



## Original article

## Interaction between parental psychosis and early motor development and the risk of schizophrenia in a general population birth cohort



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## ABSTRACT

**Background:** Delayed motor development in infancy and family history of psychosis are both associated with increased risk of schizophrenia, but their interaction is largely unstudied.

**Aim:** To investigate the association of the age of achieving motor milestones and parental psychosis and their interaction in respect to risk of schizophrenia.

**Methods:** We used data from the general population-based prospective Northern Finland Birth Cohort 1966 ( $n = 10,283$ ). Developmental information of the cohort members was gathered during regular visits to Finnish child welfare clinics. Several registers were used to determine the diagnosis of schizophrenia among the cohort members and psychosis among the parents. Altogether 152 (1.5%) individuals had schizophrenia by the age of 46 years, with 23 (15.1%) of them having a parent with psychosis. Cox regression analysis was used in analyses.

**Results:** Parental psychosis was associated ( $P < 0.05$ ) with later achievement of holding the head up, grabbing an object, and walking without support. In the parental psychosis group, the risk for schizophrenia was increased if holding the head up (hazard ratio [HR]: 2.46; degrees of freedom [df] = 1; 95% confidence interval [95% CI]: 1.07–5.66) and touching the thumb with the index finger (HR: 1.84; df = 1; 95% CI: 1.11–3.06) was later. In the group without parental psychosis, a delay in the following milestones increased the risk of schizophrenia: standing without support and walking without support. Parental psychosis had an interaction with delayed touching thumb with index finger (HR: 1.87; df = 1; 95% CI: 1.08–3.25) when risk of schizophrenia was investigated.

**Conclusions:** Parental psychosis was associated with achieving motor milestones later in infancy, particularly the milestones that appear early in a child's life. Parental psychosis and touching the thumb with the index finger had a significant interaction on risk of schizophrenia. Genetic risk for psychosis may interact with delayed development to raise future risk of schizophrenia, or delayed development may be a marker of other risk processes that interact with genetic liability to cause later schizophrenia.

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## 1. Introduction

Schizophrenia is an etiologically heterogeneous syndrome caused by genetic and environmental factors. The onset of the illness is usually in the second or third decade of life but studies have found several observable sub-clinical signs of neuropathology in infancy, childhood and adolescence [29]. Family history of psychosis is well established, as a major risk factor for schizophrenia [28,35], while one of the earliest documented developmental precursors is neuromotor dysfunction [8]. During the 1950s, Barbara Fish described children of mothers with schizophrenia to be at higher risk of pandyismaturization, considered as a marker for an inherited neurointegrative deficit in schizophrenia [8,9]. Several high-risk studies have established that there are delays in the motor development of infants genetically at risk for schizophrenia [29,8,9,25,33,23,39,10]. The findings of the general population studies support evidence from genetic high-risk research that delayed achievement of motor milestones [16,46,37,43,4], social deficiency [41] and later speech development [16] are robust risk factors for schizophrenia (see [Supplementary data, Table S1](#)).

Previous findings in the Northern Finland Birth Cohort 1966 (NFBC 1966) have provided further evidence of the association between motor delay and schizophrenia [13]. The main finding was that, a higher age for learning to stand, walk or become potty-trained was associated with increased occurrence of schizophrenia in adult life [13]. Later motor development correlated with poor school performance at the age of 16 years [14] and with later cognitive functioning in schizophrenia [45,36]. It remains unknown whether motor delay and parental psychosis are independent risk factors for schizophrenia or whether they interact to confer risk; to the best of our knowledge, no previous prospective population-based study has examined this question. The aim of this study was to examine the age of achievement of motor milestones and parental psychosis and their interaction in respect to risk of schizophrenia. We hypothesized that parental psychosis would be associated with later achievement of motor milestones and that these two risk factors together would present a higher risk of schizophrenia than either of them alone.

## 2. Method

### 2.1. Sample

The present study is a prospective study using data from the Northern Finland Birth Cohort 1966 (NFBC 1966), which is a general population-based sample. It consists of 12,068 pregnant women and their 12,058 live-born children in the provinces of Lapland and Oulu. These births represent 96% of all births in this region in year 1966 [34]. The subjects have been followed up since mid-pregnancy until 2012. At the age of 16, 11,017 of the children were alive and living in Finland, but 84 refused permission to use their data. After excluding all twins ( $n = 258$ ), the study sample consisted of 10,675 subjects. The Ethics Committee of the Northern Ostrobothnia Hospital District has given the written informed consent and approved the study design of the NFBC 1966 and keeps it under review.

### 2.2. Diagnosis of schizophrenia among the cohort members

The final sample (10,283) included 152 subjects with schizophrenia and 10,131 non-psychotic controls. Several sources of data were used to determine the diagnosis of schizophrenia in the cohort members (ICD-8/9: 295 except 295.7, ICD-10 F20, or DSM-III-R 295 except 295.7):

- the Finnish Hospital Discharge Register (FHDR) between years 1972–2012 ( $n = 127$ );
- hospital inpatient register ( $n = 112$ ), outpatient registers: specialized health care between years 1998–2012 ( $n = 64$ ) and primary health care between years 2011–2012 ( $n = 27$ );
- national registers of the Finnish Social Insurance Institute (sick days until the year 1999, disability pensions until the year 2000, reimbursable medications until the year 2006;  $n = 101$ );
- Finnish Center for Pensions until the year 2011 ( $n = 29$ );
- confirmation of the diagnosis in a subsample: hospital notes [27] and two follow-up interviews ( $n = 114$ , 75% of all schizophrenia diagnoses), at the ages of 34 years (between years 1999–2001) [19] and 43 years (between years 2008–2011).

See [Supplementary data, Table S2](#) for further details on sources of schizophrenia diagnosis. Individuals with other non-organic psychotic diagnoses ( $n = 185$ ) and mental retardation ( $n = 217$ ) were excluded, including 10 cases with both; non-organic psychosis and mental retardation.

Finnish national registries have found to be very useful and reliable sources for case detection in schizophrenia [27,31,26].

### 2.3. Parental psychosis

Parental psychosis was defined as a parent (mother and/or father) suffering from non-organic psychosis (i.e. ICD-8: 295–299; ICD-9: 295, 2961E, 2962E, 2963E, 2964E, 2967, 297–299; ICD-10: F20, F22–F29) at any time between 1964–2005. Information of the parental psychosis was gathered from the FHDR ( $n = 526$ ; 1972–2005), including outpatient registers from specialized care (1998–2005), and the disability pension register of the Finnish Center for Pensions (1964–2005;  $n = 43$ ). In the present study, 5.5% ( $n = 569$ ) of the study subjects had at least one parent with psychosis, and of them, 23 developed schizophrenia.

### 2.4. Motor developmental milestones

The information on motor, social and lingual development of the children was gathered in regular visits to the Finnish child welfare clinics by nurses and doctors interviewing the parents and observing the children during infancy and early childhood in monthly intervals [32]. This is a normal procedure in Finnish public health care and was not organized particularly for this study. The achievement times of each milestone, in months, were recorded on a separate welfare card. Before year 2007, the NFBC 1966 motor milestone information was a mixture of welfare card data on only walking and standing and parental responses to a questionnaire administered at 1 year of age [13,14]. The previous milestone information was merged with completed welfare card data so that we included the new information in cases where the same cohort member had both; new and older information on milestone attainment. In the present study, only the age of achievement of motor milestone in the first year of life (in months) was investigated as motor skills have been commonly associated with schizophrenia risks, and as this data in NFBC 1966 is more complete and detailed than that of other milestones [16,43,4,13,14]. The following milestones were addressed: being able to hold the head up, to grab an object, to turn over from back to tummy, to sit without support, to touch the thumb with the index finger, to stand up, to stand without support and to walk without support.

### 2.5. Statistical methods

Student's *t*-tests were used to compare mean values of ages (months) of achieving milestones between those with and without

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