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Early developmental milestones and risk of schizophrenia. A 45-year follow-up of the Copenhagen Perinatal Cohort

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Abstract

The aim of the present study was to investigate the relationship between age of neuromotor milestone attainment and risk of adult schizophrenia. 5765 mothers of the Copenhagen Perinatal Cohort recorded 12 developmental milestones during the child's first year of life. Cohort members were followed until they were 46–48 years old through record linkage with the Danish Psychiatric Central Research Register. The age at which milestones were met in the 92 individuals who later developed schizophrenia was compared with milestone attainment in the 691 individuals who developed other psychiatric disorders and in the 4982 cohort controls who were never admitted to a psychiatric department. Group comparisons were adjusted for gender, mother's age, father's age, parental social status, breadwinner's education, single mother status and parity. Individuals who developed schizophrenia reached all developmental milestones later than controls and differed significantly from the controls with respect to the mean age of reaching the 12 milestones. Five developmental milestones in particular (smiling, lifting head, sitting, crawling, and walking) differed significantly. Individuals who later developed psychiatric disorders other than schizophrenia reached most developmental milestones earlier than those who developed schizophrenia, but later than the controls. The two psychiatric groups only differed significantly with respect to age of walking without support. The findings corroborate and methodologically extend previous research from prospective longitudinal cohort studies suggesting developmental delays observable as early as within the first year of life. These early developmental delays may not only characterize schizophrenia, but may be associated with a range of psychiatric disorders.

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Keywords

developmental milestones; schizophrenia; neurodevelopment

1. Introduction

The majority of individuals with schizophrenia manifest diagnosable symptomatology in the second or third decade of life. Evidence suggests, however, that observable subclinical signs of neuropathology may be present in infancy and childhood (Cannon et al., 2002; Crow et al., 1995; Jones et al., 1994; Parnas et al., 1982; Ridler et al., 2006; Walker and Lewine, 1990). Deviant premorbid development in schizophrenia has been interpreted in light of the neuro-developmental hypothesis (Murray, 1994; Weinberger and Marengo, 2003), which proposes a subtle deviance in brain development, the full adverse consequences of which do not emerge until adolescence or early adulthood. Central to this hypothesis is the identification of developmental deficits preceding overt clinical symptoms of schizophrenia. Such identification may not only lend support to the hypothesis, but also facilitate the understanding of etiologic contributors to the disorder.

Results from a general population-based cohort study suggest associations of early-childhood pan-developmental impairment with psychotic symptoms and with a diagnosis of schizophreniform disorder later in life (Cannon et al., 2002). Findings from other studies suggest that infants who develop schizophrenia as adults reach neuromotor milestones later (Isohanni et al., 2001, 2004; Jones et al., 1994; Ridler et al., 2006), or manifest greater neuromotor problems in childhood and young adulthood than aged-matched controls with other diagnoses and normal comparison subjects (Rosso et al., 2000; Schiffrman et al., 2004; Walker and Lewine, 1990). In addition to studies linking early developmental milestones and later development of schizophrenia, one study reported delays in milestone attainment in offspring of women with schizophrenia (Henriksson and McNeil, 2004). Although evidence for the presence of early neuromotor deficits in children at risk for, or who eventually develop, schizophrenia is well established, the specificity of these early signs to schizophrenia is less clear (Jones and Tarrant, 2000). For example, results from a prospective study demonstrated similar, although less severe, developmental delays prior to the development of affective disorders (van Os et al., 1997). Delays in motor development have also been shown to predict adult alcohol dependence (Manzardo et al., 2005).

The aim of the current study was to investigate the relationship between schizophrenia and the age of early developmental milestone attainment in a large birth cohort. The mothers of the Copenhagen Perinatal Cohort recorded the age of milestone attainment during the first year of their child's life in a diary. These prospectively collected data from the cohort, subsequently followed for more than four decades, enabled the investigation of potential associations between early development and later schizophrenia. We hypothesized associations between late attainment of certain neuromotor, behavioral, and other developmental characteristics and increased risk of adult schizophrenia. Furthermore, we were able to investigate the specificity of these associations by comparing the age of attainment of developmental milestones in individuals who later developed schizophrenia with both individuals who had never been registered with a psychiatric disorder and individuals who developed other psychiatric disorders.

2. Method

The Copenhagen Perinatal Cohort consists of 9,125 consecutive deliveries by 8,949 pregnant women from October 1959 to December 1961 at the maternity department of the Copenhagen University Hospital, Rigshospitalet. When the cohort was established,

demographic, socioeconomic, prenatal, and postnatal medical data were recorded prospectively during pregnancy, at delivery, and at a 1-year examination (Zachau-Christiansen and Ross, 1975). The mothers were mainly residents in Copenhagen, but some were admitted on obstetrical complications or because of single mother status (Villumsen, 1970). Cohort families represent the full range of social status in Denmark. A total of 8,400 infants survived the first month after birth.

Of the detailed information available for the Perinatal Cohort, sex of the child, single mother status, parity, mother's age, father's age, parental social status, and breadwinner's education were included in statistical models to adjust for sex and family background. Parity was included as a binary variable coding whether this was the mother's first pregnancy or not. Parental social status was coded on an eight point scale and breadwinner's education on a four point scale (higher scores indicate higher status and higher education). Both variables, along with parental age, were included as continuous variables. Preliminary analyses showed significant quadratic trends for maternal and paternal age, and for these variables the regression model included squared deviations from the mean. There were no missing data on sex of the child, while the missing data rate was less than one percent on single mother status, parity, and mother's age. However, missing data was 3.3% on father's age, 17.2% on parental social status, and 18.0% on breadwinner's education. The EM algorithm was used to impute values replacing missing data for the covariates to avoid diluting the sample in regression analyses (Schafer, 1999).

2.1. Developmental milestones

Developmental data were obtained from the mothers who were instructed to use a standardized diary to record the ages in weeks or months at which the child reached 12 developmental milestones. The diary was brought to the hospital at a 1-year follow-up examination described elsewhere (Zachau-Christiansen and Ross, 1975). If the mother did not return the diary, an effort was made to obtain retrospective data on milestones. The milestones recorded during the first year of life are listed in Tables 2 and 3. Table 2 shows that the frequency of missing data tended to increase for milestones that were attained later during the first year of the child. The most likely explanation of this trend is that the number of mothers who forgot to record milestone attainment increased with time after the diary instruction at the hospital. Thus, missing data may reflect simple memory failure, but it is also possible that some of the later milestones are less distinct to the mother. Finally, walking may not have been attained by some children at the time of the one-year follow-up.

2.2. Study sample

The study sample consists of 5,765 individuals (2,934 males and 2,831 females) with a personal identification number (necessary to link with the Danish Psychiatric Central Research Register) and with available data on developmental milestones from the 1-year examination.

2.3. Psychiatric registration

Written approval to conduct a registry-based psychiatric follow-up was obtained from the regional scientific and ethics committee. The Danish Psychiatric Central Research Register has been computerized since April 1, 1969 (Munk-Jørgensen, 1997). It contains data on all admissions to Danish psychiatric inpatient facilities. The diagnostic system in use when the Register was computerized was the *International Classification of Diseases, 8th Revision* (ICD-8). In ICD-8, schizophrenia is defined by prototypic descriptions of symptoms, such as bizarre delusions, delusions of control, abnormal affect, autism, hallucinations, and disorganized thinking. In 1994, the more operational ICD-10 criteria were implemented. The cohort was followed in The Danish Psychiatric Central Research Register to identify all

admissions with a diagnosis of schizophrenia (ICD-8 code 295 or ICD-10 code F20) until May 2007. The cohort members were categorized with a history of schizophrenia if they had been admitted with one of these diagnoses. Out of 5,765 individuals, there were 92 (1.6%) cases of schizophrenia disorder (SD group), while 691 (12.0%) cohort members had been admitted to psychiatric departments and had received other diagnoses than schizophrenia (OPD group). The remaining 4,982 cohort members had never been admitted to a psychiatric department and were considered the cohort control or no disorder (ND) group.

2.4. Statistical analysis

Table 2 shows the number of valid data for the 12 developmental milestones in the SD, OPD and the ND group. There were between 10.7 and 62 percent missing data on the 12 recorded milestones. To obtain reasonable sample size for preliminary analyses of the intercorrelations among the milestones, the EM algorithm was used to impute values replacing missing data (Schafer, 1999).

To analyze the pattern of intercorrelations among the milestones, a principal component analysis was conducted on the imputed dataset. The first three components explained 67% of the variance, and both varimax and promax rotation defined three factors: 1) smiling, lifting and holding the head, 2) crawling, sitting and grabbing, and 3) standing and walking.

The imputed milestone dataset was only used for the principal component analysis, while comparisons between the three diagnostic groups were exclusively based on the observed scores on the 12 milestones. Some milestones were scored in weeks and some in months, with large differences among the means and standard deviations of the 12 registered milestones. In order to calculate mean milestone scores, the distribution of each milestone was linearly standardized to a mean of 0 and a standard deviation of 1 in the control sample consisting of the 4,982 control cohort members without psychiatric registration. Next, the means of the standardized scores were calculated for milestones 1–3, 4–8, and 9–12 (corresponding to the three factors identified in the preliminary principal component analysis). If a subject had missing data on one or more milestones, the mean of the available milestone scores was calculated. Since the first unrotated principal component explained 46% of the variance, we also calculated the mean of the scores on all 12 milestones. Finally, the three factor means and the total mean were re-standardized to a mean of 0 and a standard deviation of 1 in the control sample.

Differences between the three diagnostic groups with respect to mean factor scores and mean age of attainment of individual milestones were first evaluated using ANOVA, followed by ANCOVA adjusting for sex of the child, single mother status, parity, mother's age, father's age, parental social status, and breadwinner's education. Although we were conducting multiple tests that may leave results susceptible to Type I Error, given the uniqueness of the longitudinal dataset, our interest in avoiding Type II Error, and the pre-existing theoretical support for the work, we chose not to employ corrections for multiple tests. Sex differences have previously been demonstrated for some of the milestones (Reinisch et al., 1991), and Table 1 shows significant associations between the diagnostic classification and all covariates except father's age, which was only marginally significant.

To evaluate the influence of missing data on the results supplementary analyses were conducted using both multiple imputation and full information maximum likelihood (FIML) (Graham, 2009). Version 11 of Stata (Stata Corporation) was used to generate and analyse 40 imputed data sets, while FIML was conducted with Amos (SPSS Inc.).

3. Results

Table 2 shows mean unadjusted and adjusted age of milestone attainment in the three diagnostic groups (for the mean of all milestones and for the three factor means, higher scores indicate later age of milestone attainment). ANOVA showed significant group differences on all factor means and the following individual milestones: age at first smiling, lifting head, grasping after things, sitting without support, and walking without support. The table also presents adjusted means, with ANCOVA results indicating similar significant differences, except that age at first grasping was only marginally significant, while age at first standing without support became significant after covariate adjustment. Generally, covariate adjustment did not substantially change the group means or the significance levels. Those who later developed schizophrenia obtained a total milestone mean 0.31 SD higher than the controls, while those who later developed other psychiatric disorders obtained a mean 0.17 SD higher than the controls.

An anonymous reviewer pointed out that the OPD group is very heterogeneous with respect to diagnoses. To investigate possible differences among diagnostic subgroups we used a hierarchical diagnostic approach classifying the OPD group into non-affective, non-schizophrenic psychoses, affective disorders, anxiety/neurotic disorders, personality disorders, and other disorders. Analysis of variance revealed no significant differences among these diagnostic subgroups with respect to milestone attainment, except for walking without support. For this milestone, the p-value for the overall F test was 0.04. Pairwise comparisons showed significant differences between the personality disorder group and the affective and anxiety/neurotic disorder groups (which had the highest mean age of attaining this milestone). When interpreting this finding, the large number of statistical tests should be borne in mind, and it seems reasonable to conclude that developmental delay seems to characterize most, if not all, major diagnostic subgroups of the OPD group.

The intercorrelations among the 12 developmental milestones were all positive and significant, while the mean of all milestone scores correlated 0.71, 0.85, and 0.79 with the factors of smiling/lifting head, crawling/sitting, and standing/walking, respectively. The factor of smiling/lifting head showed relatively low correlations with the factors of crawling (0.43) and standing/walking (0.28), while the correlation between the latter two factors was 0.51.

Table 3 presents adjusted mean differences between (1) the SD group and the ND group, (2) the OPD group and the ND group, and (3) the SD group and the OPD group. The SD group differed significantly from the ND group on the mean of all milestones, the three factor means, and on age at first smiling, lifting head, sitting without support, crawling a longer distance, and walking without support. Additionally, the OPD group differed significantly from the ND group with respect to the mean of all factor scores, the three factors, age at first lifting head, sitting without support, standing without support, and walking with and without support. Lastly, the SD group differed significantly from the ND group with respect to age at first walking without support, although the two groups did not differ significantly on age at first standing without support and walking with support. Thus, the SD group attained this milestone on average more than 1 month later than the ND group, and almost 1 month later than the OPD group (this was the only significant difference between the two patient groups).

The percentages of missing milestone and covariate data were unrelated to the three group diagnostic classification except for significant associations with respect to crawling longer distances, standing with support and father's age. For the two milestones, a slightly higher percentage of missing data was observed for the OPD group than for the SD and ND groups,

while the percentage of missing data for father's age was higher for the SD group than for the two other groups. Both multiple imputation and FIML analyses showed essentially the same pattern of results as that presented in Tables 2 and 3. This was also the case for standing and walking without support although it is likely that many cases of missing data for these variables reflect the fact that the child had not reached these milestones at the time of the 1-year follow-up (multiple imputation actually showed a significant difference between the SD and ND groups with respect to standing without support).

An anonymous reviewer raised the issue of a possible correlation between age of milestone attainment and age of onset of mental disease. All correlations (both Pearson and Spearman) between milestone attainment and age of first admission were low and insignificant. For the SD group the largest Pearson correlation was -0.15 , and for the OPD group it was -0.08 .

The possible interaction between gender and diagnostic group was tested in preliminary analyses. No significant interactions were observed in a model adjusting for mother's age, father's age, parental social status, breadwinner's education, single mother status and parity (corresponding to the adjustment in table 2).

4. Discussion

Analyses revealed associations between delays in early developmental milestone attainment and later development of schizophrenia. Infants who grew up to develop schizophrenia tended to smile, lift the head, sit without support, crawl longer distance, and walk without support later than controls. All 12 milestones were on average met later among those who developed schizophrenia compared to those who did not develop a diagnosed mental illness. Although there was only one significant difference (walking without support) between individuals who developed schizophrenia and those who later developed other psychiatric disorders, future schizophrenic cohort members attained 11 of the 12 milestones later than future patients with other psychiatric disorders.

In spite of the consistent pattern of results it should be stressed that not all individuals who developed schizophrenia showed significant developmental delays. This is illustrated by the percentages of individuals attaining milestones at an age corresponding to 1 standard deviation above the mean of the ND group. For the SD, the OPD and the ND groups these percentages were 21, 18, and 14 for the mean of all milestones, and a similar pattern was observed for most other milestone means and individual milestones.

This study possesses a number of methodological advantages. It is likely that real-time documentation of milestone achievements by mothers contributes relatively reliable and valid data, and the analytic strategy in the current study capitalized on the continuous nature of the data on developmental milestones. A possible limitation of this study concerns insufficient detail about the determinants of missing data on developmental milestones. A factor that probably contributed to missing data is that milestones were only followed for the first year of life, and this limitation truncated the range of attainment dates. Another limitation is that Type I error is a possibility, as we conducted tests on 12 milestones and 4 factor means. The general trend in the measures towards later attainment of milestones in those who later develop schizophrenia, however, makes Type I error an unlikely explanation of the main findings. Additionally, the associations between the developmental milestones and future schizophrenia are consistent with findings from other cohort studies (Cannon et al., 2002; Isohanni et al., 2001; Jones et al., 1994; Ridler et al., 2006). The lack of standardized diagnostic assessment of schizophrenia and other psychiatric disorder is also a limitation. For schizophrenia, most individuals meeting the diagnostic criteria are hospitalized in Denmark before the age of 40 years (Parnas et al., 1993). For other psychiatric diagnoses than schizophrenia, scanning national registers may be considered a

valid method (Dalman et al., 2002; Stalberg et al., 2007), but it is important to keep in mind that only the most severe cases of other psychiatric disorder become admitted to hospital and hence registered. We used the broad category of other psychiatric disorder to evaluate the specificity of the association between schizophrenia and developmental delays.

One of the most consistent findings from previous longitudinal studies is that later age when first standing and walking is related to the risk of the disorder (Cannon et al., 2002; Isohanni et al., 2004; Jones et al., 1994). Our results clearly support these previous findings. Additionally, we observed inverse relationships between schizophrenia and age at first smiling and lifting the head while lying on the stomach. Smiling may be of particular interest as it may correlate with social skills or positive affect. Previous work has shown a lower rate of positive affect in the first year of life in infants who develop schizophrenia (Walker and Lewine, 1990). Systematic video-examination of a subsample of the Copenhagen Perinatal Cohort between ages 11–13 years yielded poorer sociability skills in children who later developed schizophrenia than in controls (Schiffman et al., 2004).

The literature now contains several studies linking infant neurodevelopmental delay with adult psychiatric outcomes and cognitive functioning and education in adult life (Murray et al., 2007; Taanila et al., 2005). However, it is of note that many of the previously published studies related to this topic come from the same cohort (Isohanni et al., 2001, 2004; Murray et al., 2006; Ridler et al., 2006; Taanila et al., 2005), and to our knowledge, there have been no studies that have attempted to address the specificity of a relationship between early developmental milestones and adult psychiatric outcome. Hence, our study is the first to suggest a lack of specificity between infant neurodevelopmental delay and schizophrenia when also considering other psychiatric disorders. A supplementary analysis showed few significant differences among major diagnostic categories in the OPD group, and these findings strongly suggest that developmental delays may characterise samples of psychiatric patients with mental disorders of a severity that result in admission to psychiatric inpatient facilities. Neurodevelopmental delay has been associated with lower general cognitive functioning in adult life (Taanila et al., 2005), and since premorbid IQ is not a specific marker of schizophrenia in the Copenhagen Perinatal Cohort (Mortensen et al., 2005), it is perhaps not surprising that we found lack of predictive specificity in this study.

Early neurodevelopmental impairment may reflect the effects of obstetric adversities, the expression of schizophrenia-susceptibility genes, or both (Cannon et al., 2002; Harrison, 1999). Delay in very early developmental milestones such as smiling might reflect abnormalities of the basal ganglia or amygdalae that have been implicated in spontaneous facial expressions for joy (Messinger and Fogel, 2007). With respect to other developmental milestones such as walking and standing without support, the basal ganglia, as well as the premotor cortex and cerebellum, may play important roles (Ridler et al., 2006). Other researchers (Murray et al., 2007) have suggested that suboptimal cortical-subcortical connectivity may underlie the relationship between neurodevelopmental delay and cognitive functioning in adult life and this interpretation might apply to our results as well. In addition to hereditary factors influencing the neurological underpinnings of milestone attainment, environmental factors may also play a role (Kelly et al., 2006). The primary focus has traditionally been on obstetric adversities. Milestone attainment may be mediating the effects of obstetric complications and similar to other studies of milestone attainment and later schizophrenia (Isohanni et al., 2001; Jones et al., 1994) we did not adjust for obstetric adversities (including low birth weight) that show strong association with schizophrenia (Cannon et al., 2002). In addition, early family environment may contribute to delayed neurological development and milestone attainment. This is supported by recent evidence that early childhood neglect and deprivation correlate strongly with lower superior-posterior volumes of childhood cerebellar lobes which are expected to correlate with early motor

function and milestone attainment (Bauer et al., 2009). Deprivation and neglect may be a general risk factor for psychopathology that may partly explain the non-specific association between developmental delay and mental disorder observed in the present study.

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Authors H.J.S., E.L.M., and S.A.M. conceptualized the study. H.J.S., J.M.R., and E.L.M. organized, analyzed, and interpreted the data with input from J.S. H.J.S. and E.L.M. prepared the initial manuscript. J.S. and J.M. edited the manuscript and helped conceptualize the results and implications. All authors commented on the manuscript at all stages.

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Table 1

Demographic and pregnancy characteristics in schizophrenia disorder (SD), other psychiatric disorders (OPD) and no disorder controls (ND).

Potential confounders	SD group: Number and percentage	OPD group: Number and percentage	ND group: Number and percentage	Chi-square P
Sex of child(Males)	58 (63%)	338 (49%)	2538 (51%)	0.0384
Single mother	37 (40%)	254 (37%)	1514 (30%)	0.0006
Parity (first pregnancy)	52 (57%)	314 (46%)	2483 (50%)	0.0372
	Mean (SD)	Mean (SD)	Mean (SD)	ANOVA P
Mother's age	25.76 (6.55)	25.94 (6.43)	26.66 (6.54)	0.0124
Father's age	29.91 (7.75)	29.58 (7.68)	30.29 (7.67)	0.0763
Parental social status	4.03 (1.86)	3.81 (1.65)	4.40 (1.83)	< 0.0001
Breadwinner's education	2.53 (0.79)	2.33 (0.60)	2.54 (0.74)	< 0.0001

Table 2

Observed and adjusted means in schizophrenia disorder (SD), other psychiatric disorders (OPD) and no disorder controls (ND). The p values are for the overall F in ANOVA and ANCOVA^a

Developmental Milestone ^b	SD	OPD	ND	P for overall F	Adjusted SD mean	Adjusted OPD mean	Adjusted ND mean	Adjusted p-value
Mean of milestones	0.29 (1.18) n = 92	0.18 (1.14) n = 691	0.00 (1.00) n = 4982	< 0.0001	0.31	0.17	0.00	< 0.0001
Smiling and lifting head	0.29 (1.11) n = 80	0.14 (1.17) n = 592	0.00 (1.00) n = 4401	0.0005	0.30	0.12	0.00	0.0014
Rolling, crawling, sitting and grabbing	0.18 (1.11) n = 90	0.11 (1.09) n = 660	0.00 (1.00) n = 4774	0.0086	0.22	0.13	0.00	0.0013
Standing and walking	0.25 (1.40) n = 88	0.11 (1.07) n = 652	0.00 (1.00) n = 4741	0.0034	0.27	0.11	0.00	0.0030
Individual milestones								
1. Smiles (weeks)	6.10 (2.52) n = 77	5.70 (2.72) n = 546	5.50 (2.41) n = 4120	0.0271	6.12	5.69	5.50	0.0269
2. Lifts head on stomach (weeks)	4.71 (3.26) n = 72	4.20 (3.11) n = 531	3.78 (2.56) n = 3957	< 0.0001	4.73	4.14	3.78	0.0002
3. Holds head when sitting	3.38 (1.18) n = 67	3.25 (1.31) n = 481	3.19 (1.21) n = 3662	0.2473	3.40	3.25	3.19	0.2421
4. Grasps after things	4.06 (1.20) n = 69	3.98 (1.17) n = 481	3.87 (1.09) n = 3629	0.0498	4.08	3.97	3.87	0.0582
5. Sits without support	7.18 (1.68) n = 85	7.03 (1.62) n = 612	6.85 (1.49) n = 4453	0.0045	7.23	7.07	6.84	0.0002
6. Rolls	5.85 (1.77) n = 72	5.92 (1.91) n = 477	5.82 (1.75) n = 3616	0.4540	5.90	5.92	5.81	0.4312
7. Crawls	8.89 (1.61) n = 58	8.84 (1.64) n = 434	8.77 (1.70) n = 3286	0.6484	8.94	8.86	8.76	0.4062
8. Crawls longer distance	9.74 (2.02) n = 51	9.40 (1.63) n = 364	9.32 (1.59) n = 2868	0.1255	9.78	9.43	9.31	0.0570
9. Stands with support	8.83 (2.26) n = 87	8.64 (1.84) n = 605	8.52 (1.79) n = 4415	0.2553	8.68	8.61	8.52	0.3762
10. Stands without Support	10.61 (1.86) n = 41	10.48 (1.65) n = 303	10.29 (1.55) n = 2411	0.0554	10.61	10.51	10.28	0.0293
11. Walks with support	10.10 (2.02) n = 71	10.05 (1.46) n = 496	9.90 (1.50) n = 3801	0.0690	10.12	10.04	9.90	0.0730
12. Walks without support	13.01 (2.88) n = 34	12.15 (1.81) n = 275	11.71 (1.47) n = 1908	< 0.0001	13.01	12.12	11.71	< 0.0001

^aAdjusted for gender, mother's age, father's age, parental social status, breadwinner's education, single mother status, and parity

^bThe four milestone means are in z-scores, the individual milestones are measured in months unless otherwise indicated

Table 3

Adjusted^a mean differences between schizophrenia disorder (SD), other psychiatric disorders (OPD) and no disorder controls (ND).

Developmental Milestone ^b	SD vs. ND Adjusted mean difference	SD vs. ND P	OPD vs. ND Adjusted mean difference	OPD vs. ND P	SD vs. OPD Adjusted mean difference	SD vs. OPD P
Mean of milestones	0.31 (0.10 – 0.52)	0.0034	0.17 (0.09 – 0.25)	< 0.0001	0.14 (–0.08 – 0.36)	0.2105
Smiling and lifting head	0.30 (0.07 – 0.52)	0.0099	0.12 (0.03 – 0.21)	0.0077	0.18 (–0.06 – 0.41)	0.1451
Rolling, crawling, sitting and grabbing	0.22 (0.01 – 0.43)	0.0410	0.13 (0.05 – 0.21)	0.0018	0.09 (–0.13 – 0.31)	0.4391
Standing and walking	0.27 (0.05 – 0.48)	0.0145	0.11 (0.02 – 0.19)	0.0128	0.16 (–0.06 – 0.38)	0.1626
Individual milestones						
1. Smiles (weeks)	0.61 (0.06 – 1.16)	0.0300	0.19 (–0.03 – 0.41)	0.0922	0.42 (–0.16 – 1.01)	0.1551
2. Lifts head on stomach (weeks)	0.94 (0.33 – 1.55)	0.0026	0.36 (0.12 – 0.59)	0.0036	0.59 (–0.06 – 3.47)	0.0755
3. Holds head when sitting	0.21 (–0.08 – 0.50)	0.1578	0.06 (–0.06 – 0.17)	0.3263	0.15 (–0.16 – 0.46)	0.3334
4. Grasps after things	0.20 (–0.06 – 0.47)	0.1248	0.10 (0.00 – 0.21)	0.0582	0.10 (–0.17 – 0.38)	0.4660
5. Sits without support	0.39 (0.07 – 0.70)	0.0172	0.23 (0.10 – 0.35)	0.0004	0.16 (–0.18 – 0.49)	0.3582
6. Rolls	0.08 (–0.33 – 0.49)	0.6965	0.11 (–0.06 – 0.28)	0.2097	–0.03 (–0.41 – 0.46)	0.9045
7. Crawls	0.17 (–0.27 – 0.61)	0.4429	0.10 (–0.07 – 0.27)	0.2559	0.07 (–0.39 – 0.54)	0.7571
8. Crawls longer distance	0.46 (0.02 – 0.90)	0.0407	0.12 (–0.06 – 0.29)	0.1833	0.34 (–0.13 – 0.81)	0.1512
9. Stands with support	0.16 (–0.22 – 0.54)	0.4101	0.09 (–0.06 – 0.24)	0.2422	0.07 (–0.33 – 0.47)	0.7391
10. Stands without support	0.33 (–0.16 – 0.80)	0.1859	0.23 (0.04 – 0.41)	0.0181	0.10 (–0.41 – 0.61)	0.7033
11. Walks with support	0.22 (–0.13 – 0.57)	0.2199	0.14 (0.00 – 0.28)	0.0470	0.08 (–0.30 – 0.45)	0.6844
12. Walks without support	1.30 (0.78 – 1.83)	< 0.0001	0.41 (0.22 – 0.61)	< 0.0001	0.89 (0.34 – 1.43)	0.0015

^aAdjusted for gender, mother's age, father's age, parental social status, breadwinner's education, single mother status, and parity

^bThe four milestone means are in z-scores, the individual milestones are measured in months unless otherwise indicated.