P<0.001$). The addition of the quadratic term also significantly improved model fit compared with the linear model ($P<0.001$). Also, the cubic model appeared to significantly improve model fit compared with the quadratic model ($P<0.001$). However, the fixed effect of the cubic term was small and the significant improvement mostly due to the random effects. Also, the addition of the cubic term reduced the variance associated with the linear term to zero. Therefore, to facilitate interpretation, and in the interest of comparability and parsimony, we chose to use the quadratic model. Although fractional polynomial models are sometimes used in this type of analysis, a quadratic equation appears to be an accurate estimate of growth and is easier to interpret. In summary, the model comparisons suggested that the quadratic model provided the best model fit for estimating patterns of growth.

Once the basic model for growth was established, we fitted a conditional model to examine the effect of schizophrenia-spectrum disorders on growth. We added SSD (1, case, 0, non-case) as a covariate to examine mean level differences in height. To assess growth differences between the SSD and non-SSD groups, we included an interaction term for age and SSD and an interaction term for (age)^2 and SSD in the quadratic model. All adjusted analyses controlled confounding effects of gender, maternal education, race, BMI and height, gestational age at birth and birth weight. Each model included a χ^2-test of improvement of fit to the data.

Using the methods described above we also estimated the basic model for growth from age 2½ to 9 years. Separate analyses were performed for early life (birth to age 2½ years) and later childhood (2½ to 9 years) because growth during these periods is regulated by different mechanisms (Karlberg, 1987; Reiter & Rosenfeld, 2003). Additionally, previous research suggests that growth during the first 2 years of life is more variable than growth in later childhood and abnormal growth patterns may be indicative of problems during prenatal development (Tanner, 1994; Reiter & Rosenfeld, 2003). Hence, we predicted that early life (birth to 2½ years) would be associated with the most pronounced growth deficit in individuals who later developed schizophrenia. Previous studies also demonstrated gender differences in growth patterns in healthy samples (Karlberg, 1987) and in the risk and correlates of schizophrenia (Goldstein *et al* 2002; Aleman *et al*, 2003). Thus, all analyses were performed on the entire cohort as well as being further stratified by gender in order to determine whether differences in growth patterns between individuals in the SSD and non-SSD groups varied by gender.

In addition to assessments using the multilevel growth model, we calculated the linear slope (linear change in height by age) for each participant by using maximum likelihood estimates from the basic growth models for both early life (birth to age 2½ years) and later childhood (2½ to 9 years). A feature of this program is the ability to output the empirical Bayesian estimates of the linear slope of height for each participant over the defined periods (McArdle *et al*, 2005). The linear slopes provide additional information about differences between the SSD and non-SSD groups observed from the multilevel models.

Results

Sample characteristics are summarised in Table 1. Men were overrepresented in the SSD group, whereas gender was more evenly distributed among the cohort sample. The SSD sample included a higher proportion of Black people. The mothers of those in the SSD group had fewer years of education, and their maternal pre-pregnancy BMI was higher. There was no difference in maternal height between the SSD and non-SSD groups and maternal height was normally distributed in both groups. Gestational age at birth was slightly higher in the SSD sample but the groups did not differ with respect to birth length or weight.

Change in height

The first step in the analyses was to determine the best model fit for estimating growth in our cohort, which is referred to as the basic model. As noted in the statistical analysis section, we determined that the quadratic model, allowing between-participant variance, provided the best model fit for estimating growth (i.e. height=β_0+age+age^2+error). With respect to the early-life model, the average height at birth for the entire sample was 52.06 cm (Table 2). On average, female babies were 0.82 cm shorter at birth than the males (51.64 cm and 52.46 cm respectively). For the entire sample there was a linear increase with age of 30.27 cm per year (Table 2). Rates of growth declined with age and were best described by a model with a linear and quadratic term. In accordance with normal growth patterns

(Karlberg, 1987), growth during childhood was slower than during early life and the girls remained shorter than the boys (Table 2).

Association between potential confounders and height

We found the expected relationships between the confounders and variability in height at birth and age 2½ years. Compared with the White participants, Black participants were significantly shorter at birth but taller at age 2½ years. Mothers with a higher level of educational attainment tended to have offspring who were taller at birth and at age 2½ years. Pre-pregnancy maternal BMI was positively correlated with birth length, and greater gestational age at birth was associated with increased birth length and height at age 2½ years.

Association between growth velocity and SSD

The results from the final models assessing the relationship between change in height and schizophrenia-spectrum disorders are presented in Table 3. Each model controlled for all main effects; however, only relevant estimates are presented; the results for all interaction terms are presented in the online data supplement to this paper. In Table 3, the term representing the final estimate for the relationship between growth and schizophrenia spectrum disorders is labelled the 'Effect of gender and SSD on growth, cm/year)'. Gender was included in the final estimate because patterns of growth differ between males and females (Karlberg, 1987). Furthermore, one of the goals of the analyses was to explore gender differences in the relationship between growth and schizophrenia. This estimate indicated that in SSD group growth was approximately 1 cm per year slower during early life than in the non-SSD group (B=−1.12, 95% CI −2.04 to −0.20, P=0.017), and the difference was significantly modified by gender. The difference was greater after controlling for potential confounders (B=−1.55, 95% CI −2.52 to −0.57, P=0.002). In analyses stratified by gender, in females in the SSD group growth was approximately 1 cm per year slower than in the non-SSD group (females only model; unadjusted, B= −1.03, 95% CI −1.73 to −0.33, P=0.004; adjusted, B=−1.26, 95% CI −2.00 to −0.53, P=0.001). No significant difference in growth velocity between males in the SSD and non-SSD group was observed. There was no overall or gender-specific difference in birth length between the groups or in isolated measures of height (Table 3).

Table 4 provides the average linear slope stratified by gender and SSD status. Dunnett's two-sided t-tests were used to compare the linear change in growth between groups stratified by gender. 'Male non-SSD' was used as the reference category. The results suggest that females with SSD, on average, grew 0.84 cm per year slower than males without SSD (P<0.001); and females without SSD grew 0.23 cm per year slower than males without (P<0.001). There was no sigificant difference in growth between males with and without SSD (Fig. 2).

In contrast to early life, patterns of growth during later childhood were not significantly different between the SSD and non-SSD groups (B=−0.16, 95% CI −0.61 to 0.29, P=0.478), even after controlling for potential confounders (B=−0.21, 95% CI −0.70 to 0.28, P=0.389) (Table 3). Although we did not include the linear growth models stratified by gender for later childhood, the average linear growth estimates (Table 4) showed that girls in the SSD group continued to grow slightly more slowly, but the difference was no longer statistically significant.

In addition to assessing patterns of growth using measures of height, we also examined changes in weight and BMI. Birth weight did not differ between the SSD and non-SSD groups even after stratifying by gender. Weight gain was slightly slower in the SSD group

during early life (adjusted models, B=−0.21; 95% CI=−0.64 to 0.22, *P*=0.342) and later childhood (B=−0.28; 95% CI −0.66 to 0.11, *P*=0.160), but the effect was not statistically significant. Change in BMI during infancy was comparable between the SSD and non-SSD (adjusted models, B=0.07, 95% CI −0.49 to 0.62, *P*=0.814). During later childhood there was a trend toward a slower change in BMI in the SSD group (adjusted models, B=−0.23, 95% CI −0.46 to 0.01, *P*=0.059).

Discussion

This is the first study, to our knowledge, to use serial measurements and a multilevel statistical analysis to contrast patterns of early growth between people who subsequently developed a schizophrenia-spectrum disorder and those who did not. The results provide evidence that growth velocity during early life is slower in individuals who later develop schizophrenia. Furthermore, the association between delayed physical growth and adult schizophrenia was only observed in women. In contrast to previous studies, we did not find a significant difference in birth length or weight between the SSD and non-SSD groups in our cohort. We also found that isolated measures of height did not significantly differ between the two groups. Examination of patterns of growth using a series of successive rather than isolated measurements provides a more sensitive assessment of developmental abnormalities. This may explain why some studies using isolated measurements failed to find a significant difference in height between participants with schizophrenia and controls.

Our results are consistent with conclusions drawn from a previous study suggesting that the presence of delayed physical growth during early life is associated with later schizophrenia (Fish, 1959). However, that study, unlike ours, looked at a small high-risk sample, which included offspring of mentally ill parents, and thus the conclusions may not be generalisable to other populations. We have extended these findings by demonstrating this effect in a population-based cohort.

Catch-up growth and schizophrenia

Catch-up growth occurs when a period of delayed growth is followed by accelerated growth, beyond the normal rate for age (Kay's & Hindmarsh, 2006). Previous assessments of growth patterns in individuals with psychosis suggest that growth during development is atypical: these individuals are more likely to be shorter at birth but taller as adults, or taller at birth but shorter as adults (Gunnell *et al*, 2003, 2005a). This suggests that people who develop psychosis in adulthood may experience 'catch-up' or 'catch-down' growth during development. Our study was unable to contrast the growth patterns of individuals in the SSD group who were smaller at birth and those who were larger because few participants fell into these categories. A second way to identify whether catch-up growth occurred is to examine whether individuals in the female SSD group grew more rapidly than those in the female non-SSD group during later childhood; however, this is not evident from our data. None the less, it is possible that catch-up growth might occur later in development. Future assessments of adolescent growth are necessary to explore this theory further.

Growth hormone–insulin-like growth factor axis

Our finding of slower growth velocity during early life in women with schizophrenia adds to the accumulating evidence that mechanisms responsible for the regulation of physical growth may have a role in the pathogenesis of this disorder. Although the connection between growth and schizophrenia remains to be fully elucidated, the extant literature suggests that slower growth during infancy is indicative of premorbid disruption in the growth hormone–insulin-like growth factor (GH–IGF) axis, which plays a major part in the regulation of both prenatal and postnatal growth (Le Roith *et al*, 2001). Growth during

prenatal development and infancy is primarily regulated by IGF–1, as well as by insulin and nutrition, whereas growth hormone begins to play a critical part during late infancy and early childhood (Karlberg *et al*, 1987).

Although no previously published study has examined the association between IGF–1 levels during infancy and postnatal growth in babies born of average size, a study of adults found that lower adult IGF–1 was associated with a deceleration in growth during the first year of life, but not with birth length, weight or ponderal index (Ben-Shlomo *et al*, 2003). The results from a longitudinal assessment of a large cohort suggest that IGF–1 may also be influential in regulating growth during childhood (Rogers *et al*, 2006).

The link between IGF–1 and other adult diseases such as heart disease, diabetes and hypertension has already been established (Barker *et al*, 1993; Sandhu *et al*, 2002). The association between birth weight and adult coronary heart disease prompted the theory that poor foetal nutrition or an insult during a critical period of development might have a long-term impact on an individual's risk of developing a number of chronic diseases later in life – referred to as the 'foetal origins of disease hypothesis' (Barker, 1994). More recently it has been suggested that exposures operating throughout the life course might have a long-term impact on adult disease risk (Ben-Shlomo & Kuh, 2002). One biological mechanism that might mediate associations of foetal and childhood growth with adult disease is perturbation of the GH–IGF axis, leading to reduced IGF–1 secretion (Barker *et al* 1993; Fall *et al*, 1995). It has been suggested that if disruption of the GH–IGF axis occurs, growth during infancy would most probably be the period of development affected (Fall *et al*, 1995) because IGF–1 is more influential during infancy than during any other developmental period. Although there are alternative explanations, research linking schizophrenia and prenatal exposures such as maternal infection (Brown, 2006) and poor prenatal nutrition (Susser & Lin, 1992) provides support for the foetal origins of disease hypothesis as a potential explanation for the association between slower postnatal growth and schizophrenia.

IGF–1, neurodevelopment and schizophrenia

Although the idea is speculative, it is worth considering that a disruption in IGF–1 might be a cause of abnormalities in neurodevelopment consistent with schizophrenia. This has been postulated to explain the observation that adults with schizophrenia are typically shorter than healthy controls, and such disruption may also be partially responsible for documented neurological abnormalities such as ventricular enlargement (Gunnell & Holly, 2004).

Our findings should also be considered in light of the literature on other premorbid disturbances in schizophrenia. This body of work suggests that delays in speech and neuromotor development (Jones *et al*, 1994) and poor intellectual functioning (David *et al*, 1997) are early-life precursors of adult schizophrenia. The link between premorbid neurocognitive functioning and the GH–IGF axis is supported by a recent study of healthy children, which found a positive correlation between IGF–1 levels and performance on the Wechsler Intelligence Scale for Children (Gunnell *et al*, 2005b). Hence, it is possible that cognitive abnormalities and poor intellectual functioning observed prior to the development of schizophrenia might occur in part because of a dysregulation in the GH–IGF axis.

Nutrition

Nutrition also has a significant role in the regulation of growth during early life (Karlberg, 1987). Short stature and stunted growth due to malnutrition have been associated with lower scores on tests of cognitive functioning and poor educational achievement (Stathis *et al*, 1999; Strauss, 2000; Berkman *et al*, 2002). In order to explore the potential role of nutrition, we assessed changes in weight and BMI during development using similar analyses to those

conducted for height. No significant difference in weight or BMI between the SSD and non-SSD groups was found during early infancy. Although we did not detect any difference in weight change during later childhood, there was a trend toward slower change in BMI among participants in the SSD group. This is consistent with previous studies demonstrating associations between thinness in childhood (Wahlbeck *et al*, 2001), low BMI in adolescence (Gunnell *et al*, 2005a) and adult schizophrenia. Because our effect size was small, further assessments are necessary to determine whether malnourishment is responsible for the association between growth during infancy and adult schizophrenia.

Gender differences

Another noteworthy finding from our study is that gender appears to moderate the relationship between growth and schizophrenia. Women with schizophrenia-spectrum disorder grew more slowly during their early life, whereas men with the disorder did not. Although the precise neurobiological mechanisms responsible for this finding are unclear, it is known that there are gender differences not only in growth during early life, but also in secretion of and sensitivity to growth hormone and IGF–1 during development (Ong *et al*, 2002; Geary *et al*, 2003). Furthermore, gender differences in symptoms, age at onset, clinical course and treatment outcome in schizophrenia have been well documented (Leung & Chue, 2000). Brain imaging studies have also identified abnormal patterns of sexually dimorphic areas in schizophrenia with gender-specific differences in these abnormalities (Goldstein *et al*, 2002). Hence, it is worth speculating that if females are more sensitive to IGF–1, they might be differentially affected by a disruption in the GH–IGF axis that could give rise to schizophrenia through neurodevelopmental mechanisms. Clearly, further research is necessary to determine the causes of gender-specific differences in the association between growth during early life and schizophrenia.

Limitations of the study

Although the results from this study are informative, a few limitations must be noted. First, since height is difficult to measure (especially during infancy), and a systematic procedure was not implemented to enhance the accuracy of measurements, it is possible that some of our measurements might have been compromised by error. Since it is unlikely that individuals in the SSD sample were more prone to measurement error than those in the non-SSD sample, this would result in non-differential misclassification error associated with height. Because the analysis included multiple measurements of each individual, it is unlikely that measurement error would produce spurious results. Second, we had to rely on maternal height as a proxy measure for target height because there were insufficient data on paternal height. It is unlikely that our inability to control properly for genetic height potential compromised the results, because the estimates from the adjusted and unadjusted models were comparable. Third, on average there were fewer measurements of height during later childhood (six measurements) than in early life (nine measurements). Fewer measurements might have limited the ability to detect a difference in patterns of growth. Linear growth models are sufficiently sensitive, however, to estimate individual growth trajectories based on two data points, so that a reduction in the number of measurements does not necessarily diminish our ability to detect a significant effect. Fourth, our analysis included a modest number in the SSD group (*n*=70), which might have reduced our power to detect a significant difference. Future studies of patterns of growth including a larger number of individuals with the disorder are necessary to provide more confidence in our findings.

Regardless of these methodological considerations, our study provides further support for the hypothesis that growth during early development is atypical in individuals with schizophrenia. These results indicate that growth during early life is slower in girls – but not

boys – who go on to develop schizophrenia. In contrast, growth velocity during later childhood was not associated with subsequent disease status. This work also adds to the accumulating evidence for a neurodevelopmental origin of schizophrenia. Future studies assessing factors important in the regulation of growth during early life, such as growth hormone and IGF–1, will be necessary to determine the molecular and cellular mechanisms underlying the potential relationship between slowed growth and schizophrenia.

Acknowledgments

References

Aleman A, Kahn RS, Selten J. Sex differences in the risk of schizophrenia. Archives of General Psychiatry 2003;60:565–571. [PubMed: 12796219]

Barker, DJP. Mothers, Babies and Disease in Later Life. BMJ Publishing; 1994.

Barker DJ, Gluckman PD, Godfrey KM, et al. Fetal nutrition and cardiovascular disease in adult life. Lancet 1993;341:938–941. [PubMed: 8096277]

Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. International Journal of Epidemiology 2002;31:285–293. [PubMed: 11980781]

Ben-Shlomo Y, Holly J, McCarthy A, et al. An investigation of fetal, postnatal and childhood growth with insulin-like growth factor I and binding protein 3 in adulthood. Clinical Endocrinology 2003;59:366–373. [PubMed: 12919161]

Berkman DS, Lescano AG, Gilman RH, et al. Effects of stunting, diarrhoeal disease, and parasitic infection during infancy on cognition in late childhood: a follow-up study. Lancet 2002;359:564–571. [PubMed: 11867110]

Brown AS. Prenatal infection as a risk factor for schizophrenia. Schizophrenia Bulletin 2006;32:200–202. [PubMed: 16469941]

Chen H, Cohen P. Using individual growth model to analyze the change in quality of life from adolescence to adulthood. Health and Quality of Life Outcomes 2006;4:10–17. [PubMed: 16504035]

Cohen, J.; Cohen, P.; West, SG., et al. Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences. 3rd. Erlbaum; 2003.

Cole TJ. The LMS method for constructing normalized growth standards. European Journal of Clinical Nutrition 1990;44:45–60. [PubMed: 2354692]

David AS, Malmberg A, Brandt L, et al. IQ and risk for schizophrenia: a population-based cohort study. Psychological Medicine 1997;27:1311–1323. [PubMed: 9403903]

Fall CH, Pandit AN, Law CM, et al. Size at birth and plasma insulin-like growth factor-1 concentrations. Archives of Disease in Childhood 1995;73:287–293. [PubMed: 7492190]

Fish B. Longitudinal observations of biological deviations in a schizophrenic infant. American Journal of Psychiatry 1959;116:25–31. [PubMed: 13661444]

Geary MP, Pringle PJ, Rodeck CH, et al. Sexual dimorphism in the growth hormone and insulin-like growth factor axis at birth. Journal of Clinical Endocrinology and Metabolism 2003;88:3708–3714. [PubMed: 12915659]

Goldstein JM, Seidman LJ, O'Brien LM, et al. Impact of normal sexual dimorphisms on sexual differences in structural brain abnormalities in schizophrenia assessed by magnetic resonance imaging. Archives of General Psychiatry 2002;59:154–164. [PubMed: 11825137]

Gunnell D, Holly JM. Do insulin-like growth factors underlie associations of birth complications, fetal and pre-adult growth with schizophrenia? Schizophrenia Research 2004;67:309–311. [PubMed: 14984894]

Gunnell D, Rasmussen F, Fouskakis D, et al. Patterns of fetal and childhood growth and the development of psychosis in young males: a cohort study. American Journal of Epidemiology 2003;158:291–300. [PubMed: 12915493]

Gunnell D, Harrison G, Whitley E, et al. The association of fetal and childhood growth with risk of schizophrenia. Cohort study of 720,000 Swedish men and women. Schizophrenia Research 2005a; 79:315–322. [PubMed: 16125903]

Gunnell D, Miller LL, Rogers I, et al. Association of insulin-like growth factor I and insulin-like growth factor-binding protein-3 with intelligence quotient among 8- to 9-year-old children in the Avon Longitudinal Study of Parents and Children. Pediatrics 2005b;116:e681–e686. [PubMed: 16263982]

Jones P, Rodger B, Murray R, et al. Childhood developmental risk factors for adult schizophrenia in the British 1946 birth cohort. Lancet 1994;344:1402. [PubMed: 7968077]

Karlberg J. On the modelling of human growth. Statistics in Medicine 1987;6:185–192. [PubMed: 3589247]

Karlberg J, Engstrom I, Karlberg P, et al. Analysis of linear growth using a mathematical model. I. From birth to three years. Acta Paediatrica Scandinavica 1987;76:478–488. [PubMed: 3604665]

Kay's SK, Hindmarsh PC. Catch-up growth: an overview. Pediatric Endocrinology Reviews 2006;3:365–378. [PubMed: 16816805]

Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of census-based methodology. American Journal of Public Health 1992;382:703–710. [PubMed: 1566949]

Le Roith D, Scavo L, Butler A. What is the role of circulating IGF-I? Trends in Endocrinology and Metabolism 2001;12:48–52. [PubMed: 11167121]

Leung A, Chue P. Sex differences in schizophrenia, a review of the literature. Acta Psychiatrica Scandinavica Supplementum 2000;401:3–38. [PubMed: 10887978]

Littell, RC.; Milliken, GA.; Stroup, WW., et al. SAS System for Mixed Models. SAS Institute; 1996.

McArdle, JJ.; Aber, MS. An introduction to latent growth models for developmental data analysis. In: Little, TD.; Schnabel, KU.; Baumert, J., editors. Modeling Longitudinal and Multi-level Data: Practical Issues, Applied Approaches, and Specific Examples. Erlbaum; 2000. p. 69-108.

McArdle JJ, Small BJ, Bäckman L, et al. Longitudinal models of growth and survival applied to the early detection of Alzheimer's disease. Journal of Geriatric Psychiatry and Neurology 2005;18:234–241. [PubMed: 16306246]

Nurnberger JI, Blehar MC, Kaufmann CA, et al. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. Archives of General Psychiatry 1994;51:849–859. [PubMed: 7944874]

Ong K, Kratzsch J, Kiess W, et al. Circulating IGF-I levels in childhood are related to both current body composition and early postnatal growth rate. Journal of Clinical Endocrinology and Metabolism 2002;87:1041–1044. [PubMed: 11889159]

Reiter, EO.; Rosenfeld, RD. Normal and aberrant growth. In: Larsen, PR.; Kronenberg, HM.; Melmed, S., et al., editors. Williams Textbook of Endocrinology. Saunders; 2003. p. 1003-1079.

Rogers I, Metcalfe C, Gunnell D, et al. IGF-I and growth in height, leg length and trunk length between ages 5 and 10 years. Journal of Clinical Endocrinology and Metabolism 2006;91:2514–2519. [PubMed: 16670160]

Sandhu MS, Heald AH, Gibson JM, et al. Circulating concentrations of insulin-like growth factor-I and development of glucose intolerance; a prospective observational study. Lancet 2002;359:1740–1745. [PubMed: 12049864]

Schaefer CA, Brown AS, Wyatt RJ, et al. Maternal prepregnant body mass and risk of schizophrenia in adult offspring. Schizophrenia Bulletin 2000;26:275–286. [PubMed: 10885630]

Stathis SL, O'Callaghan MJ, Williams GM, et al. Behavioural and cognitive associations of short status at 5 years. Journal of Paediatrics and Child Health 1999;35:562–567. [PubMed: 10634984]

Strauss RS. Adult functional outcome of those born small for gestational age: twenty-six year follow-up of 1970 British Birth Cohort. JAMA 2000;283:625–632. [PubMed: 10665702]

Susser E, Lin S. Schizophrenia after prenatal exposure to the Dutch Hunger Winter of 1944–1945. Archives of General Psychiatry 1992;49:983–989. [PubMed: 1449385]

Susser ES, Schaefer CA, Brown AS, et al. The design of the prenatal determinants of schizophrenia study. Schizophrenia Bulletin 2000;26:257–273. [PubMed: 10885629]

Tanner JM. Growth from birth to two: a critical review. Acta Medica Auxologica 1994;26:7–45.

Wahlbeck K, Forsen T, Osmond C, et al. Association of schizophrenia with low maternal body mass index, small size at birth, and thinness during childhood. Archives of General Psychiatry 2001;58:48–52. [PubMed: 11146757]

World Health Organization. International Statistical Classification of Diseases and Related Health Problems (ICD–10). WHO; 1978.
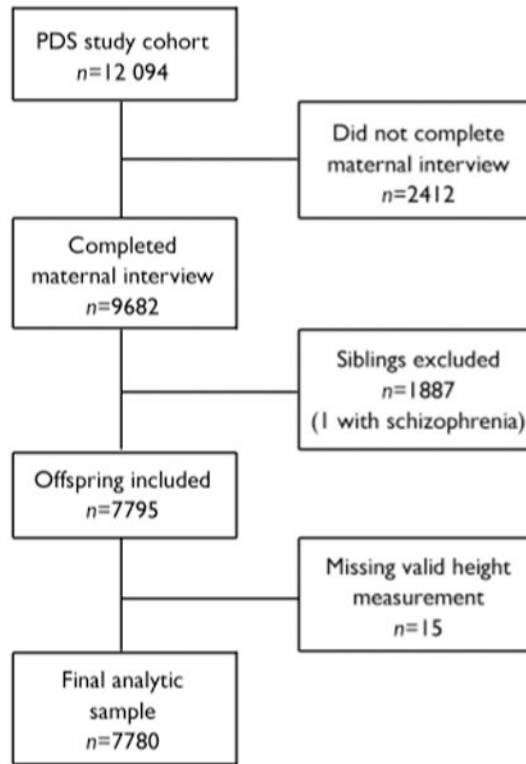
Fig. 1.
Study profile (PDS, Prenatal Determinants of Schizophrenia).
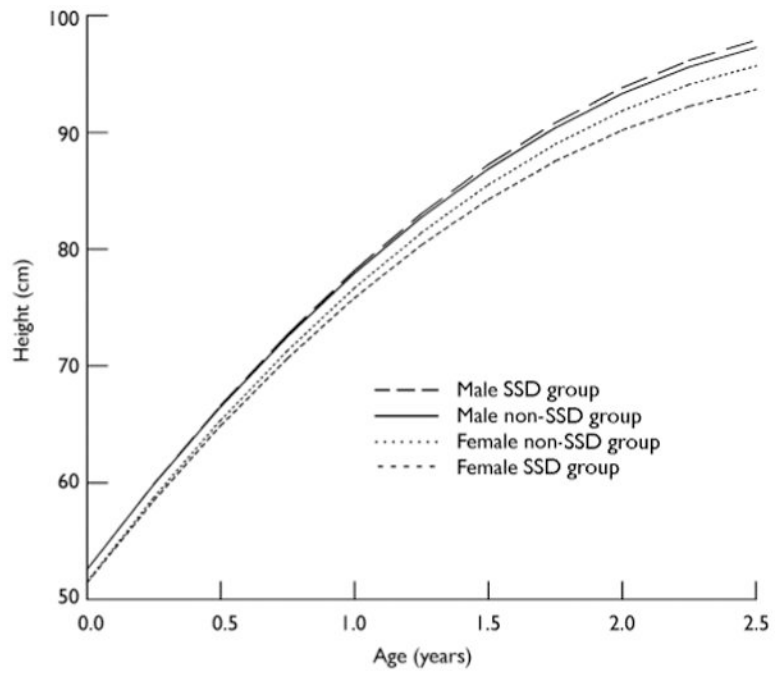
Fig. 2.
Early-life growth trajectory and schizophrenia-spectrum disorders (SSD).

Table 1

Sample characteristics (*n*=7780)

	SSD group (*n*=70)	Non-SSD group (*n*=7710)
Gender, *n* (%)		
Male	46 (66)	3932 (51)
Female	24 (34)	3778 (49)
Maternal ethnicity, *n* (%)[1]		
White	34 (49)	5018 (65)
Black	31 (45)	2091 (27)
Other	4 (6)	592 (8)
Maternal education, *n* (%)[2]		
Less than high school	15 (25)	1374 (18)
High school, trade school	25 (41)	3050 (40)
High school plus some college	12 (20)	1930 (25)
College graduate	9 (15)	1341 (17)
Maternal BMI, *n* (%)[3]		
Low (19.9 kg/m^2 or less)	14 (23)	1529 (23)
Average (20.0–26.9 kg/m^2)	37 (60)	4462 (68)
Above average (27.0–29.9 kg/m^2)	5 (8)	366 (6)
High (30.0 kg/m^2 or above)	6 (10)	187 (3)
Gestational age at birth (days): mean (s.d.)[4]	283 (14)	280 (16)
Maternal height[5]		
Height, cm: mean (s.d.)	163.36 (6.19)	162.46 (6.39)
z-score: mean (s.d.)	0.14 (0.96)	−0.01 (0.99)
Birth length[6]		
Length, cm: mean (s.d.)	51.59 (2.77)	51.52 (2.61)
z-score: mean (s.d.)	−0.01 (1.07)	0.00 (0.99)
Birth weight[7]		
Weight, kg: mean (s.d.)	3.35 (0.54)	3.33 (0.5)
z-score: mean (s.d.)	0.02 (1.04)	0.00 (0.98)
Height at age 2½ years[8]		
Height, cm: mean (s.d.)	89.47 (3.34)	91.20 (3.73)
z-score: mean (s.d.)	−0.43 (0.81)	0.01 (1.00)
Height at age 9 years[9]		
Height, cm: mean (s.d.)	128.43 (3.83)	132.74 (6.30)
z-score: mean (s.d.)	−0.64 (0.53)	−0.01 (0.99)
BMI at age 2½ years[10]		
BMI, kg/m^2: mean (s.d.)	16.76 (1.68)	16.61 (1.41)
z-score: mean (s.d.)	0.05 (1.20)	−0.01 (1.00)
BMI at age 9 years[11]		

	SSD group (*n*=70)	Non-SSD group (*n*=7710)
BMI, kg/m^2: mean (s.d.)	16.83 (1.00)	17.33 (2.62)
z-score: mean (s.d.)	0.06 (0.38)	−0.00 (1.00)

BMI, body mass index; SSD, schizophrenia-spectrum disorder.

[1] Missing/invalid data: SSD group, *n*=1; non-SSD group, *n*=9.

[2] Missing/invalid data: SSD group, *n*=9; non-SSD group, *n*=15.

[3] Missing/invalid data: SSD group, *n*=8; non-SSD group, *n*=1166.

[4] Missing/invalid data: SSD group, *n*=1; non-SSD group *n*=78.

[5] Missing/invalid data: SSD group, *n*=3; non-SSD group, *n*=137.

[6] Missing/invalid data: non-SSD group, *n*=29.

[7] Missing/invalid data: non-SSD group, *n*=26.

[8] Missing/invalid data: SSD group, *n*=60; non-SSD group, *n*=6258.

[9] Missing/invalid data: SSD group, *n*=65; non-SSD group, *n*=7086.

[10] Missing/invalid data: SSD group, *n*=59; non-SSD group, *n*=6263.

[11] Missing/invalid data: SSD group, *n*=65; non-SSD group, *n*=7091.

Table 2
Estimated fixed effects assessing the basic growth model

	Basic growth model		
	B	95% Cl	P
Early life (birth to 2½ years)			
Entire sample (*n*=7780)			
Mean height at birth, cm (intercept)	52.06	52.01 to 52.11	<0.001
Linear change in height, cm/year	30.27	30.12 to 30.37	< 0.001
Quadratic change in height, cm/year^2	−6.69	−6.73 to −6.64	< 0.001
Females only (*n*=3802)			
Mean height at birth, cm (intercept)	51.64	51.57 to 51.72	< 0.001
Linear change in height, cm/year^2	29.53	29.39 to 29.67	< 0.001
Quadratic change in height, cm/year^2	−6.37	−6.44 to −6.30	< 0.001
Males only (*n*=3978)			
Mean height at birth, cm (intercept)	52.46	52.39 to 52.54	< 0.001
Linear change in height, cm/year	30.95	30.80 to −31.10	< 0.001
Quadratic change in height, cm/year^2	−6.98	−7.04 to −6.91	< 0.001
Later childhood (2½−9 years)			
Entire sample (*n*=7353)			
Mean height at age 2½ years, cm (intercept)	90.51	90.42 to 90.61	< 0.001
Linear change in height, cm/year	7.97	7.92 to 8.02	< 0.001
Quadratic change in height, cm/year^2	−0.22	−0.23 to −0.22	< 0.001

Table 3

Estimated fixed effects assessing growth patterns and adult schizophrenia

	Unadjusted model			Adjusted model		
	B	95% CI	P	B	95% CI	P
Early life (birth to 2½ years)						
Entire sample (n=7780)						
Mean height at birth, cm (intercept)	52.59	52.51 to 52.66	< 0.001	38.76	38.24 to 39.28	< 0.001
Linear change in height, cm/year	30.37	30.26 to 30.48	< 0.001	30.37	30.25 to 30.48	< 0.001
Quadratic change in height, cm/year^2	−6.69	−6.74 to −6.64	< 0.001	−6.69	−6.74 to −6.65	< 0.001
Effect of SSD on birth length, cm	−0.09	−0.77 to 0.58	0.784	−0.20	−0.64 to 0.24	0.375
Effect of SSD on linear growth, cm/year	0.35	−0.82 to 1.52	0.560	0.74	−0.53 to 2.01	0.253
Effect of gender[1] and SSD on growth, cm/year	−1.12	−2.04 to −0.20	0.017	−1.55	−2.52 to −0.57	0.002
Females only (n=3802)						
Mean height at birth, cm (intercept)	51.64	51.57 to 51.72	< 0.001	38.51	37.79 to 39.23	< 0.001
Linear change in height, cm/year	29.54	29.40 to 29.68	< 0.001	29.54	29.39 to 29.68	< 0.001
Quadratic change in height, cm/year^2	−6.37	−6.44 to −6.30	< 0.001	−6.37	−6.44 to −6.31	< 0.001
Effect of SSD on birth length, cm	−0.02	−0.87 to 0.83	0.968	−0.02	−0.57 to 0.52	0.936
Effect of SSD on growth, cm/year	−1.03	−1.73 to −0.33	0.004	−1.26	−2.00 to −0.53	0.001
Males only (n=3978)						
Mean height at birth, cm (intercept)	52.46	52.39 to 52.54	< 0.001	38.42	37.66 to 39.18	< 0.001
Linear change in height, cm/year	30.94	30.79 to 31.09	< 0.001	30.95	30.79 to 31.10	< 0.001
Quadratic change in height, cm/year^2	−6.97	−7.04 to −6.91	< 0.001	−6.98	−7.05 to −6.91	< 0.001
Effect of SSD on birth length, cm	−0.03	−0.70 to 0.64	0.921	−0.16	−0.59 to 0.28	0.480
Effect of SSD on growth, cm/year	0.06	−0.52 to 0.64	0.836	0.26	−0.37 to 0.89	0.420
Later childhood (2½ to 9 years)						
Entire sample (n=7353)						
Mean height at age 2½ years, cm (intercept)	91.00	90.87 to 91.13	< 0.001	88.36	86.91 to 89.81	< 0.001
Linear change in height, cm/year	7.94	7.89 to 7.99	< 0.001	7.94	7.89 to 7.99	< 0.001
Quadratic change in height, cm/year^2	−0.22	−0.23 to −0.22	< 0.001	−0.22	−0.23 to −0.22	< 0.001
Effect of SSD on height at age 2½ years, cm	0.53	−0.73 to 1.80	0.408	0.17	−1.11 to 1.46	0.790
Effect of SSD on linear growth, cm/year	−0.08	−0.62 to 0.46	0.769	−0.04	−0.63 to 0.55	0.896

Effect of gender and SSD on growth, cm/year[1]

	Unadjusted model			Adjusted model		
	B	95% CI	P	B	95% CI	P
Effect of gender and SSD on growth, cm/year[1]	−0.16	−0.61 to 0.29	0.478	−0.21	−0.70 to 0.27	0.389

SSD, schizophrenia-spectrum disorders: presence of SSD=1, absence of SSD=0.

[1] Gender is categorised as female=1, male=0.

Table 4

Differences in linear growth stratified by gender for participants with and without schizophrenia-spectrum disorders (SSD)

	n	Linear growth, cm/year Mean (s.d.)	Difference in linear growth Mean (s.d.)	*P*
Early life (birth to 2½ years)				
Male non-SSD	3940	29.92 (0.96)	Reference	Reference
Female non-SSD	3785	29.69 (0.91)	−0.23 (0.02)	<0.001
Male SSD	46	30.00 (0.81)	0.07 (0.14)	0.948
Female SSD	24	29.08 (1.26)	−0.84 (0.19)	<0.001
Later childhood (2½ to 9 years)				
Male non-SSD	3712	9.06 (0.45)	Reference	Reference
Female non-SSD	3573	9.05 (0.45)	−0.02 (0.01)	0.356
Male SSD	43	9.16 (0.39)	0.10 (0.07)	0.383
Female SSD	24	8.96 (0.46)	−0.10 (0.09)	0.640