Svetlana Filatova

INCIDENCE OF SCHIZOPHRENIA AND ASSOCIATIONS OF SCHIZOPHRENIA AND SCHIZOTYPY WITH EARLY MOTOR DEVELOPMENTAL MILESTONES
INCIDENCE OF SCHIZOPHRENIA AND ASSOCIATIONS OF SCHIZOPHRENIA AND SCHIZOTYPY WITH EARLY MOTOR DEVELOPMENTAL MILESTONES

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**Abstract**

Schizophrenia is a complex mental health disorder and its etiology can be investigated based on different theoretical prerequisites. The present thesis examines schizophrenia from the neurodevelopmental and psychosis continuum perspectives. Neurodevelopmental theories of schizophrenia see abnormalities in the developing nervous system as early predictors of vulnerability to the disease. Schizophrenia can be seen also as a progressive disorder and a continuum of symptomatology from personality traits (schizotypy) to full-blown schizophrenia. The aim of the present thesis is to study incidence of schizophrenia; prevalence of schizotypy; and associations between schizophrenia and schizotypy with early motor developmental milestones.

The research design includes prospective cohort studies and systematic review, and meta-analysis.

In two successive Northern Finland Birth Cohorts (NFBC) studies, 20 years apart (1966 and 1986), the incidence of schizophrenia remained the same, but the incidence of other psychoses and therefore all psychoses was higher in NFBC 1986. In NFBC 1966, mean schizotypy scores were among the lowest and the highest scores among 24 general population studies.

When early motor developmental milestones were investigated in the meta-analyses (3 to 5 studies), a significant small effect size for walking, sitting, and standing unsupported was found with respect to adult schizophrenia. When schizotypy outcome was studied in the NFBC 1966, later achievement of turning from back to tummy, touching thumb with index finger, standing up, sitting unsupported, and walking with support were found to be associated with an increase in schizotypy scales and varied somewhat by gender.

To conclude, there have been changes in the incidence of all psychoses but not in schizophrenia between the two NFBCs. This is in line with other studies on the trends of incidence of psychoses, which highlights the role of changes in diagnostic systems and practices that can influence rates. In this project, mean schizotypy scores were both among the highest and the lowest estimates in the studies on schizotypy in the general population. Early motor developmental milestones were both predictors of schizophrenia and schizotypy, and thus this finding supports both the neurodevelopmental and psychosis continuum approaches to the aetiology of schizophrenia.

**Keywords:** birth cohort, incidence, motor milestone, risk factors, schizophrenia, schizotypy
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Tiivistelmä


Asiasonat: ilmaantuvuus, motorinen kehitys, riskitekijät, skitsofrenia, skitsotypaalisuus, syntymäkohortti
To my family
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Svetlana Filatova

Oulu, July 2017
# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% CI</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>APA</td>
<td>American Psychiatric Association</td>
</tr>
<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>GWAS</td>
<td>Genome-wide Association Studies</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>IQ</td>
<td>Intelligence Quotient</td>
</tr>
<tr>
<td>MeSH</td>
<td>Medical Subject Headings</td>
</tr>
<tr>
<td>NFBC</td>
<td>Northern Finland Birth Cohort</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
</tr>
<tr>
<td>PAS</td>
<td>Perceptual Aberration Scale</td>
</tr>
<tr>
<td>PhAS</td>
<td>Physical Anhedonia Scale</td>
</tr>
<tr>
<td>RDoC</td>
<td>Research Domain Criteria</td>
</tr>
<tr>
<td>SAS</td>
<td>Social Anhedonia Scale</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SES</td>
<td>Socio-economic Status</td>
</tr>
<tr>
<td>SNP</td>
<td>Single-Nucleotide Polymorphism</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Original publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals I-III:


In addition, some unpublished data has been added to this doctoral thesis.
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1 Introduction

Schizophrenia is a complex mental health illness characterized by the distortion of thinking, perception, and the sense of self. It is a highly disabling disease (Whiteford et al. 2013) and has significant negative public health impacts such as excess mortality (Saha et al. 2007), social disability (Świtaj et al. 2012) and stigma (Gerlinger et al. 2013), burden on caregivers (Awad & Voruganti 2008), and social costs (Knapp et al. 2004).

The aetiology of schizophrenia remains unclear, but several theories attempt to explain its origins. These models include the vulnerability-stress model (Zubin & Spring 1977, Walker & Diforio 1997, Gispen-de Wied 2000), gene-environment interaction model (van Os et al. 2008), the two-hit hypothesis (Maynard et al. 2001), the hybrid model (Salokangas et al. 2001, van Os et al. 2008), and the neurodevelopmental model (Murray & Lewis 1987, Weinberger 1987). According to the hybrid model, the progression of a disease can possibly be reversed under early intervention (van Os et al. 2008), while according to the neurodevelopment model, abnormal processes that started during infancy will result in abnormal ageing (Nour & Howes 2015). Nevertheless, none of these theories alone can explain the origins of schizophrenia.

The onset of schizophrenia is usually in adolescence or adulthood (Mueser & McGurk 2004), but exploration of the early childhood period is crucial for identifying risk factors of the disease. Furthermore, birth cohort design is advantageous for examining disease aetiology.

The concept of schizophrenia was established by Emil Kraepelin in 1909 and first introduced by Eugen Bleuer in 1911. However, the symptoms of the disease had been already observed in ancient and medieval societies (Kasper & Papadimitriou 2009).

The course of schizophrenia is characterized by a prodromal stage when motor, cognitive, emotional, and behavioural deviations can be observed and the first episode of psychosis that triggers contact with a mental health professional. During a lifetime, there can be multiple psychotic episodes with remissions, or psychotic symptoms can be prevalent (Harvey & Davidson 2002, Jääskeläinen et al. 2013).

The broad scope of schizophrenia symptoms has been studied since the 1950s. The oldest scales used a single-factor approach, while in the 1990s, models had three to five factors (Kasper & Papadimitriou 2009). The most commonly used dimensions are positive and negative (Mueser & McGurk 2004, Picchioni & Murray 2007). Positive symptoms include hallucinations, delusions, or peculiar...
behaviours, negative symptoms can be represented by social withdrawal, emotional blunting, and anhedonia. However, other symptoms such as cognitive, depressive, and deficit syndrome are also recognized (Kasper & Papadimitriou 2009).

Historically, there have been some differences in the diagnosis of schizophrenia across countries. For instance, Scandinavian psychiatrists have used a narrow definition of schizophrenia with a focus on poor outcome, and those with a better prognosis were classified as having schizophreniform psychoses (Warner 2004). Currently, schizophrenia is most often diagnosed using the 10th International Classification of Diseases (ICD) (WHO 1992) and the 5th revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM) (APA 2013). These two diagnostic systems are quite similar, but in ICD-10 the duration of symptoms is to be at least 1 month, while in DSM-5, it is at least 6 months. In addition, the DSM-5 (APA 2013) has no subtypes of schizophrenia such as paranoid, catatonic, or disorganized. The ICD-11 system is currently under development. The psychotic disorders block will include schizophrenia, schizoaffective disorder, acute and transient psychotic disorder, schizotypal disorder, delusional disorder, other primary psychotic disorders, and unspecified primary psychotic disorders. The following subtypes from ICD-10 will be omitted in the ICD-11 due to diagnostic invalidity: paranoid, hebephrenic, catatonic, undifferentiated, post-schizophrenic depression, residual, simple, other, and unspecified. It is not recommended to use the schizophreniform disorder in ICD-11, but schizotypal disorder will remain mostly unchanged. Symptoms, courses and cognitive qualifiers will be introduced (Gaebel 2012).

Increasing evidence supports that schizophrenia is an illness that is not dichotomous in nature. It is a progressive disorder with a continuum from schizotypal traits to full-blown disease (van Os et al. 2009). The schizophrenia continuum is strongly supported by evidence of shared genetic liability between schizotypy, schizotypal personality disorder, and schizophrenia, and similar neurological origins (Chemerinski et al. 2013, Nelson et al. 2013, Barrantes-Vidal et al. 2015). It has been estimated that in about 80% of individuals, psychotic experiences will disappear over time, while 20% will suffer from persistent psychotic experiences, and 7% will be diagnosed with a psychotic disorder (Van Os & Reininghaus 2016). The risk of developing schizophrenia also depends on the extent of exposure to environmental risk factors.

In the present thesis, schizophrenia is explored from the neurodevelopmental and psychosis continuum perspectives as its complex nature should be approached from different theoretical prerequisites.
2 Review of literature

2.1 Schizophrenia continuum

According to psychosis continuum theories, the same symptoms as in individuals with schizophrenia can be observed in the general healthy population (van Os et al., 2009). In the absence of disease, these symptoms can be referred to as psychotic-like experiences (Kelleher & Cannon 2011), psychosis proneness, schizotypy, and so on (van Os et al. 2009). There are two approaches to studying the psychosis continuum: the quasi-dimensional model primarily based on the work of Meehl (Meehl 1962, Meehl 1989) and the fully-dimensional model based on the work of Claridge (Claridge 1972, Claridge 1987). Meehl suggests the term “schizotaxia”, a defect in neurointegrative processes, which under certain circumstances can give rise to schizotypy (De Rosse & Karlsgodt 2015). According to this model, the psychosis continuum is a range between abnormal personality characteristics to clinical psychotic symptoms. On the other hand, Claridge’s model suggests that psychotic symptoms are distributed on a population level. These symptoms can be adaptive or destructive, depending on variations in some other characteristics such as e.g. intelligence (De Rosse & Karlsgodt). For instance, some creative people can display psychotic symptom characteristics but never suffer from schizophrenia (Mohr & Claridge 2015). Still, it is not clear which of the models better fits the available evidence (De Rosse & Karlsgodt). An example of studies implying a psychosis continuum are two meta-analyses on incidence and prevalence (van Os et al., 2009, Linscott & van Os 2013), and cohort studies that have found associations between subclinical psychotic symptoms and later disease in longitudinal analyses (Poulton et al. 2000, Hanssen et al. 2005, Welham et al. 2009, Fisher et al. 2013).

2.1.1 Schizotypy

The schizotypy concept was introduced by Meehl (Meehl 1962), and since then, it has been used to describe a complex of personality traits related to schizophrenia that include magical thinking, peculiar behaviour, and strange speech (Nelson et al. 2013). Schizophrenia can be seen as the extreme expression of schizotypy (Kwapil & Barrantes-Vidal 2015). The structure of schizotypy corresponds to the positive and negative dimensions of schizophrenia (Barrantes-Vidal et al. 2013). Positive
schizotypy is described as anomalous experiences, odd beliefs, and negative affect, while negative schizotypy refers to anhedonia, anergia, and reduced positive affect (Vollema & van den Bosch 1995). In medical research, schizotypy is seen as a risk factor, a link in the chain towards schizophrenia (Barrantes-Vidal et al. 2015). However, there are discussions as to whether the relationship between schizotypy and schizophrenia is discrete or continuous. There is evidence that supports both approaches (Rawlings et al. 2008a, Van Os & Reininghaus 2016).

The quasi-dimensional approach suggests that schizotypy is a genetic vulnerability; a person either possesses it or not (Nelson et al. 2013). The fully dimensional approach sees schizotypy as a representation of central nervous system variations. According to this, schizotypy can be distributed on a scale from low to high among a population, and it defines a person’s vulnerability to the disease (Claridge & Davis 2003, Rawlings et al. 2008b).

A study by Mason (2015) identified 22 valid scales for measuring schizotypy from both a clinical and a personality perspective. These scales are, for example, the Oxford-Liverpool Inventory of Feelings and Experiences (Mason et al. 1995), the Paranoia/Suspiciousness Questionnaire (Rawlings & Freeman 1996), the Community Assessment of Psychic Experiences (Stefanis et al. 2002), and the Wisconsin Schizotypy Scales (Winterstein et al. 2011).

2.1.2 Schizotypal personality disorder

Eccentric thinking, bizarre behaviour, suspiciousness, and social withdrawal characterize these types of disorders; however, schizotypal personality disorder lacks the features required for a diagnosis of schizophrenia (Table 1). This disorder can be seen either as a form of schizotypy or a premorbid stage of schizophrenia (Raine 2006).

20
Table 1. Diagnostic guidelines for schizotypal personality in ICD-10.

<table>
<thead>
<tr>
<th>Diagnosis and (ICD-10 code)</th>
<th>Diagnostic guidelines (WHO, 1992)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizotypal personality (F21)</td>
<td>a) inappropriate or constricted affect (the individual appears cold and aloof); b) behaviour or appearance that is odd, eccentric, or peculiar; c) poor rapport with others and a tendency to social withdrawal; d) odd beliefs or magical thinking, influencing behaviour and inconsistent with subcultural norms; e) suspiciousness or paranoid ideas; f) obsessive ruminations without inner resistance, often with dysmorphophobic, sexual, or aggressive contents; g) unusual perceptual experiences including somatosensory (bodily) or other illusions, depersonalization, or derealization; h) vague, circumstantial, metaphorical, overelaborate, or stereotyped thinking, manifested by odd speech or in other ways, without gross incoherence; i) occasional transient quasi-psychotic episodes with intense illusions, auditory or other hallucinations, and delusion-like ideas, usually occurring without external provocation.</td>
</tr>
</tbody>
</table>

2.1.3 Schizophrenia and the schizophrenia spectrum

According to ICD-10, schizophrenia is diagnosed if at least one of symptoms a-d, or at least two of symptoms e-h are present for more than one month (Table 2). Schizophrenia has nine subtypes: paranoid, hebephrenic, catatonic, undifferentiated, post-schizophrenic depression, residual, simple, other, and unspecified.

Disorders that do not fulfil the criteria for schizophrenia, and are therefore differentiated, are schizoaffective disorders and delusional disorders.

Schizoaffective disorders are a group in which both affective and schizophrenic symptoms are present during the same episode of illness (Table 2). Schizoaffective disorder has five subtypes: manic type, depressive type, mixed type, other, and unspecified.

Delusional disorders constitute a heterogeneous group of disorders that share persistent delusions as a feature (Table 2).

Schizophreniform disorder is diagnosed in DSM 5, ICD-8 and ICD-9. However, it is no longer in ICD-10 because if the duration of symptoms is one month, it can be classified as schizophrenia.
Diagnostic guidelines for schizophrenia, schizoaffective, and delusional disorder in ICD-10 are described in Table 2.

**Table 2. Diagnostic characteristics of schizophrenia, schizoaffective, and delusional disorder in ICD-10.**

<table>
<thead>
<tr>
<th>Diagnosis and (ICD 10 code)</th>
<th>Diagnostic guidelines (WHO, 1992)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia (F20)</td>
<td>At least one of the following:</td>
</tr>
<tr>
<td></td>
<td>a) Thought echo, thought insertion or withdrawal, or thought broadcasting.</td>
</tr>
<tr>
<td></td>
<td>b) Delusions of control, influence, or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception.</td>
</tr>
<tr>
<td></td>
<td>c) Hallucinatory voices giving a running commentary on the patient's behaviour, or discussing him between themselves, or other types of hallucinatory voices coming from some part of the body.</td>
</tr>
<tr>
<td></td>
<td>d) Persistent delusions of other kinds that are culturally inappropriate and completely impossible (e.g. being able to control the weather, or being in communication with aliens from another world).</td>
</tr>
<tr>
<td></td>
<td>Or at least two of the following:</td>
</tr>
<tr>
<td></td>
<td>e) Persistent hallucinations in any modality, when occurring every day for at least one month, when accompanied by delusions (which may be fleeting or half-formed) without clear affective content, or when accompanied by persistent over-valued ideas.</td>
</tr>
<tr>
<td></td>
<td>f) Neologisms, breaks, or interpolations in the train of thought, resulting in incoherence or irrelevant speech.</td>
</tr>
<tr>
<td></td>
<td>g) Catatonic behaviour, such as excitement, posturing or waxy flexibility, negativism, mutism, and stupor.</td>
</tr>
<tr>
<td></td>
<td>h) &quot;Negative&quot; symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses (it must be clear that these are not due to depression or to neuroleptic medication).</td>
</tr>
</tbody>
</table>
### Schizoaffective disorder (F25)

A diagnosis of schizoaffective disorder should be made only when both definite schizophrenic and definite affective symptoms are prominent simultaneously, or within a few days of each other, within the same episode of illness, and when, as a consequence of this, the episode of illness does not meet criteria for either schizophrenia or a depressive or manic episode. The term should not be applied to patients who exhibit schizophrenic symptoms and affective symptoms only in different episodes of illness. It is common, for example, for a schizophrenic patient to present with depressive symptoms in the aftermath of a psychotic episode (see post-schizophrenic depression). Some patients have recurrent schizoaffective episodes, which may be of the manic or depressive type or a mixture of the two. Others have one or two schizoaffective episodes interspersed between typical episodes of mania or depression. In the former case, schizoaffective disorder is the appropriate diagnosis. In the latter, the occurrence of an occasional schizoaffective episode does not invalidate a diagnosis of bipolar affective disorder or recurrent depressive disorder if the clinical picture is typical in other respects.

### Delusional disorder (F22)

Delusions constitute the most conspicuous or the only clinical characteristic. They must be present for at least 3 months and be clearly personal rather than subcultural. Depressive symptoms or even a full-blown depressive episode may be present intermittently, provided that the delusions persist at times when there is no disturbance of mood. There must be no evidence of brain disease, no or only occasional auditory hallucinations, and no history of schizophrenic symptoms (delusions of control, thought broadcasting, etc.).

### 2.1.4 Other psychoses

Other psychoses are bipolar disorders with psychotic features, major depressive disorders with psychotic features, and brief psychoses. This group of disorders is related to schizophrenia disorders based on the presence of psychotic feature in a clinical picture (Table 3).

Diagnostic guidelines for bipolar disorders with psychotic features, major depressive disorders with psychotic features, and brief psychoses are described in Table 3.
Table 3. Diagnostic guidelines for bipolar disorder with psychotic features, major depressive disorder with psychotic features, and brief psychosis in ICD-10.

<table>
<thead>
<tr>
<th>Diagnosis (ICD-10 code)</th>
<th>Diagnostic guidelines (WHO, 1992)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar disorder with psychotic features (F302, F312, F315)</td>
<td>F30.2: The clinical picture is that of a more severe form of mania. Inflated self-esteem and grandiose ideas may develop into delusions, and irritability and suspiciousness into delusions of persecution. In severe cases, grandiose or religious delusions of identity or role may be prominent, and flight of ideas and pressure of speech may result in the individual becoming incomprehensible. Severe and sustained physical activity and excitement may result in aggression or violence, and neglect of eating, drinking, and personal hygiene may result in dangerous states of dehydration and self-neglect. If required, delusions or hallucinations can be specified as congruent or incongruent with the mood. &quot;Incongruent&quot; should be taken as including affectively neutral delusions and hallucinations; for example, delusions of reference with no guilty or accusatory content, or voices speaking to the individual about events that have no special emotional significance. F31.2: a) the current episode must fulfill the criteria for mania with psychotic symptoms; and b) there must have been at least one other affective episode (hypomanic, manic, depressive, or mixed) in the past. F31.5: a) the current episode must fulfill the criteria for a severe depressive episode with psychotic symptoms; and b) there must have been at least one hypomanic, manic, or mixed affective episode in the past.</td>
</tr>
<tr>
<td>Major depressive disorder with psychotic features (F323, F333)</td>
<td>F32.3: A severe depressive episode in which delusions, hallucinations, or depressive stupor are present. The delusions usually involve ideas of sin, poverty, or imminent disasters, responsibility for which may be assumed by the patient. Auditory or olfactory hallucinations are usually of defamatory or accusatory voices or of rotting filth or decomposing flesh. Severe psychomotor retardation may progress to stupor. If required, delusions or hallucinations may be specified as mood-congruent or mood-incongruent. F33.3: a) the criteria for recurrent depressive disorder should be fulfilled, and the current episode should fulfill the criteria for severe depressive episode with psychotic symptoms; and b) at least two episodes should have lasted a minimum of 2 weeks and should have been separated by several months without significant mood disturbance.</td>
</tr>
</tbody>
</table>
Diagnosis (ICD-10 code) | Diagnostic guidelines (WHO, 1992)
--- | ---
Brief psychosis (F23, F24) | F23: a) the onset must be acute (from a nonpsychotic state to a clearly psychotic state within 2 weeks or less); b) there must be several types of hallucination or delusion, changing in both type and intensity from day to day or within the same day; c) there should be a similarly varying emotional state; and d) in spite of the variety of symptoms, none should be present with sufficient consistency to fulfill the criteria for schizophrenia or for manic or depressive episode.
F24: A delusional disorder shared by two or more people with close emotional links. Only one of the people suffers from a genuine psychotic disorder; the delusions are induced in the other(s) and usually disappear when the people are separated.

2.2 Incidence and prevalence of schizophrenia and schizophrenia-related psychoses

2.2.1 Incidence and prevalence of schizotypy

The meta-analysis conducted by van Os et al. (2009) includes studies on prevalence (n=35) and on incidence (n=6) of the psychosis continuum. Median prevalence was 5.3% and the median incidence rate was 3.1% for psychotic experiences in the general population (van Os et al. 2009). Since this meta-analysis included a broad definition of psychosis continuum, e.g. schizotypy, psychotic-like experiences, subclinical psychotic experiences, etc., it may complicate the comparison of studies (Nelson et al. 2013) and conclusions drawn on incidence and prevalence of schizotypy. Later meta-analysis of cohort studies (n=61) have examined psychotic experiences in children and adults (Linscott & van Os 2013). It shows a median annual incidence of 2.5% and a prevalence of 7.2% for psychotic experiences. The differences in these two meta-analyses were explained partially by self-reported data on psychotic experiences in the earlier one, which could result in an overestimation of incidence rates.

A meta-analysis of gender differences in the Wisconsin schizotypy scales in the general population found 34 studies (including two with unpublished data) on the Perceptual Aberration Scale (PAS), the Social Anhedonia Scale (SAS), and the Physical Anhedonia Scale (PhAS) (Miettunen & Jääskeläinen 2010), and since then, 17 new studies have been identified (Table 4). This meta-analysis concludes that men have higher negative schizotypy (SAS and PhAS) than women, but the
differences in positive schizotypy (PAS) are not statistically significant (Miettunen & Jääskeläinen 2010).

The majority of studies on schizotypy were conducted among undergraduate students (Table 4). The mean estimates obtained from these studies allowed the evaluation of the distribution of schizotypy in the general population.
### Table 4. Studies of mean of schizotypy scales.

<table>
<thead>
<tr>
<th>Reference (year)</th>
<th>Location</th>
<th>Scale</th>
<th>Mean (SD) men</th>
<th>Mean (SD) women</th>
<th>Population</th>
<th>Sample size (Men/women)</th>
<th>Mean age of the sample (SD)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bailer et al. (2004)</td>
<td>Germany</td>
<td>SAS</td>
<td>9.50 (4.84)</td>
<td>9.90 (4.9)</td>
<td>9.20 (4.7)</td>
<td>students and employees</td>
<td>83 (35/48)</td>
</tr>
<tr>
<td>Berry et al. (2006)</td>
<td>United Kingdom</td>
<td>SAS</td>
<td>9.80 (6.25)</td>
<td>11.98 (6.85)</td>
<td>8.95 (5.97)</td>
<td>students</td>
<td>323 (91/232)</td>
</tr>
<tr>
<td>Brown et al. (2008)</td>
<td>North Carolina, USA</td>
<td>PAS</td>
<td>5.48 (5.40)</td>
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<td>N/R</td>
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<td>5.78 (4.69)</td>
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<td>NR</td>
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<td>10.55 (5.28)</td>
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<td>Barcelona, Spain</td>
<td>PAS</td>
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<td>NR</td>
<td>undergraduate students</td>
<td>547(82/456)</td>
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Note: SAS = Symptom Assessment Scale, PAS = Personality Assessment Scale, PhAS = Personality and Social Functioning Scale, N/R = Not Reported, NR = Not Recorded.
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<th>Population</th>
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<th>Mean age of the sample (SD)*</th>
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<td>------------</td>
<td>------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Schofield and Mohr (2013)</td>
<td>Bristol, UK</td>
<td>PhAS</td>
<td>12.94 (6.86)</td>
<td>14.60 (7.63)</td>
<td>11.26 (5.54)</td>
<td>undergraduate students and general population</td>
<td>159 (80/79)</td>
<td>22.21 (7.20)</td>
</tr>
<tr>
<td>Tsuang et al. (2016)</td>
<td>Taiwan</td>
<td>PAS</td>
<td>5.4 (4.3)</td>
<td>5.7 (4.3)</td>
<td>5.2 (4.3)</td>
<td>undergraduate students</td>
<td>3485 (1597/1848)</td>
<td>men: 19.9 (2.6), women: 19.7 (2.8)</td>
</tr>
<tr>
<td>Tully et al. (2014)</td>
<td>Boston, USA</td>
<td>SAS</td>
<td>12.71 (11.08)</td>
<td>13.88 (11.22)</td>
<td>11.71 (10.96)</td>
<td>general population</td>
<td>108 (50/58)</td>
<td>30.95 (12.87)</td>
</tr>
<tr>
<td>Yon et al. (2009)</td>
<td>Amiens, France</td>
<td>PAS</td>
<td>3.48 (3.44)</td>
<td>N/R</td>
<td>N/R</td>
<td>undergraduate students</td>
<td>399 (33/366)</td>
<td>24.03 (7.17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SAS</td>
<td>7.96 (5.01)</td>
<td>N/R</td>
<td>N/R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PhAS</td>
<td>15.97 (6.46)</td>
<td>N/R</td>
<td>N/R</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* or age range of the sample; a: Standard Deviation; b: Not Reported
In PAS, the lowest mean was 2.03 in men in the previous study in NFBC 1966 (Miettunen et al. 2011) and 1.53 in women (Camisa et al. 2005), and the highest was 8.78 in men (Graves & Weinstein 2004) and 10.92 in women (Scherbarth-Roschmann & Hautzinger 1991) (Figure 1).

In SAS, the lowest mean was 7.31 in men and 5.00 in women (Camisa et al. 2005), and the highest mean was 13.88 in men (Tully et al. 2014) and 9.33 in women (Kosmadakis et al. 1995) (Figure 2).

In PhAS, the lowest mean was 9.64 in men and 6.79 in women (Meyer & Hautzinger 1999), and the highest mean was 17.94 in men in NFBC 1966 (Miettunen et al. 2011) and 15.95 in women (Leventhal et al. 2006) (Figure 3).
Fig. 1. Distribution of mean score of PAS by study and gender.
Fig. 2. Distribution of mean score of SAS by study and gender.
Fig. 3. Distribution of mean score of PhAS by study and gender.
2.2.2 Incidence and prevalence of schizophrenia and other psychoses

The incidence of schizophrenia has been studied since the 1960s in high-income countries (Warner 2004) without agreement on its trajectories over time; some studies have reported a decline in its incidence (Takei et al. 1996, Brewin et al. 1997, Suvisaari et al. 1999, Ösby et al. 2001) or either an increase (Häfner & ander Heiden 1986, Bamrah et al. 1991) or no change (Allardycce et al. 2000, Kirkbride et al. 2009). This is partially explained by challenging methodology, but is also due to the lack of proper data to explore the incidence. Valid knowledge of incidence rates is needed to estimate the burden of a disease and health care planning (McGrath et al. 2008).

A systematic review by McGrath et al. (2008) includes 158 studies on the incidence and 188 studies on the prevalence of schizophrenia and other psychoses. The median incidence rate was 15.2/100,000 persons, and lifetime prevalence was 7.2/1,000 persons. The differences in incidence rates are explained by variability in the phenotype and genotype of a disease, as well as by heterogeneity of environmental factors (McGrath et al. 2008). The lifetime prevalence of schizophrenia in Finland has been reported to range between 2.2 and 4.6%, depending on region, the highest being in Northern Finland (Perälä et al. 2008). The incidence of schizophrenia is higher among men, but there are no gender differences in the incidence of all psychoses (Barajas et al. 2015).

2.3 Neurodevelopmental theories of schizophrenia

Many researchers have contributed to the exploration of schizophrenia from the neurodevelopmental theories perspective, which focus on the variety of aspects of brain development that can cause this condition (Weinberg & Levitt 2011). Recent evidence supporting these theories are congenital abnormalities, e.g. agenesis of corpus callosum; environmental risk factors, e.g. an increase in obstetric and perinatal complications; genetics findings, e.g. cell proliferation and axonal outgrowth; and gene-environment interactions findings, e.g. microdeletions and microduplications (Fatemi & Folsom 2009). There is substantial research on the risk factors of schizophrenia although many of the potential risk factors have not been identified yet.
2.4 Risk factors of schizophrenia and related outcomes

2.4.1 Risk factors of schizophrenia and other psychoses

Schizophrenia is a highly heritable disease. Currently, the focus of research is on genome-wide association studies (GWAS) that explore associations between single-nucleotide polymorphism (SNPs) and the disease’s traits. Recently, 128 independent SNP associations with schizophrenia were identified in a large multi-stage GWAS study (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014).

Some risk factors may be specific for schizophrenia spectrum disorders (i.e. schizophrenia, schizoaffective disorder, schizophreniform disorder, and other schizophrenia spectrum disorders) and some for affective psychoses (i.e. bipolar disorder with psychotic features, mania, major depressive disorder with psychotic features), and other affective psychoses (Laurens et al. 2015). The systematic review by Laurens et al. (2015) concludes that both of these groups share risk factors such as obstetric complications, childhood psychopathology, cognitive markers, and motor dysfunction. However, there is a lack of available prospective data for affective psychoses.

Risk factors of schizophrenia can also be divided according to time period i.e. time of conception, pre-and perinatal periods, and early and later life; some of these have already been meta-analysed (Matheson et al. 2011).

Risk factors at conception

At conception, a family history of psychosis (Rasic et al. 2013) or other psychiatric diseases, older paternal age (Miller et al. 2011), and male sex (Aleman et al. 2003) are risk factors. These factors have a moderate to high effect according to a meta-review by Matheson et al. (2011).

Prenatal and perinatal risk factors

Predictors of schizophrenia include several prenatal and perinatal factors. Moderate to high risk has been linked with obstetric complications (maternal diabetes, birth weight <2000 g, emergency caesarean section, congenital malformations, uterine antony, rhesus factor) (Cannon et al. 2002a), maternal influenza during pregnancy (Selten et al. 2009) and perinatal brain damage (Jones et al. 1998) have been shown
to be moderate to high predictors of schizophrenia. A higher latitude and cooler climate at birth (Davies et al. 2003, Saha et al. 2006, Kinney et al. 2009), maternal diet during pregnancy (Kinney et al. 2009), and maternal stress (Khashan et al. 2008, Malaspina et al. 2008) had a low to moderate effect (Matheson et al. 2011).

**Early life risk factors**

Several meta-analyses have found that central nervous system infections (Khandaker et al. 2012), parental socioeconomic status (Agerbo et al. 2015), adversities and trauma (Varese et al. 2012, Matheson et al. 2013a), migration (McGrath et al. 2004; Tortelli et al. 2015), social withdrawal (Matheson et al. 2013b), and deviance in parental communication in childhood (de Sousa et al. 2014, Roisko et al. 2014) are associated with adult schizophrenia. This is true also for minor physical anomalies (Weinberg et al. 2007), motor deficits, IQ and academic achievement (Dickson et al. 2012, Khandaker et al. 2011), and externalizing and internalizing behaviours in childhood (Tarbox & Pogue-Geile 2008).

**Later life risk factors**

Later life factors associated with schizophrenia are urban living (Vassos et al. 2012), socioeconomic status (Saha et al. 2005), cannabis use (Moore et al. 2007), exposure to chlamydia pneumoniae and toxoplasma gondii (Gutierrez-Fernandez et al. 2015, Torrey et al. 2007), traumatic brain injury (Molloy et al. 2011), adverse life events (Beards et al. 2013), tobacco use (Gurillo et al. 2015), and hearing impairments (Linszen et al. 2016).

**Risk factors of schizophrenia and other psychoses in the Northern Finland Birth Cohort (NFBC) 1966 and 1986**

NFBC 1966 and 1986 have contributed significantly to knowledge regarding risk factors of schizophrenia and other psychoses by identifying several risk factors in addition to the above-mentioned ones (Jääskeläinen et al. 2015). According to NFBC 1966, unwanted pregnancy (Myhrman et al. 1996), high parental social class at birth among women (Mäkikyrö et al. 1997), grand multiparity (Kempainen et al. 2000), mother’s antenatal depression (Mäki et al. 2010), early motor developmental milestones (Isohanni et al. 2001), both excellent and poor school performance among men (Isohanni et al. 1998, Isohanni et al. 1999) were found to
be associated with an increased risk of schizophrenia and other psychoses (Jääskeläinen et al. 2015). The younger NFBC 1986 has not been studied as intensively as NFBC 1966 due to the young age of the cohort members. Nevertheless, cannabis use in adolescence was associated with prodromal symptoms of psychosis (Miettunen et al. 2008), and physical inactivity was predictive of psychoses (Koivukangas et al. 2010).

2.4.2 Risk factors of schizotypy

Only recently has the intensive exploration of the risk factors of schizotypy begun, but more research is needed. A variety of concepts have been used to study schizotypy, which complicates the conclusions drawn from studies. Several reviews have been done (Nelson et al. 2013, Linscott & van Os 2013, Ettinger et al. 2014, Barrantes-Vidal et al. 2015), and schizotypy has shown risk factors similar to schizophrenia. However, several studies have also suggested specific predictors for negative schizotypy (Kaszorowski et al. 2009, Theleritis et al. 2012) and positive schizotypy (Holahan et al. 2005), even if the majority of the identified risk factors are predictors of both of these schizotypy dimensions. Thus, it seems important to report risk factors according to these dimensions.

Risk factors of positive schizotypy

Prenatal influenza (Machón et al. 2002), older parental age (Grattan et al. 2015), obstetric complications (i.e. maternal infection, maternal diabetes, need for resuscitation) (Zammit et al. 2009), dermatoglyphic anomalies (i.e. absolute finger ridge count) (Chok et al. 2005), and gait abnormalities (Mohr et al. 2004) have been shown to be associated with positive schizotypy.

Risk factors of negative schizotypy

Maternal smoking during pregnancy is a factor that was associated with negative schizotypy only in NFBC 1966 (Lahti et al. 2009). Furthermore, the genes associated with schizophrenia were predictive of social and physical anhedonia traits measured by SAS and PhAS (Tomppo et al. 2009, Bader et al. 2012).
Risk factors of both positive and negative schizotypy


2.5 Early motor developmental milestones

Early motor developmental milestones are crucial for the assessment of child development. During the first year of life, an infant progresses from lying prone to walking unsupported (Johnson & Blasco 1997). The achievement of each specific motor milestone changes interactions with the environment and supports independent mobility (Gerber et al. 2010). Early motor developmental milestones have sometimes been divided into gross (related to large muscles) and fine (related to hand/wrist). An evaluation of early motor milestones can be done and recorded by caregivers or by trained health specialists (Wijnhoven et al. 2004); there are also several existing scales for milestones. A review by Bedford et al. (2014) identifies at least 14 scales measuring motor domain in children (such as the Bayley Scales of Infant and Toddler Development or Child Development Inventory, etc.).

A World Health Organization Motor Development Study, with the aim of establishing a standard for child development, selected six milestones: sitting without support, standing with assistance, hands and knees crawling, walking with assistance, standing and walking alone. (Onis et al. 2006a). Sitting without support is acquired the earliest and walking alone the latest in life, but there are also some age overlaps (Onis et al. 2006a). Differences in physical growth by sex have been observed (Onis et al. 2006b), but these differences were not significant to the achievement of milestones (Onis et al. 2006c).
2.5.1 Early motor developmental milestones and schizophrenia-related outcomes

Studies exploring an association between motor abnormalities and the development of schizophrenia began in 1952 with a high risk study by Fish (1957) in New York (Fish 1957). This research was followed by other studies in the United States (Goldstein 1987, Erlenmeyer-Kimling 1997), Denmark (Shulsinger et al. 1984), Sweden (McNeil & Kaij 1987), and Israel (Mirsky et al. 1995). High risk studies in this area include the offspring of individuals with schizophrenia and identify a strong genetic predisposition and increased rate of general neuromotor signs (e.g. involuntary hand movements, retardation of visual development, etc.) in this group. However, the type of study population limited these studies, and thus findings could not be generalized nor could a clear contribution of gene and/or environment be established. This issue was somewhat addressed by population cohort studies (Jones et al. 1994, Crow et al. 1995, Rosso et al. 2000, Isohanni et al. 2001, Cannon et al. 2002b, Isohanni et al. 2004), which found that delays in motor development and/or motor coordination predicted schizophrenia in adulthood.

In the literature, early motor development milestones can be defined as risk factors (Jones et al. 1994), antecedents (Matheson et al. 2011), markers (Isohanni et al. 2004), or precursors of schizophrenia (Laurens et al. 2015). It reflects uncertainty in the use of epidemiological terms and subjectivity in a distinction between those terms (Burt 2001, Laurens et al. 2015). Schizophrenia is associated with delays in standing up, standing with or without support, as well as walking with support in NFBC 1966 (Isohanni et al. 2001, Keskinen et al. 2015). However, it is not clear if these findings are consistent with other studies in regards to types of milestones and effect size.

Several developmental studies have suggested that motor abnormalities can be seen as a marker of vulnerability to schizophrenia-related outcomes (Fish et al. 1992, Walker et al. 1999, Lenzenweger & Maher 2002). However, the link between early motor developmental milestones and schizotypy has not been studied.

2.6 Motor function and schizophrenia

Several studies have explored other aspects of motor development in relation to schizophrenia. It has been found that poor motor coordination and neuromotor abnormalities are associated with schizophrenia (Crow et al. 1995; Cannon et al. 1999a, Isohanni et al. 2001, Rosso et al. 2000, Schiffman et al. 2009; Walker et al.
In addition, children at risk of schizophrenia performed worse on standard tests of motor skills (Cannon et al. 2002b) and on subjects involving motor coordination, i.e. handcrafts and sports (Cannon et al. 1999b). Meta-analysis by Dickson et al. (2012) based on 4 studies (Cannon et al. 2002b; Rosso et al. 2000; Schiffman et al. 2004, Walker et al. 1994) found that motor function by the age of 16 years is associated with schizophrenia (Cohen’s d=0.56, 95% CI 0.38-0.74).

2.7 Prevention and treatment

Earlier identification of schizophrenia (i.e. in the prodromal stage) and treatment have shown to be an effective prevention strategy (Mueser & McGurk 2004, Picchioni & Murray 2007, van Os & Kapur 2009). Several guidelines have been developed for the prevention and treatment of schizophrenia by the American Psychiatric Association (Lehman et al. 2004), the National Institute for Health and Care Excellence (NICE 2014) and the World Health Organization (WHO 2016). The treatment consists of pharmacological and psychological approaches, the combinations of which have been found to be beneficial, especially second-generation antipsychotics (without extrapyramidal side effects) such as risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole (Lehman et al. 2004, WHO 2016). Psychological interventions include, e.g. assertive community treatment, family psychoeducation, supported employment, social skills training, teaching illness-management skills, and cognitive behaviour therapy (Lehman et al. 2004, Mueser & McGurk 2004).
3 Aims and research questions

3.1 Aims

The main aims of this thesis were to explore: a) time trends of incidence of schizophrenia; b) the level of schizotypy scores in NFBC 1966, and c) the association of early motor developmental milestones with schizophrenia and schizotypy.

3.2 Research questions

1. Did changes occur in incidence and early risk factors of schizophrenia and other psychoses between NFBC 1966 and NFBC 1986?
2. Do changes in potential risk factors influence changes in the incidence of schizophrenia and other psychoses between the two cohorts?
3. What is the level of schizotypy scores in men and women in NFBC 1966?
4. Which early motor developmental milestones predict schizophrenia, and what is their effect size?
5. Which early motor developmental milestones predict schizotypy?
4 Materials and methods

An overview of the studies included in this thesis is presented in Table 5.

4.1 Data collection and study samples

4.1.1 Study population in NFBC 1966 and 1986 (I and III)

In Study I, both NFBC 1966 and NFBC 1986 were used, but in Study III only NFBC 1966 was used. NFBC 1966 consists of 12,058 live-born children, and NFBC 1986 consists of 9,432 live-born children. The cohort members were followed beginning with their mothers’ pregnancies and the data was collected in two northern areas of Finland (Oulu and Lapland) (Rantakallio 1969). For general information regarding NFBC, see the webpage (www.oulu.fi/nfbc).

In Study I, exclusion criteria were: a) death or emigration before age 12; or b) denial to use the data. These criteria resulted in the exclusion of 901 cases from NFBC 1966 and 105 cases from NFBC 1986.

The exclusion criteria in the Study III were: a) receiving a schizophrenia diagnosis before the age of 31 years or a having mental disability; b) having a score of more than 3 on the Infrequency scale; c) denial to access the data; or d) being a twin. These criteria resulted in the exclusion of 821 cases.

4.1.2 Study population in meta-analysis (II)

The size of the study population in the original Study II ranged from 14,233 to 19,810 according to the early motor developmental milestone (Table 5). Exclusion criteria were: a) an unstandardized assessment of schizophrenia; b) the onset of schizophrenia before the age of 12 years; c) an assessment of the early motor developmental milestone after the age of 13; or d) studying other exposure (e.g. motor function) rather than the early motor developmental milestone being studied (Figure 1 in original publication II).
Table 5. Overview of the original studies included in this thesis.

<table>
<thead>
<tr>
<th>Study</th>
<th>I Research question</th>
<th>II Data source</th>
<th>III Data source</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Are there changes in incidence and early risk factors of schizophrenia and other psychoses between NFBC 1966 and NFBC 1986? Do the changes in potential risk factors influence the changes in the incidence of schizophrenia and other psychoses.</td>
<td>NFBC 1966 and NFBC 1986 population registers</td>
<td>NFBC 1966 questionnaire on schizotypal traits administered at the age of 31 years population registers, welfare card data</td>
</tr>
<tr>
<td>II</td>
<td>Which early motor developmental milestones predict schizophrenia on a larger scale, and what is the effect size?</td>
<td>Pubmed, PsycINFO and Scopus database</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Are early motor developmental milestones associated with schizotypy?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study design</th>
<th>Follow-up period</th>
<th>Population</th>
<th>Exposure variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort study</td>
<td>Until the age of 27 years</td>
<td>NFBC 1966 (N=12,058)</td>
<td>sex</td>
</tr>
<tr>
<td>Cohort study</td>
<td>Until the age of 31 years</td>
<td>NFBC 1986 (N=9,432)</td>
<td>parental psychosis</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>N/A</td>
<td></td>
<td>mother’s education at birth</td>
</tr>
<tr>
<td>Cohort study</td>
<td>Until the age of 31 years</td>
<td>NFBC 1966 (N=4,588)</td>
<td>place of residence at birth</td>
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<td></td>
<td></td>
<td></td>
<td>walking unsupported</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>standing unsupported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>sitting unsupported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>holding head up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>walking with support</td>
</tr>
<tr>
<td>Study</td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td></td>
<td>maternal age at birth</td>
<td>grabbing object</td>
<td>capable of standing up (lifting themselves)</td>
</tr>
<tr>
<td></td>
<td>paternal age at birth</td>
<td></td>
<td>touching thumb with index finger (like a tweezer)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>turning from back to tummy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gripping an object (grabbing object)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>holding head up</td>
</tr>
<tr>
<td>Outcome variable</td>
<td>schizophrenia and other psychoses</td>
<td>broad schizophrenia</td>
<td>schizotypy (negative and positive)</td>
</tr>
<tr>
<td>Covariates</td>
<td>None</td>
<td>None</td>
<td>parental psychosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>father's socioeconomic status</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>place of residence</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>parental age</td>
</tr>
<tr>
<td>Measures</td>
<td>Incidence of first diagnosis of schizophrenia and other psychoses</td>
<td>Hedges' g measuring the effect size with 95% CI</td>
<td>unstandardized regression coefficient (B2) with 95% CI</td>
</tr>
<tr>
<td></td>
<td>Hazard ratio (HR) with 95% confidence interval (CI) of the first diagnosis of psychoses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>Cox regression</td>
<td>Random effect meta-analysis</td>
<td>Hierarchical linear regression</td>
</tr>
</tbody>
</table>
Data on schizophrenia and other psychoses

The data on schizophrenia and other psychoses, defined according to ICD-8 (1968-1986), ICD-9 (1987-1995) or ICD-10 (1966-2012), was collected from the following registers: a) the Care register for Health Care; b) the Finnish outpatient registers; c) the Social Insurance Institutions registers (i.e. on reimbursable medicines, sick days, and disability pensions); d) the Finnish Centre for Pensions (on disability pensions) (Appendix 1). These registers showed high quality data (Sund 2012).

In the present thesis, ICD-8, ICD-9 (DSM-III-R), and ICD-10 criteria were used due to the longitudinal nature of the data (i.e. due to changes in the diagnostic system in Finland from 1966-1989) (Table 6). Finnish psychiatrists followed the Bleulerian diagnosis principle (schizophrenia being the preferred diagnosis for manic-depressive illness) during the period of ICD-8 (Salokangas 1985). From 1987-1995, new diagnostic criteria were adopted, with a modification from DSM-III-R, with a narrower definition of schizophrenia and a new requirement for a 6-month duration of symptoms (Kuoppasalmi et al. 1989).

Table 6. Diagnostic categories of psychotic disorder based on ICD-8 to 10 (Study I).

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia*</td>
<td>295, 2954</td>
<td>295, 2954</td>
<td>F20</td>
</tr>
<tr>
<td>Schizophrenia spectrum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td>2957</td>
<td>2957</td>
<td>F25</td>
</tr>
<tr>
<td>Delusional disorder</td>
<td>297</td>
<td>297</td>
<td>F22</td>
</tr>
<tr>
<td>Bipolar disorder (with psychotic features)</td>
<td>2961-2969</td>
<td>2962E, 2963E, 2964E, 2967</td>
<td>F302, F312, F315</td>
</tr>
<tr>
<td>Major depressive disorder (with psychotic features)</td>
<td>2960, 2980</td>
<td>2961E</td>
<td>F323, F333</td>
</tr>
<tr>
<td>Brief psychosis</td>
<td>298 (except 2980)</td>
<td>2988</td>
<td>F23, F24</td>
</tr>
<tr>
<td>Other nonorganic psychoses</td>
<td>299</td>
<td>2989</td>
<td>F28, F29</td>
</tr>
</tbody>
</table>

*And schizophreniform disorder
Data on schizotypy

In the present thesis, schizotypy was assessed using the Perceptual Aberration Scale (PAS) (Chapman et al. 1978), the Revised Physical Anhedonia Scale (PhAS), and the Social Anhedonia (SAS) Scale (Chapman et al. 1976) (Appendix 2). These scales were developed based on Meehl’s theory of schizotypy and have proven to be good predictors of schizophrenia spectrum disorders in prospective studies (Chapman et al. 1994, Gooding et al. 2005, Miettunen et al. 2011). A backtranslated (from English to Finnish) questionnaire was administered to participants in the 31-year follow up. It consisted of these scales with true/false questions (scored 0/1). In the original Study III, the Schizoidia Scale (Golden & Meehl 1979), the Bipolar 2 Scale (Akiskal et al. 1995), and the Hypomanic Personality Scale (Eckblad & Chapman 1986) were also included (See Study III manuscript).

Data on exposures and covariates

Data on parental psychosis (yes/no) and mental disability (yes/no) was acquired from the same sources as the psychoses data of the cohort members.

Data on a maternal education (basic education/secondary education/higher education) at the birth of a child, paternal socioeconomic status (low and high), the place of residence at birth (urban/rural), paternal age, and being a twin were collected from the population register and linked with the cohort data.

Health care professionals access the achievement of early motor developmental milestones during a child’s monthly visits to child welfare centres. The card used in NFBC 1966 to evaluate the achievement of early motor developmental milestones is presented in Appendix 3. These early motor developmental milestones are similar to the ones defined by the WHO motor study (Onis et al. 2006a).

4.1.4 Data collection in meta-analysis (II)

Three databases (i.e. PubMed, PsycINFO and Scopus) were searched in July 2015, and the following indexing terms (MeSH or Key words) were included: [(infant OR child*OR early) AND (schizophr*OR psychosis OR schizoaff* OR psychotic) AND (impairment OR delay OR skill OR ability OR function OR deficit OR coordination OR performance OR problem OR milestone* OR complication* OR complication*)]
risk* OR functioning OR precursor* OR predictor*) AND (motor OR movement OR neuromuscular OR psychomotor OR neuromotor OR development*)]. These three databases have shown good coverage of mental health research (Löhönen et al. 2009), and thus were included in the Study II. An updated search was performed by the thesis author only in PubMed and Scopus in May 2017 as the University of Oulu no longer had access to the PsycINFO database.

The search in the databases was performed with the help of an information specialist. Abstracts were screened by three reviewers working independently. The flow chart of the final selected articles is presented in Appendix 4.

4.2 Missing data

**Missing data (I)**

In NFBC 1966, the missing cases (in brackets) for covariates were mother’s education at birth (n=196), maternal age (n=87), and paternal age (n=620). In NFBC 1986, the missing cases for covariates were maternal education at birth (n=1392), place of residence (n=233), and paternal age (n=95). There were no missing data on schizophrenia and other psychoses diagnoses as these were collected using registers.

**Missing data (II)**

Before the final stage of the selection of studies, one study was excluded due to incomplete reporting of estimates, and there was no possibility to retrieve them. Missing data due to reporting, in the included studies, was evaluated against quality criteria and is discussed in more detail in the result section.

**Missing data (III)**

In Study III, 7,173 (59%) cohort members did not respond to the 31-year old schizotypy scales questionnaire (at least to one scale). The amount of missing data regarding early motor developmental milestones varied from 12% (walking unsupported) to 69% (touching thumb with index finger). Some data on paternal SES (n=3), maternal age (n=1), and paternal age (n=813) was missing.
4.3 Statistical analysis

Study I analysis

Cox regression in univariate analyses was applied to examine relationships between exposures and outcomes. Changes in risk factors-incidence association were also studied using Cox regression in a multivariate analysis with the pooled cohorts’ data: cohort membership as a predictor and other potential risk factors as covariates. Censoring points in the analyses were the time of emigration and death (information from the Population Register Centre).

To compare the distribution of the categorical (sex, parental psychosis, maternal education, place of residence, maternal and paternal age) and the continuous variables (onset age of psychosis), the Chi-square and Student’s t-test were used, respectively. Data analyses were performed in SPSS Statistics version 21.

Study II analysis

The quality of selected studies were evaluated against a scale by Downs and Black (1998) with small modifications (See Table 2 in the original publication II), which proved to be a reliable assessment instrument (Sanderson et al. 2007).

Estimates from the selected studies were extracted, and only milestones studied at least three times were analysed. A random effect model was applied (Field & Gillett 2010), and individual effect sizes were presented using Hedges’ g with a 95% Confidence Interval (95% CI) estimate (Borenstein et al. 2010). This estimate is a variation of Cohen’s d for a small sample size, and the effect sizes can be interpreted as small (0.2), moderate (0.5), large (0.8), and very large (1.3) (Cohen 1992).

An I² test was applied to estimate the heterogeneity across studies (range from 0% to 100%) with 0% indicating no, 25% low, 50% moderate, and 75% high (Higgins et al. 2003). The analyses were performed in Stata version 11.

Study III analysis

Before the analysis, the schizotypy scales were assessed for normality (Field 2013), and only PAS and SAS required transformation. Mean schizotypy scores with standard deviations were calculated. To study an association between early motor developmental milestones and schizotypy, univariate linear regression and
hierarchical linear regression with covariates were applied. The analyses were performed separately for both genders due to evidence of a difference in scores on schizotypal scales (Leung & Psych 2000, Miettunen & Jääskeläinen 2010). All analyses were performed in SPSS 21.

4.4 Ethical issues and personal involvement

Ethical issues

There are two ethical approvals relevant to this project. These were approved by the Ethics Committee of the University Hospital of Oulu on 22nd of May 2006 and 18th of February 2008 (EETTMK 91/2011). The overall study plan for the cohorts was accepted by the ethical committee of the Northern Ostrobothnia Hospital district on 27th of February 2003. Data protection was scrutinized by the Privacy Protection Agency and according to the principles of the Finnish Ministry of Health and Social Affairs. Each cohort member was assigned an ID number that allowed confidentiality to be maintained. All participants have the right to withdraw their data from use at any time.

Personal involvement

The author of this thesis planned all three original publications and the dissertation together with her three supervisors. The collected data was available at the beginning of the project. The author performed the statistical analyses of the data following the advice of the research group’s statisticians and wrote all first and last versions of the original publications. The author managed the submission, revision, and resubmission process for all of the studies. In Study II, PhD Noora Hirvonen conducted databases searches, and PhD candidates Aislinne Freeman and Ivana Ivandic conducted the abstracts check along with the author of this thesis.
Results

5.1 Changes in incidence and early risk of schizophrenia and other psychoses between NFBC 1966 and NFBC 1986 (Research question 1)

The incidence of schizophrenia did not differ between the two cohorts set 20 years apart and was 0.45% in NFBC 1966 and 0.42 % in NFBC 1986 (p=0.751) (Table 7). However, the incidence of all psychoses increased from 1.01% in NFBC 1966 to 1.90% in NFBC 1986 (p<0.001). In addition, a shift in types of diagnosis was observed. In NFBC 1986, more cases on the schizophrenia spectrum, affective psychoses (bipolar disorder, major depression), and other psychoses (brief psychosis, other non-organic psychoses) were found than in NFBC 1966.

Table 7. Cumulative incidence (%) of different psychotic disorders in the cohorts by the age of 27 years.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>NFBC 1966 (N=11621)</th>
<th>NFBC 1986 (N=9329)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>53 (0.45%)</td>
<td>39 (0.42%)</td>
<td>0.751</td>
</tr>
<tr>
<td>Schizophrenia spectrum*</td>
<td>8 (0.06%)</td>
<td>11 (0.12%)</td>
<td>0.257</td>
</tr>
<tr>
<td>Bipolar disorder with psychotic features</td>
<td>5 (0.04%)</td>
<td>17 (0.18%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Major depressive episode with psychotic features</td>
<td>2 (0.02%)</td>
<td>27 (0.29%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Brief psychosis</td>
<td>13 (0.11%)</td>
<td>20 (0.21%)</td>
<td>0.078</td>
</tr>
<tr>
<td>Other nonorganic psychoses</td>
<td>37 (0.32%)</td>
<td>63 (0.68%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td>118 (1.01%)</td>
<td>177 (1.90%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Note: schizophrenia spectrum includes schizoaffective disorder and delusional disorder

A gender-specific difference in trends of incidence of all the psychoses was observed (Figure 4). Women had significantly more psychoses than men between the ages of 16 and 18 in NFBC 1986 (p<0.001). In addition, the women in NFBC 1986 had a significantly earlier mean age of onset of all psychoses than the women in NFBC 1966 (i.e. 20.15 (SD 3.88) v. 21.74 (SD 3.36), p = 0.018).
Fig. 4. Cumulative incidence of psychoses among men and women in the NFBC 1966 and 1986.

In NFBC 1966, more cases of parental psychoses were observed, more mothers had only a basic education, more individuals lived in rural areas, and had a younger paternal age compared to NFBC 1986 (p<0.001). In both cohorts, only parental psychosis predicted a higher risk of schizophrenia with about a threefold risk increase: HR1966: 3.01 (95% CI 1.82-4.76), HR1986: 2.99 (95% CI 1.91-4.67) (see Table 4 in original publication I).
5.2 Do changes in potential risk factors influence changes in the incidence of schizophrenia and other psychoses between the two cohorts (Research question 2)

In both cohorts, the occurrence of potential risk factors varied within 20 years e.g. more individuals lived in urban areas and had a higher education in NFBC 1986 (see Table 3 in original publication 1).

The results showed that a crude hazard ratio of adult schizophrenia was 1.88 (95% CI 1.49-2.38) in NFBC 1986 compared to NFBC 1966, and when adjusted for sex, parental psychosis, mother’s education, place of residence, and paternal age, it remained significant with HR 1.73 (95% CI 1.35-2.23). Thus, changes in the studied factors did not influence changes in the incidence of schizophrenia and other psychoses between the two cohorts.

5.3 What are the mean schizotypy scores in men and women in the Northern Finland Birth Cohort 1966? (Research question 3)

In PAS, men had a mean score (SD) of 1.94 (2.87) and women had a mean score of 2.53 (3.25). In SAS, it was 10.97 (5.91) in men and 8.03 (4.70) in women. In PhAS, it was 17.85 (7.21) in men and 12.55 (5.78) in women (Supplementary Table 1 in Study III manuscript).

5.4 Early motor developmental milestones and schizophrenia (Research question 4)

Six eligible studies were identified (Table 8) and five early motor developmental milestones were studied in the meta-analysis:

- walking unsupported (5 studies)
- standing unsupported (4 studies)
- sitting unsupported (4 studies)
- holding head up (3 studies)
- grabbing object (3 studies)
Table 8. The summary of the studies on early motor developmental milestones and schizophrenia included in the systematic review and meta-analyses.

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Sample, Follow-up</th>
<th>Early motor developmental milestone (age 0 to 13 years)</th>
<th>Method of milestone assessment</th>
<th>Age at milestone assessment(s) and at data collection</th>
<th>Covariates</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannon et al. (2002b)</td>
<td>Dunedin Birth Cohort, New Zealand</td>
<td>1972-1973, 36 schizophreniform individuals, 642 healthy controls, 278 individuals with anxiety/depression, 20 individuals with mania followed until age of 26 years</td>
<td>Sitting up, Walking</td>
<td>mothers recall (only if certain) to the nearest month when their child attained milestones</td>
<td>Sex, Social class</td>
<td>Risk of schizophrenia when learned late: Walking unsupported</td>
</tr>
<tr>
<td>Clarke et al. (2011)</td>
<td>Helsinki Birth Cohort, Finland</td>
<td>1961-1969, 189 individuals with schizophrenia, 189 healthy controls followed until age of 31-39 years</td>
<td>Keeping head up, Turning over, Sitting unsupported, Standing with and without support, Walking with and without support</td>
<td>child health cards that have been in general use since 1962</td>
<td>Obstetric complications, Matched by sex and year of birth</td>
<td>Risks of schizophrenia when learned late: Sitting without support, Standing with and without support, Walking with and without support</td>
</tr>
<tr>
<td>Authors (year)</td>
<td>Sample, Follow-up</td>
<td>Early motor developmental milestone (age 0 to 13 years)</td>
<td>Method of milestone assessment</td>
<td>Age at milestone assessment(s) and at data collection</td>
<td>Covariates</td>
<td>Results</td>
</tr>
<tr>
<td>---------------</td>
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<td>------------------------------------------------------</td>
<td>--------------------------------</td>
<td>---------------------------------------------</td>
<td>------------</td>
<td>---------</td>
</tr>
<tr>
<td>Jones et al. (1994) 1946 British Cohort, United Kingdom</td>
<td>30 individuals with schizophrenia, 4,716 Controls followed until age of 43 years</td>
<td>Sitting, Standing, Walking without support</td>
<td>recalled by mothers retrospectively, nearest month at age 2 years</td>
<td>Sex, Social class</td>
<td>Cumulative effect of developmental delay: with every additional delayed milestone, the odds of developing schizophrenia increased by 20%</td>
<td></td>
</tr>
</tbody>
</table>
| Keskinen et al. (2015) & Isohanni et al. (2001)* 1966 Northern Finland Birth Cohort, Finland | 152 individuals with schizophrenia, 10,131 Controls followed until age of 46 | Keeping head up, Grabbing object, Turning from back to tummy, Touch thumb with index finger, Standing up | Child welfare records collected by nurses and doctors interviewing the parents and observing the children during infancy and early childhood during | Gender, Perinatal risk, Antenatal maternal depression, Family type, Social class | Risks of schizophrenia when learned late: Speech, Gross motor milestones. The greatest difference was for walking. Risk of schizophrenia when learned late: Standing and walking without support.
<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Sample, Follow-up</th>
<th>Early motor developmental milestone (age 0 to 13 years)</th>
<th>Method of milestone assessment</th>
<th>Age at milestone assessment(s) and at data collection</th>
<th>Covariates</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sørensen et al. (2010)</td>
<td>92 individuals with schizophrenia from Copenhagen Perinatal Cohort, Denmark</td>
<td>Standing, walking and sitting without support</td>
<td>regular visits to the clinics</td>
<td>obtained from mothers who were instructed to use a standard diary to recall age at which the milestone was reached prospectively, at age 1 year</td>
<td>Gender, Parental age, Parental social status, Breadwinner’s education, Single mother status, Parity</td>
<td>Risks of schizophrenia when learned late: Smiling</td>
</tr>
<tr>
<td>1959-1961 Copenhagen Perinatal Cohort, Denmark</td>
<td>691 individuals with other psychiatric disorder</td>
<td>Lifting head on stomach, Head holding when sitting, Grasping after things, Sitting without support, Rolling, Crawling, Crawling longer distance, Standing with/without support, Walking with/without support</td>
<td>obtained from mothers who were instructed to use a standard diary to recall age at which the milestone was reached prospectively, at age 1 year</td>
<td>obtained from mothers who were instructed to use a standard diary to recall age at which the milestone was reached prospectively, at age 1 year</td>
<td>Gender, Parental age, Parental social status, Breadwinner’s education, Single mother status, Parity</td>
<td>Risks of schizophrenia when learned late: Smiling</td>
</tr>
<tr>
<td>4,982 healthy cohort controls followed until age of 46-48 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*This study was excluded from the meta-analysis due to an overlap with a study in the same sample.*
Walking, sitting, and standing unsupported had a small effect size on adult schizophrenia \[ g=0.46, 95\% \text{ CI} (0.27-0.64), p<0.001; g=0.28, 95\% \text{ CI} (0.16-0.40), p<0.001; g=0.18, 95\% \text{ CI} (0.05-0.31), p=0.007 \]. Keeping head up and grabbing an object had a non-significant effect \[ g=0.10, 95\% \text{ CI} (-0.08-0.15) p=0.09; g=0.04, 95\% \text{ CI} (-0.08-0.15) p=0.55 \] (See Figure 2 in the original publication II). Heterogeneity was moderate and statistically non-significant for the walking unsupported milestone \( I^2=53.4\%; p=0.072 \), and it was not significant for the other four early motor developmental milestones.

The selected studies fulfilled the majority of the quality assessment criteria (on average 15 criteria), however, descriptive characteristics of participants were missing in two studies, and the characteristics of lost to follow up were missing in three of them (See Table 2 in the original publication II).

### 5.5 Early motor developmental milestones and schizotypy
(Research question 5)

In total, six (four in men and two in women) significant early motor developmental milestone-schizotypy associations were found in the analysis adjusted for covariates: parental psychosis, paternal and maternal age, urban/rural residence at birth, and father’s SES (Table 9).

In men:
- Delay in achievement of walking with support and touching thumb with index finger was associated with 0.01 (p=0.038) and 0.02 (p=0.014) increase in PAS score, respectively
- Delay in achievement of capability of standing up and sitting unsupported was associated with 0.32 (p=0.046) and 0.38 (p=0.046) increase in PhAS score, respectively

In women:
- Delay in achievement of turning from back to tummy was associated with 0.33 (p=0.014) increase in PhAS score and 0.05 (p=0.006) increase in SAS score, respectively.

In addition, an association between sitting unsupported and an increase in SAS score was found in women (p=0.036) but only in the unadjusted analysis.
Table 9. Linear regression analyses of nine early motor developmental milestones and schizotypal scales by gender at age of 31 years.

<table>
<thead>
<tr>
<th>PAS^a</th>
<th>Women</th>
<th>Univariate model</th>
<th>Multivariate model^1</th>
<th>Men</th>
<th>Univariate model</th>
<th>Multivariate model^1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>B^2</td>
<td>95 % CI</td>
<td>p-value</td>
<td>B^2</td>
<td>95 % CI</td>
</tr>
<tr>
<td>Walking unsupported</td>
<td>0.01</td>
<td>-0.00</td>
<td>0.238</td>
<td>0.01</td>
<td>-0.01</td>
<td>0.229</td>
</tr>
<tr>
<td>Standing unsupported</td>
<td>0.01</td>
<td>-0.00</td>
<td>0.129</td>
<td>0.01</td>
<td>-0.00</td>
<td>0.122</td>
</tr>
<tr>
<td>Walking with support</td>
<td>0.01</td>
<td>-0.00</td>
<td>0.259</td>
<td>0.01</td>
<td>-0.01</td>
<td>0.352</td>
</tr>
<tr>
<td>Capable of standing up (lifting themselves)</td>
<td>0.01</td>
<td>-0.00</td>
<td>0.104</td>
<td>0.01</td>
<td>-0.00</td>
<td>0.117</td>
</tr>
<tr>
<td>Touching thumb with index finger (like a tweezer)</td>
<td>0.01</td>
<td>-0.01</td>
<td>0.297</td>
<td>0.01</td>
<td>-0.01</td>
<td>0.382</td>
</tr>
<tr>
<td>Sitting unsupported</td>
<td>0.01</td>
<td>-0.00</td>
<td>0.136</td>
<td>0.01</td>
<td>-0.00</td>
<td>0.150</td>
</tr>
<tr>
<td>Turning from back to tummy</td>
<td>0.08</td>
<td>-0.00</td>
<td>0.079</td>
<td>0.01</td>
<td>-0.00</td>
<td>0.075</td>
</tr>
<tr>
<td>Activity</td>
<td>Women</td>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Univariate model</td>
<td>Multivariate model</td>
<td>Univariate model</td>
<td>Multivariate model</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B²</td>
<td>95 % CI</td>
<td>p-value</td>
<td>B²</td>
<td>95 % CI</td>
<td>p-value</td>
</tr>
<tr>
<td>Griping an object (grabbing object)</td>
<td>0.01</td>
<td>-0.02 - 0.03</td>
<td>0.595</td>
<td>0.01</td>
<td>-0.02 - 0.03</td>
<td>0.620</td>
</tr>
<tr>
<td>Holding head up</td>
<td>-0.01</td>
<td>-0.03 - 0.02</td>
<td>0.577</td>
<td>-0.01</td>
<td>-0.03 - 0.02</td>
<td>0.643</td>
</tr>
<tr>
<td>Walking unsupported</td>
<td>0.09</td>
<td>0.07 - 0.11</td>
<td>0.331</td>
<td>0.11</td>
<td>-0.06 - 0.198</td>
<td>0.26</td>
</tr>
<tr>
<td>Standing unsupported</td>
<td>0.08</td>
<td>0.10 - 0.12</td>
<td>0.387</td>
<td>0.12</td>
<td>-0.07 - 0.218</td>
<td>0.30</td>
</tr>
<tr>
<td>Walking with support</td>
<td>0.06</td>
<td>0.11 - 0.12</td>
<td>0.512</td>
<td>0.07</td>
<td>-0.09 - 0.383</td>
<td>0.32</td>
</tr>
<tr>
<td>Capable of standing up</td>
<td>0.08</td>
<td>0.16 - 0.15</td>
<td>0.582</td>
<td>0.09</td>
<td>-0.13 - 0.442</td>
<td>0.31</td>
</tr>
<tr>
<td>Sitting unsupported</td>
<td>0.19</td>
<td>0.08 - 0.16</td>
<td>0.166</td>
<td>0.18</td>
<td>-0.09 - 0.203</td>
<td>0.44</td>
</tr>
</tbody>
</table>

*PhAS*: N=933-2445, N=911-2373, N=729-1943, N=716-1890
<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th>Men</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate model</td>
<td>Multivariate model</td>
<td>Univariate model</td>
<td>Multivariate model</td>
</tr>
<tr>
<td></td>
<td>B²</td>
<td>95 % CI</td>
<td>p-value</td>
<td>B²</td>
</tr>
<tr>
<td>Turning from back to tummy</td>
<td>0.32</td>
<td>0.06 – 0.16</td>
<td>0.33</td>
<td>0.07 – 0.14</td>
</tr>
<tr>
<td>Gripping an object (grabbing object)</td>
<td>0.38</td>
<td>-0.06 – 0.09</td>
<td>0.38</td>
<td>-0.06 – 0.092</td>
</tr>
<tr>
<td>Holding head up</td>
<td>0.20</td>
<td>-0.19 – 0.318</td>
<td>0.23</td>
<td>-0.17 – 0.264</td>
</tr>
<tr>
<td>Walking unsupported</td>
<td>-0.00</td>
<td>-0.03 – 0.932</td>
<td>0.00</td>
<td>-0.03 – 0.945</td>
</tr>
<tr>
<td>Standing unsupported</td>
<td>0.01</td>
<td>-0.02 – 0.429</td>
<td>0.01</td>
<td>-0.02 – 0.493</td>
</tr>
<tr>
<td>Walking with support</td>
<td>0.01</td>
<td>-0.01 – 0.283</td>
<td>0.01</td>
<td>-0.01 – 0.303</td>
</tr>
<tr>
<td>Capable of standing up (lifting up)</td>
<td>0.01</td>
<td>-0.02 – 0.410</td>
<td>0.01</td>
<td>-0.02 – 0.444</td>
</tr>
<tr>
<td>Touching thumb (like a tweezer)</td>
<td>-0.02</td>
<td>-0.06 – 0.322</td>
<td>0.03</td>
<td>-0.07 – 0.191</td>
</tr>
</tbody>
</table>

SAS: N=930-2442  N=908-2370  N=727-1939  N=714-1886
<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate model</td>
<td>Multivariate model</td>
</tr>
<tr>
<td></td>
<td>$B^2$  95% CI p-value</td>
<td>$B^2$  95% CI p-value</td>
</tr>
<tr>
<td>Sitting</td>
<td>0.04 (0.004 – 0.036) 0.036</td>
<td>-0.00 (0.06 – 0.055)</td>
</tr>
<tr>
<td>unsupported</td>
<td>0.08 (0.07)</td>
<td>0.05 (0.09)</td>
</tr>
<tr>
<td>Turning</td>
<td>0.05 (0.02 – 0.106) 0.006</td>
<td>0.05 (0.02 – 0.006)</td>
</tr>
<tr>
<td>back to tummy</td>
<td>0.09 (0.09)</td>
<td>0.09 (0.09)</td>
</tr>
<tr>
<td>Gripping an object</td>
<td>0.02 (0.04 – 0.443) 0.03</td>
<td>-0.03 (0.376)</td>
</tr>
<tr>
<td>(grabbing object)</td>
<td>0.08 (0.08)</td>
<td>0.09 (0.09)</td>
</tr>
<tr>
<td>Holding head up</td>
<td>0.04 (0.02 – 0.166) 0.04</td>
<td>-0.01 (0.139)</td>
</tr>
<tr>
<td></td>
<td>0.10 (0.10)</td>
<td>0.10 (0.10)</td>
</tr>
</tbody>
</table>

1Adjusted for parental psychosis, paternal and maternal age, residence at birth, father’s SES; 2 B refers to the unstandardized regression coefficient derived from linear regression analyses; 3 95% Confidence Interval; a: Perceptual Aberration Scale (log-transformed); b: Physical Anhedonia Scale; c: Social Anhedonia Scale (square-root transformed)
Discussion

The aims of the present thesis were to contribute to knowledge on the incidence of schizophrenia and schizotypy and examine if there is an association with early motor development.

*Incidence of schizophrenia and other psychoses in NFBC 1966 and 1986*

Study I showed that there was a significant increase in the incidence of all psychoses, including schizophrenia, between the two cohorts from 1.01% in NFBC 1966 to 1.90% in NFBC 1986. The incidence of a major depressive episode with psychotic features and other nonorganic psychoses was also significantly higher in NFBC 1986. However, when measured separately, incidences of schizophrenia, schizophrenia spectrum, bipolar disorder with psychotic features, or brief psychosis did not differ between the cohorts.

The time trajectories in the incidence of schizophrenia in high-income countries were reported as being inconclusive, showing a decline, no change or increase (Warner 2004). Previously, the higher prevalence of schizophrenia was found in an isolated part of north-eastern Finland compared with other regions of Finland (Hovatta *et al.* 1997). Nevertheless, the regions included in the present study were located in two of the northernmost areas of Finland, and, in general, the incidence of psychosis cannot be explained entirely by the significant contribution of genetic predisposition.

The changes in the incidence of schizophrenia and other psychoses can be caused by changes in the diagnostic system and practices (Munk-Jørgensen 1986, Allardyce *et al.* 2000, Sorvanen *et al.* 2006). Within the cohorts’ follow-up period, the diagnostic system changed from ICD-8 via ICD-9 to ICD-10. The earlier diagnostic system had a narrower definition of schizophrenia and required a 6-month duration of symptoms. (Kuoppasalmi *et al.* 1989). In ICD-10, the required duration of symptoms is 1 month. Two earlier studies on diagnostic practices in NFBC 1966 showed that 43% and 48% schizophrenia cases were diagnosed as schizophreniform disorder and other psychosis, respectively (Isohanni *et al.* 1997, Moilanen *et al.* 2003). No such studies on diagnostic validity were conducted in NFBC 1986. In the present study, schizophreniform disorder was included in the narrow schizophrenia category.

The increase in the incidence rates in NFBC 1986 could be a result of health system changes and improved awareness about mental illness symptoms. In
Finland, during the period from 1997-2010, outpatient mental health visits increased from 1.6 million to 2.3 million (Pirkola & Sohlman 2005), and from 1991-2003, the admissions of adolescent patients with psychoses more than doubled (Salokangas et al. 2011). In the present study, a significant increase in a diagnosed major depressive episode with psychotic features was found. This can be explained, at least to some extent, by earlier help-seeking behaviour among adolescents, especially those with affective symptoms. Similarly, a Danish study exploring time trends in the incidence of first-time diagnosed bipolar and depressive disorders concluded that the increase could be related to earlier identification among adolescents and overall mental health awareness (Jensen et al. 2016).

Only parental psychosis was a significant predictor of schizophrenia in both cohorts. This was in line with previous findings on parental psychosis and schizophrenia (Rasic et al. 2013).

**Do the changes in potential risk factors influence the changes in incidence of schizophrenia and other psychoses between the two cohorts?**

The changes in potential risk factors’ distributions did not influence the difference in the incidence of schizophrenia and other psychoses between NFBC 1966 and NFBC 1986. The proportions of risk factors both decreased and increased between the two cohorts. For example, urban residence and higher mother’s education were more common in NFBC 1986. However, the quality of health care improved, and more infants with low birth weight should have survived. Some risk factors such as cannabis use were not collected in NFBC 1966, but no schizophrenia cases with cannabis use were observed in this cohort (Koskinen et al. 2010). NFBCs have a low prevalence of non-Finnish parents, thus, migration probably should not have strongly affected the incidence of schizophrenia and other psychoses.

**Mean scores for schizotypy scales in the NFBC 1966**

PAS, PhAS, and SAS were studied in NFBC 1966. The pooled mean PAS score of all studies was 4.70 for men and 4.98 for women (Figure 1), which is higher than the estimates in NFCB 1966 (1.94 and 2.53) (Figure 1).

The SAS mean scores in NFBC 1966 were higher than the pooled estimates of all studies for both men and women (10.97 vs 9.52 and 8.03 vs 4.70) (Figure 2).

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When PhAS mean scores were compared for men, they were higher than the pooled mean of all studies (17.85 vs 14.59), while for women, the scores were similar (12.55 and 11.91) (Figure 3).

The differences in mean estimates between the studies can be related to age and type of population included, as well as to the prevalence of some risk factors and cultural influences (Goulding et al. 2009). For instance, students and general population individuals of the same age may differ in intellectual abilities (Dawson et al. 2005). It should be noted that the estimates for schizotypy from some countries are either underrepresented or not available. Thus, conclusions about cultural differences cannot be drawn. However, in NFBC 1966, the positive schizotypy was the lowest compared to other studies, and physical anhedonia in men was the highest.

Early motor developmental milestones and schizophrenia: meta-analysis

The main result of the Study II was that three early motor developmental milestones (i.e. walking unsupported, sitting unsupported, and standing unsupported) predicted adult schizophrenia with a small, but significant effect size. This was also seen in the recent meta-analysis by Burton et al. (2015) with respect to the milestone of walking and familial risk of psychosis (g=0.44; p<0.01).

The quality of the included studies was good according to the assessment scale, but in some studies, descriptive characteristics of participants and lost to follow-up were missing. Thus, it was not possible to evaluate if the included populations were heterogeneous or not. Overall, few studies explored some of the early motor developmental milestones (e.g. grabbing an object or turning over), which identifies the need for further examination.

The achievement of early motor developmental milestones is an important step in child maturation that can influence the child’s social interaction (Campos et al. 2000, Clearfield 2011) and cognition (Khandaker et al. 2011, Dickson et al. 2012). It is reasonable that delays in early motor milestones development may predict adult schizophrenia, but findings from other studies show that they are also related to alcohol dependence (Manzardo et al. 2005) and a high level of neuroticism (Flensborg-Madsen et al. 2013).
Early motor developmental milestones and schizotypy

In Study III, five early motor developmental milestones were associated with adult schizotypy: turning from back to tummy, touching thumb with index finger, sitting unsupported, standing up, and walking with support. In general, a delay in a milestone predicted higher scores on PAS, SAS, and PhAS. The findings of the meta-analysis (Study II) confirmed the predictive value of early motor development milestones (walking, sitting, and standing unsupported) for adult schizophrenia, and, thus, it was hypothesized that milestones also can be used to predict schizotypal traits. The findings of Study III confirmed this hypothesis.

Gender differences were found in types of milestone-scale associations. However, it seems challenging to explain the neurobiological mechanism of these differences. For instance, why turning from back to tummy was associated with SAS in women and walking with support was associated with PAS in men. However, more delayed milestone-schizotypy associations were found among men than women. This suggests that men are more vulnerable to neurodevelopmental abnormalities. Previously, Castle & Murray (1991) proposed that men are predisposed to a neurodevelopmental type of schizophrenia, and women to a schizoaffective type. In addition, according to meta-analysis, women tend to have lower social and physical anhedonia (Miettunen & Jääskeläinen 2010). Thus, it can be that delays in early motor developmental milestones influence men and women’s personalities in a different way.

These findings add to an approach to schizotypy as a risk factor of schizophrenia and show that it has similar neurobiological origins. However, as mentioned before in previous section, early motor developmental milestones are not specific only to schizophrenia.

Schizophrenia continuum and role of early motor developmental milestones

An increase in incidence rates of all psychoses between two cohorts can be explained, at least to some extent, by diagnostic system changes and denotes these systems limitations. Recently, research domain criteria (RDoC) were suggested as an alternative to DSM classification. (Cuthbert 2014). These criteria are based on seven constructs (negative valence systems, positive valence systems, cognitive systems, systems for social processes, and arousal/modulatory systems) and units
of analysis that include genes, molecules, cells, circuits, physiology, behaviour, self-reports, and paradigms. However, RDoC should be considered as a framework for research purposes rather than a diagnostic system. In other words, RDoC supports approaches that examine mental illnesses as a continuous phenomenon. van Os et al. (2009) have underlined that schizophrenia is a multi-factorial disease, but there is no evidence that interacting risk factors have a threshold effect. Furthermore, schizophrenia and schizotypy have similar dimensions: negative and positive, which implies a continuum (Vollema & van den Bosch 1995). Lastly, according to van Os et al. (2009), similar risk factors and the small differences between prevalence and incidence rates of schizotypy support the notion of a schizophrenia continuum.

Evidence from epidemiological, developmental, and neuroimaging studies support the neurodevelopmental theories of schizophrenia (Owen et al. 2011). The evidence is, for example, increased frequency of obstetric complications, increased prenatal viral and bacterial infections in individuals with schizophrenia, changes in the expression of proteins that participate in the early migration of neurons and glia, and an enlargement of the cerebroventricular system (Fatemi & Folsom 2009). Therefore, the findings of Study II, which examined the role of early motor developmental milestones, are in line with the neurodevelopmental theory. Similarly, early motor developmental milestones are associated with schizotypy. Neurodevelopmental evidence also supports the notion of a schizophrenia continuum. Thus, the findings of the present project are an important addition to the theory linking schizotypy with schizophrenia.

5.6 Limitations

In Study I, the incidence rates could have been affected by changes in the diagnostic system and health care system. The sample included only treated and help-seeking cases, which could result in missing cases with milder manifestations. In addition, more available early risk factors could have been studied, for example, birth weight. However, some of the risk factors e.g. cannabis use or childhood adversities were not collected in NFBC 1966.

In Study II, the amount of studies was low (e.g. estimates of two studied milestones grabbing object and holding head up were calculated based only on three studies) and the included populations were not clearly described in all of studies. Milestones data is not intended to be used for research, thus it may affect the quality of its recording (e.g. some studies had to rely on the mother’s memory).
In meta-analyses, missing data can be related to reporting biases. On the other hand, publication bias results in non-existence if studies with negative results are not published. An attempt to estimate publication biases was made in Study II by using the funnel plot asymmetry test, Egger’s regression (Egger et al. 1997), and the trim and fill method. However, due to the low number of studies (<10) in the meta-analysis of the present thesis, these tests lacked power (Deeks et al. 2008).

In Study III, missing data in scales and on milestones, especially earlier ones, could have resulted in either the under- or over-estimation of the risk for schizotypy. For instance, there was more missing data on men. However, a previous study on schizotypy in NFBC 1966 conducted additional analyses and found that non-participation was unlikely to influence results (Miettunen et al. 2011). Data on the Magical Ideation Scale (Eckblad and Chapman 1983) that is commonly used to identify individuals at risk of psychosis were not available. There were some additional risk factors that it was not possible to include, for example, early neglect or reduced stimulation during infancy (Flensborg-Madsen et al. 2013). It was also mentioned previously that early motor development milestones predicted some other mental health deviations, which means a lack of specificity in the earlier identification of individuals at risk.

5.7 Strengths

This project utilizes the high quality data of NFBC 1966 and 1986 collected prospectively and linked with nationwide population registers with high validity. It had a long follow-up, and data on milestones was collected prospectively and based on frequent visits. In a systematic review and meta-analysis, several databases were included, which allowed an extensive literature search. In Study III, a large representative sample was available on schizotypal traits in the general population (NFBC 1966).
6 Conclusions

The higher incidence of all psychoses in NFBC 1986 than in NFBC 1966 may indicate a real increase in incidence rates or changes in diagnostic practices and earlier psychosis identification. In NFBC 1966, positive schizotypy was lower than in other studies, but negative schizotypy was higher. Early motor developmental milestones were associated with both schizophrenia and schizotypy. The findings suggest that men and women could be predisposed to different subtypes of schizotypy and schizophrenia. Overall, the findings of the present project contribute to knowledge of the neurodevelopmental origin of schizophrenia and the schizophrenia continuum.

6.1 Implications

Nowadays neurodevelopment theories and the psychosis continuum are the leading theories used to explain schizophrenia aetiology (Insel 2010). Therefore, the identification of risk factors is crucial for understanding the disease. On the other hand, earlier identification of psychosis has a positive impact on disease trajectory and the quality of life of individuals who suffer from the disease from late adolescence or early adulthood (McGorry et al. 2008). The results of the present project can be utilized to improve health care services for individuals at risk. Monitoring incidence rates is essential for understanding disease development, the identification of risk factors, and health care planning. Accurate assessment and documentation of schizotypy have a prognostic importance. Further, neurobiological markers i.e. early motor developmental milestones should be taken into consideration for earlier identification of individuals predisposed to a disease. Prevention strategies should be aimed at children with motor developmental delays and those who show both neurobiological and personality markers predisposed to psychosis. This can be implemented through increasing awareness and screening in day care or health centres and schools.

6.2 Remaining questions

Monitoring time trends of schizophrenia and other psychoses is beneficial for health care planning. However, monitoring time trends is methodologically challenging. Monitoring the risk factors that are specific to a current time-period is
needed, but some of the risk factors have not yet been identified. Time trends of other potential risk factors should be studied and compared between NFBC 1966 and 1986.

Despite that it was possible to estimate the effect sizes of five early motor developmental milestones in Study II, there is a lack of studies on some other early motor developmental milestones. Furthermore, the studied outcomes were heterogeneous and do not allow us to distinguish the effect of early motor developmental milestones on narrowly and broadly defined schizophrenia. Gender differences in types of milestones-schizotypy scales associations were found in Study III. However, the neurobiological mechanism of these differences is unclear. The identification of factors that contribute to specific subtypes of schizotypy, and thus the development of prevention strategies targeting subtypes of schizophrenia, still requires further investigation. Lastly, early motor developmental milestones are also associated with some other mental health impairments apart from schizophrenia, and probably with other health conditions. In addition, other potential risk factors of schizotypy should be explored. These should be considered as possible future research directions.
References


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Saha, S., Chant, D., & McGrath, J. (2007). A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time?. Archives of general psychiatry, 64(10), 1123-1131. doi:10.1001/archpsyc.64.10.1123


Appendix 1

Data collection by different registers for schizophrenia and other psychoses.
## Appendix 2

**Schizotypy scales used in the 31-year follow-up of the Northern Finland 1966 Birth Cohort.**

<table>
<thead>
<tr>
<th>Scale (abbreviation)</th>
<th>Number of items</th>
<th>Description of high scores</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perceptual Aberration Scale (PAS)</td>
<td>35</td>
<td>Distorted perception of own body and other objects</td>
<td>(Chapman et al., 1978)</td>
</tr>
<tr>
<td>Revised Physical Anhedonia Scale (PhAS)</td>
<td>61</td>
<td>Decreased ability to experience physical and sensory pleasures</td>
<td>(Chapman et al., 1976)</td>
</tr>
<tr>
<td>Revised Social Anhedonia Scale (SAS)</td>
<td>40</td>
<td>Exaggerated lack of interest in social interactions</td>
<td>(Chapman et al., 1976)</td>
</tr>
</tbody>
</table>
## Appendix 3

Chart used for recording the achievement times of the infant milestones in NFBC 1966.

<table>
<thead>
<tr>
<th>Developmental Milestone (months)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
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</thead>
<tbody>
<tr>
<td>walking without support</td>
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<tr>
<td>standing without support</td>
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<td>walking with support</td>
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<tr>
<td>capable to stand up (lift themselves up)</td>
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<tr>
<td>touch thumb with index finger (like a tweezers)</td>
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<td>sitting without support</td>
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<td>first tooth eruption</td>
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<tr>
<td>turning from back to tummy</td>
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<tr>
<td>make a grip on object (grab object)</td>
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<td>able to hold head up when you lift their arms</td>
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<td>making sounds</td>
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</table>

*Bold lines represent normal range of milestones’ achievement in months*
Appendix 4

Data collection for the review and meta-analysis of early motor developmental milestones and schizophrenia.
Original publications


Reprinted with permission from Elsevier and Cambridge University Press (I and II).

Original publications are not included in the electronic version of the dissertation.
1421. Lemma, Siria (2017) Migration and adhesion associated molecules in lymphoma biology and their potential roles as biomarkers


1423. Suuronen, Noora- Maria (2017) Cognitive and behavioral characteristics of frontotemporal lobar degeneration


1426. Karhu, Toni (2017) Isolation of novel ligands for MAS-related G protein-coupled receptors X1 and X2, and their effect on mast cell degranulation

1427. Mantere, Tuomo (2017) DNA damage response gene mutations and inherited susceptibility to breast cancer

1428. Salokorpi, Niina (2017) Treatment of craniosynostoses

1429. Männikkö, Niko (2017) Problematic gaming behavior among adolescents and young adults : relationship between gaming behavior and health


1431. Lavander, Päivi (2017) Nimikesuojattujen ja laillistettujen ammattihenkilöiden työnjako yliopistosairaalan muuttuvassa toimintaympäristössä


1435. Ramsay, Hugh (2017) Predictors of psychosis risk and neurocognitive deficits

1436. Kuitunen, Hanne (2017) DLBCL, primary and secondary central nervous system involvement, treatment and prophylaxis
Svetlana Filatova

INCIDENCE OF SCHIZOPHRENIA AND ASSOCIATIONS OF SCHIZOPHRENIA AND SCHIZOTYPY WITH EARLY MOTOR DEVELOPMENTAL MILESTONES

UNIVERSITY OF OULU GRADUATE SCHOOL; UNIVERSITY OF OULU, FACULTY OF MEDICINE