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# RISKS, CORRELATES, AND CONSEQUENCES OF THE EXTENDED PSYCHOSIS PHENOTYPE

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# Risks, correlates, and consequences of the extended psychosis phenotype

## THESIS FOR DOCTORAL DEGREE (Ph.D.)

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# ABSTRACT

Psychotic disorders such as schizophrenia entail substantial suffering for the affected individuals and their networks. Traditionally, these disorders come as diagnosable entities that you either have or have not. However, recent epidemiological research has shown that symptoms of psychotic disorder, i.e., psychotic experiences, are common in the general population, especially during adolescence, and that these experiences are correlated with the development of psychosis. Thus, the traditionally binary psychosis phenotype can be extended to also include psychotic experiences. Despite efforts, little is known about the causes, correlates and consequences of the "extended psychosis phenotype". Therefore, this thesis aimed to shed new light on these aspects of this broadly defined psychosis phenomenon.

In studies I and II, data from the Child and Adolescent Twin Study in Sweden (CATSS) were used to examine childhood neuropsychiatric problems (here language and mathematical problems, autistic traits, and general neuropsychiatric problems) as risk factors of adolescent psychotic experience (and juvenile mania symptoms). When possible, twin models were additionally used to disentangle the relative contributions of genetic and environmental influences in the observed associations. Results showed that childhood problems with communication, reading and mathematics, but not speech, predicted adolescent psychotic experiences. Further, it was found that the association between childhood autistic traits was explained by general neuropsychiatric problems. The twin models revealed that the same set of genes produce susceptibility for the studied childhood neuropsychiatric problems and adolescent psychotic experiences.

In study III, data from the National Patient Register was used to determine if Darier disease, a rare skin disease, would correlate with schizophrenia or bipolar disorder in the general population. The hypothesis was based on the shared common ectodermal origin of skin and brain. We found that individuals with Darier disease had a 2-fold elevated risk of being diagnosed with schizophrenia, and a 4-fold excess risk of being diagnosed with bipolar disorder, compared with matched comparison subjects.

In study IV, CATSS data was linked to the National Patient Register to examine consequences of adolescent psychotic experiences. Results revealed that adolescents reporting psychotic experiences had elevated risks of being diagnosed with alcohol or substance misuse, or suicide attempt.

In sum, we found that adolescent psychotic experiences are neurodevelopmental phenomena that share genetic etiological factors with childhood neuropsychiatric problems. Further, we demonstrated population associations between Darier disease and schizophrenia, and bipolar disorder. Lastly, we observed that adolescent psychotic experiences are associated with adverse consequences.

These results confirm the neurodevelopmental origin of the extended psychosis phenotype, including psychotic experiences, and highlight the need for cross-professional monitoring of adolescents reporting psychotic experiences.

# LIST OF SCIENTIFIC PAPERS

I. Cederlöf, M., Östberg, P., Pettersson, E., Anckarsäter, H., Gumpert, C., Lundström, S., & Lichtenstein, P. (2014). Language and mathematical problems as precursors of psychotic-like experiences and juvenile mania symptoms. *Psychological Medicine*, 44(06), 1293-1302.

II. Cederlöf, M., Pettersson, E., Sariaslan A., Larsson, H., Östberg, P., Kelleher, I., Långström, N., Hellner Gumpert, C., Lundström, S., & Lichtenstein, P. (2015). The association between childhood autistic traits and adolescent psychotic experiences is explained by general neuropsychiatric problems. *American Journal of Medical Genetics Part B,* DOI: 10.1002/ajmg.b.32386.

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IV. Cederlöf, M., Kuja-Halkola, R., Larsson, H., Sjölander, A., Östberg, P., Lundström, S., Anckarsäter, H., Kelleher, I., & Lichtenstein, P. (Manuscript). A longitudinal study of adolescent psychotic experiences and later drug use disorder and suicide attempt.

# RELATED SCIENTIFIC PAPERS NOT INCLUDED IN THESIS

V. Cederlöf, M., Gotby, A. O., Larsson, H., Serlachius, E., Boman, M., Långström, N., Landén, M., & Lichtenstein, P. (2014). Klinefelter syndrome and risk of psychosis, autism and ADHD. *Journal of Psychiatric Research*, 48(1), 128-130.

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XIII. Cederlöf, M., Larsson, H., Lichtenstein, P., Almqvist, C., Serlachius, E., Ludvigsson, J. (under review). Nationwide population-based cohort study of psychiatric disorders and suicidality in patients with Ehlers-Danlos syndrome and hypermobility syndrome, and their siblings.

# CONTENT

| List of abbreviations. | |
|---|---|
| ADHD | Attention-Deficit, Hyperactivity Disorder |
| ASD | Autism Spectrum Disorder |
| A-TAC | The Autism-Tics, AD/HD, and other Comorbidities inventory |
| APA | The American Psychiatric Association |
| CATSS | The Child and Adolescent Twin Study in Sweden |
| DSM | The Diagnostic and Statistical Manual of Mental Disorders |
| DZ | Dizygotic |
| GWAS | Genome-wide association studies |
| HR | Hazard ratio |
| ICD (8-10) | The International Classification of Diseases and related health problems |
| MGR | The Multi-Generation Register |
| MZ | Monozygotic |
| NPR | The National Patient Register |
| OR | Odds Ratio |
| RR | Risk Ratio |
| SAMS | The Small Area Marketing Statistics Register |
| STR | The Swedish Twin Register |
| TPR | The Total Population Register |
| WHO | World Health Organization |

# 1 BACKGROUND

## 1.1 A BRIEF INTRODUCTION TO RESEARCH INTO RISKS, CORRELATES AND CONSEQUENCES OF PSYCHOSIS

Hallucinations and delusions are probably as old as the human species, and have historically been regarded as intercessions from gods or demons (Kelleher, Jenner & Cannon, 2010). In modern times, however, such perceptual experiences have until recently generally been seen as signs of psychotic illness, but as discussed in subsequent sections of this thesis, findings from epidemiological studies have challenged our understanding of psychotic phenomena.

As the matter of fact, epidemiological research has played a central role in the history of psychosis research, and ever since the first psychosis researchers interviewed their patients about their developmental histories (e.g. Bleuler, 1911/1950), there has been an appreciation of the notion that the developmental trajectories of children who will develop a psychotic disorder as adults differ in important ways from children who will not develop a psychotic disorder. A number of small, but nevertheless interesting, studies followed-up and confirmed the initial observations made by Bleuler, including a number of papers from the pioneers Barbara Fish (e.g. Fish,1957) and Israel Kolvin (e.g. Kolvin et al., 1971).

Decades later, when the first large birth cohorts were established in England and New Zeeland, several prospective studies, where children were observed from early childhood into adulthood, provided robust evidence for a range of developmental deficits across domains of cognition, motor and social behavior in children who would develop schizophrenia as adults (Jones et al., 1994; Done et al., 1994; Cannon et al., 2002). Clearly, these large-scale prospective studies have contributed substantially to the understanding of the etiology of schizophrenia. This research field has recently started to explore risk factors of psychotic symptoms in the general population (i.e., psychotic experiences), an area that might provide additional clues to the etiology of schizophrenia and has

several advantages compared with research based on individuals with schizophrenia. For example, samples sizes are considerably larger, there is virtually no interference from psychotropic drugs, and secondary illness effects does not constitute a major problem (David, 2010; Rössler et al., 2011). Still, at the time of writing, only a couple of studies have used longitudinal data to examine risk factors of psychotic experiences in the general population.

Even though the so called "Kraepelinian dichotomy", that is, the division of psychotic and bipolar (affective) disorders, has been preserved in Western psychiatry for more than a century, several etiological and clinical elements are shared between schizophrenia and bipolar disorder, as evidenced by the invention of the intermediate category schizoaffective disorder (Murray et al., 2004; Craddock & Owen, 2010). However, despite the substantial genetic overlap between the disorders (Lichtenstein et al., 2009), epidemiological studies have also shown that several important differences are present, for example regarding neurodevelopment; children who will develop bipolar disorder as adults do not differ from children who will not, with regards to characteristics associated with schizophrenia development (Murray et al., 2004).

The co-occurrence of schizophrenia, or bipolar disorder, with other psychiatric disorders is relatively well studied (Buckley et al., 2009), and in addition, some physical disorders seem to occur more often in these disorders than what would be expected by chance. Such "comorbid" conditions can also be referred to as correlates. An increasingly popular extension of studies of correlates of schizophrenia is to also examine the occurrence of the "other" disorder in relatives to individuals with schizophrenia. By doing so, it is possible to elucidate if two disorder occur as a result of shared familial (including genetic) risk factors.

The consequences of psychosis is also a long-standing research area, and it is now well established that for example schizophrenia increases mortality and produces social ill health and deprivation. However, surprisingly little is known about consequences of adolescent psychotic experiences, even though studies have shown that they are associated with elevated risk of adult psychotic disorder (Poulton et al., 2000) and suicidal behavior (Kelleher et al., 2013a). Given the continuity between psychotic experiences and schizophrenia, it is conceivable that consequences of schizophrenia also apply to adolescent

psychotic experiences. This possibility has not been explored sufficiently to date, most probably due to a lack of longitudinal datasets with large enough sample sizes.

## 1.2 SCHIZOPHRENIA

Schizophrenia is a psychotic disorder that has been described as the worst disorder affecting mankind (Tandon et al., 2008), and it is arguably the most classic psychiatric disorder. This is because in contrast to most other psychiatric disorders, the features that define the disorder have remained essentially unchanged for more than a century (Heckers et al., 2013). Schizophrenia is a top ten cause of disease-related disability (World Health Organization, 2001) and affects about 0.7% of the population (Saha et al., 2005). The disorder is characterized by positive symptoms (e.g., hallucinations, delusions and disorganized thought/speech processes), negative symptoms (e.g., anhedonia and lack of activity), but also cognitive disturbances such as problems with attention, concentration and memory. The age of onset is usually in the early twenties, with a slightly later onset in women than in men (Häfner et al., 1992).

Schizophrenia was originally defined by Emil Kraepelin (1904, 1919), who conceptualized the disorder as an early onset and rapidly deteriorating form of dementia, which he labeled "dementia praecox". A few years later, the Swiss psychiatrist Eugen Bleuler (1911/1950) essentially validated Kraepelins observations and coined the term schizophrenia, as he did not agree with the concept of rapid deterioration from onset to dementia. Bleuler also added further details to diagnostics, by describing how certain cognitive and affective functions become distorted and/or disorganized in the disorder (McGlashan, 2011). As an example, he described the content of auditory hallucinations in the following way:

> "The voices not only speak to the patient, but they pass electricity through the body, beat him, paralyze him, take his thoughts away.."

In this description, one can extract perceptual ("The voices not only speak to the patient.."), emotional (.."beat him, paralyze him"), and cognitive ("..take his thoughts away..") components in the hallucinations. Bleuler's descriptions became very influential for the diagnostic criteria in the first version of the Diagnostic and Statistical Manual of Mental Disorders (DSM, APA 1952).

A couple of decades after the major contributions of Bleuler was published, Kurt Schneider paved the way for a schizophrenia definition that emphasized psychotic symptoms much more than did Kraepelin and Bleuler (Schneider, 1959). These symptoms, i.e., auditory hallucinations and delusions, have since then been referred to as "Schneiderian first-rank symptoms", and formed a central part of the diagnosis from the DSM-III to the present version (Moscowitz & Heim, 2011; APA, 2013).

The DSM-5 (APA, 2013), which puts less emphasis on the distinction between schizophrenia and other psychotic disorders than previous versions, define psychotic disorders through five domains of psychopathology: hallucinations, delusions, disorganized thought/speech, negative symptoms, and disorganized/abnormal motor behavior. In addition, gradients and dimension of psychosis have been introduced, with the ambition to capture more of the considerable variability regarding outcomes, social functioning, response to treatment, and symptom profile that characterizes psychotic disorders. In this context, the current definition of schizophrenia necessitates that it lasts for more than one month, is not secondary to some other disorder, involve at least two psychopathological domains, and that there is a decrease in the level of functioning below the level achieved before to the onset of the clinical disorder (Heckers et al., 2013). Even though this definition is indeed similar to earlier versions of the DSM, it apparently tries to capture the dimensional structure of psychosis, albeit within the frames of a traditional categorical system.

### 1.2.1 Etiology

Despite extensive efforts and long-standing research, the etiology of schizophrenia has remained an enigma for decades, and is still not very well understood. Familial factors, and especially genetic factors, have been strongly implicated; twin studies indicate a heritability of around 80% (Sullivan, Kendler and Neale, 2003) and the recurrence risk, i.e., the risk of schizophrenia in first-degree relatives to individuals with the disorder, is increased by a factor of ten (Lichtenstein et al., 2006).

Recently, a progress seldom seen in psychiatry research has been observed in the area of molecular genetic schizophrenia research: the most recent genome-wide association study (GWAS) from the Schizophrenia Working Group of the Psychiatric Genomic consortium (2014) has provided important clues into etiological processes of the disorder. In this study, 108 (about 130 in the latest unpublished data) biologically plausible locations in the genome (i.e., loci) were identified, out of which 83 had not been reported previously. Several identified risk loci included genes involved in glutamatergic transmission and synaptic plasticity, which is consistent with one of the leading pathophysiological theories of schizophrenia (Javitt, 2012). One of the other most influential theories, the dopamine hypothesis, which postulates that the disorder is closely related to an excess of dopamine-relation neuronal activity (Meltzer & Stahl, 1976) was also supported in the study, as an association probably implicating the dopamine $D_2$ receptor gene and schizophrenia was observed (O'Donovan, 2015). Further, epidemiological findings have suggested that dysregulation in the immune system is causally linked to schizophrenia (Benros, Mortensen & Eaton, 2012). This hypothesis, commonly referred to as the immunological hypothesis of schizophrenia, was also supported, as associations were enriched at enhancers that are active in tissues involved in immunological functioning. Finally, associations with schizophrenia were markedly enriched at brain-relevant enhancers, providing tentative support for a neurodevelopmental component in the etiology of schizophrenia, in keeping with the neurodevelopmental model of the disorder.

### 1.2.2 The neurodevelopmental model

A model of great heuristic importance for the etiology of schizophrenia is the neurodevelopmental model, which was formulated almost 30 years ago (Murray & Lewis, 1987; Weinberger, 1987). This model, today supported by evidence from several lines of research, posits that the frank disorder is the consequence of aberrant neurodevelopmental processes or events that occur well before the onset of the clinical disorder. Even though the temporality is essential in this model, the negative genetic and/or environmental "hits" and processes can occur anywhere from the time of conception to late adolescence. It should be noted that the concept of premorbid aberrations in schizophrenia date back to the days of Bleuler (1911/1950) and Kraepelin (1919), who used retrospective patient interview data to pinpoint the illness course from before the first prodromal symptoms, to the onset of the overt disorder.

Apparently, neurodevelopmental models vary substantially with regards to the timing and specificity of the genetic and environmental insults of interest, but the majority of research has focused on prenatal brain development (Rapoport et al., 2005).

### 1.2.3 Precursors

In keeping with the neurodevelopmental model, a plethora of studies have identified a wide range of neurodevelopmental problems and deviations in children who will later develop schizophrenia, compared with children who will develop other non-psychotic psychiatric disorders, or no psychiatric disorder at all. Starting with obstetric complications, it has been found that especially complications during pregnancy (e.g. diabetes), problems with fetal growth and status at delivery (e.g. low birth weight or small head circumference), and delivery complications (e.g. caesarian section or lack of oxygen) are related to an elevated risk of schizophrenia (Fish, 1992; Cannon, Jones & Murray, 2002; Rapoport et al., 2005). The causal nature of such complications in etiology of schizophrenia is usually assumed (Rapoport et al., 2005), but somewhat difficult to corroborate based on available data; there is always a possibility that the associations are due to a shared liability of both for example infections and psychiatric disorder.

A host of research implicates pan-domain neurodevelopmental disturbances in early childhood as important features in the developmental trajectories of psychosis. For example, Kolvin and colleagues (1971), and Crow et al. (1995) found that childhood (expressive) language and mathematical problems were important in the development of schizophrenia. Furthermore, in influential studies, childhood problems with motor behavior (Walker, Savoie & Davis, 1994; Erlenmeyer-Kimling et al., 2000 ) and receptive language (Cannon et al., 2002) were associated with adult psychotic disorder. In the same vein, two British and one Australian birth cohort studies (Jones et al., 1994; Done et al., 1994; Welham et al., 2010) have evidenced that delays in speech and/or motor development predict later psychosis. Pre-morbid developmental deficits have been documented also in other cognitive domains, as well as in social capabilities (Jones et al., 1994; Done et al., 1994, Olin & Mednick, 1996; Cannon et al., 2002).

A relatively recent study has presented data suggesting that a (relative) decline in verbal ability and other cognitive abilities during adolescence are associated with elevated risks of adult psychosis, but only in men (MacCabe et al., 2013). This novel and intriguing finding indicates that disturbance also in late neurodevelopment may be part of the trajectory to psychosis for some individuals, and is in line with the brain changes reported in adolescents who will later develop schizophrenia (Pantelis et al., 2003; Rapoport et al., 2005). Notably, the degree of the impairments described above is associated with earlier age of onset and severity of schizophrenia in a dose-response fashion (Rapoport et al., 2005), which indicates that these ongoing premorbid processes could be causally related to schizophrenia.

It is well established that adult schizophrenia more often than not is preceded by a childhood-onset psychiatric disorder. Premorbid psychopathologies are thus important precursors of schizophrenia, which was demonstrated in an elegant and influential paper by Julia Kim-Cohen (2003). She performed a follow-back analysis of a prospective cohort study, and found that 74% of individuals with schizophrenia had received a psychiatric diagnosis before age 18 and 50% before age 15. In her study, the commonest pre-psychotic disorders were conduct disorder and anxiety disorder. Further, many researchers have focused on the

earliest so-called "prodromal" phases of psychosis. In essence, the psychosis prodrome denotes a pre-psychotic disturbance representing deviations from previous experiences and behaviors (Yung & McGorry, 1996). According to Alison Yung and Patrick McGorry, two Australian pioneers in this research field, the psychosis prodrome is a highly significant condition, as it is:

> ".. potentially important for early diagnosis and management of psychotic disorders, early detection of relapse, prospective studies of high-risk individuals, and prognosis" (Yung & McGorry, 1996, p. 355).

The most commonly described signs and symptoms of prodromal psychosis are presented in Table 1.2.3, in alphabetical order.

**Table 1.2.3. Signs and symptoms of prodromal psychosis.**

| Symptoms | References |
|---|---|
| Anhedonia | Chapman, 1966; Docherty et al., 1978; Huber et al., 1980; Hambrecht et al.,1994; Addington et al., 2015. |
| Anxiety | Docherty et al., 1978; Subotnik & Neuchterlein, 1988; Häfner et al., 1992; Hambrecht et al., 1994; Meyer et al., 2005. |
| Apathy | Chapman, 1966; Docherty et al., 1978; Häfner et al., 1992; Hambrecht et al., 1994. |
| Concentration problems | Chapman, 1966; Huber et al., 1980; Heinrichs & Carpenter, 1985; Häfner et al., 1992; Hambrecht et al., 1994; Meyer et al., 2005; Aston et al., 2012; Addington et al., 2015. |
| Decreased general functioning | Bleuler,1911/1950; Kraepelin, 1919; Chapman, 1966; Huber et al., 1980; Häfner et al., 1992; Cornblatt et al., 2003. |
| Changes in sense of self or other people | Chapman, 1966; Stein, 1967; Huber et al., 1980; Häfner et al., 1992; Hambrecht et al., 1994. |

| | |
|---|---|
| Depression | Chapman, 1966; Huber et al., 1980; Birchwood et al., 1989; Hambrecht et al., 1994; Meyer et al., 2005; Aston et al., 2012. |
| Disruptive behaviors | Varsamis & Adamson, 1971; Heinrichs & Carpenter, 1985; Subotnik & Neuchterlein, 1988; Häfner et al., 1992; Meyer et al., 2005. |
| Guilt feelings | Subotnik & Neuchterlein, 1988; Häfner et al., 1992; Hambrecht et al., 1994. |
| Irritability | Bleuler, 1911/1950; Chapman, 1966; Docherty et al., 1978; Hambrecht et al. 1994; Aston et al., 2012. |
| Obsessive-compulsive symptoms | Bleuler, 1911/1950; Chapman, 1966; Docherty et al, 1978; Hambrecht et al., 1994; Meyer et al., 2005; Niendam et al., 2009. |
| Perceptual abnormalities | Chapman, 1966; Bowers, 1968; Varsamis & Adamson, 1971; Subotnik & Neuchterlein, 1988; Hambrecht et al., 1994; Schultze-Lutter et al., 2012; Addington et al., 2015. |
| Psychosomatic complaints | Bleuler, 1911/1950; Huber et al., 1980; Heinrichs & Carpenter, 1985; Häfner et al., 1992; Hambrecht et al., 1994; Meyer et al., 2005 |
| Sleep disturbance | Bowers, 1968; Huber et al.,1980; Heinrichs & Carpenter, 1985; Häfner et al., 1992; Hambrecht et al., 1994; Aston et al., 2012; Addington et al., 2015. |
| Social withdrawal | Chapman, 1966; Docherty et al., 1978; Birchwood et al., 1989; Häfner et al., 1992; Hambrecht et al., 1994; Cornblatt et al., 2003; Meyer et al., 2005; Aston et al., 2012; Addington et al., 2015. |
| Suspiciousness | Stein, 1967; Varsamis & Adamson, 1971; Subotnik & Neuchterlein 1988; Birchwood et al., 1989; Hambrecht et al., 1994; Schultze-Lutter et al., 2012; Addington et al., 2015. |

As presented in Table 1.2.3, the prodromal signs and symptoms are notoriously unspecific to psychosis. Yung & McGorry (1996, p. 361) have described that the typical pathway from these first prodromal phenomena to the first "frank" psychotic symptoms goes via a trajectory including attenuated psychotic symptoms, accompanied by changes in behavior. Several other possible trajectories have however been suggested, for example by James Chapman (1966), who believed that the initial prodromal phase consisted of "psychosis-specific" subjective cognitive symptoms, such as problems to attend to relevant information, and conversely, to filter out irrelevant information, which were then followed by apparent behavior changes (e.g. problems with motility and speech). Chapmans view was that these particular symptoms and signs occur well before any overt psychotic symptoms become evident.

### 1.2.4 Correlates

Research has clearly shown that individuals with schizophrenia have elevated rates of an extensive selection of adverse disorders and conditions, ranging from other psychiatric disorders and somatic disorders, to socio-economic deprivation (Wicks et al., 2005). Such co-occurring phenomena are usually referred to as correlates, although this term is most commonly used to describe cross-sectional data. Table 1.2.4 lists the most frequently reported correlates that are relevant for this thesis, namely psychiatric and somatic disorders, in alphabetical order.

**Table 1.2.4. Frequently reported correlates of schizophrenia.**

| Correlate | References |
|---|---|
| *Psychiatric disorders* | |
| Major affective disorders | McGlashan & Carpenter, 1976; Elk et al., 1986; Kendler et al., 1993. |
| Alcohol, and substance misuse | Strakowski et al., 1993; Kendler et al., 1993; Cassano et al., 1998. |

| | |
|---|---|
| Anxiety disorders | Boyd, 1986; Kendler et al., 1993; Cassano et al., 1998; Pokos & Castle, 2006. |
| Eating disorders | Ferguson & Damluji, 1988; Andrew & Harris, 1994; Cassano et al., 1998. |
| Intellectual disability | Penrose, 1938; Turner, 1989; Doody et al., 1998; Hemmings, 2006; Morgan et al., 2008. |
| Language disorders | DeLisi, 2001; Covington et al., 2005; Condray, Steinhauer & Goldstein, 1992; Condray, 2005. |
| Neuropsychiatric disorders | Takeuchi et al., 1986; Sverd, Montero & Gurevich, 1993; Ståhlberg et al., 2004; Larsson et al., 2013. |
| Obsessive-compulsive disorder | Boyd, 1986; Cassano et al., 1998, Tibbo & Warneke, 1999; Kayahan et al., 2005; Cederlöf et al., 2014. |
| Personality disorders | Mueser et al., 1997; Moran & Hodgins, 2004. |
| *Somatic disorders* | |
| Acute intermittent porphyria | Propping, 1983; Cederlöf et al., 2015. |
| Cardiovascular disease | Baldwin, 1979; Hennekens et al., 2005. |
| Chromosomal syndromes | Murphy, Jones & Owen, 1999; Basset & Chow, 2008; Cederlöf et al., 2014. |
| Metabolic syndrome | Ryan & Thakore, 2002; McEvoy et al., 2005; Saari et al., 2005, de Hert al., 2013. |

### 1.2.5 Consequences

Schizophrenia is a life-shortening disorder; the mortality is approximately doubled and individuals with schizophrenia are eight times more likely to die from traumatic injuries than individuals without the disorder (Allebeck et al., 1989). Furthermore, fitness is poor (Power et al., 2013), and it is well established that most individuals with schizophrenia experience a decline in social functioning already in the early stages of the disorder (Häfner et al., 1995). Moreover, many individuals with schizophrenia will develop an alcohol or substance misuse, even though these disorders may very well precede the onset of schizophrenia as well (Hambrecht & Häfner, 1996).

The global functioning problems in individuals with psychosis is evidenced by the finding that, at least in Sweden, informal caregivers spend on average 22.5 hours per week. Further, about 14% of their disposable incomes on activities related to care (Flyckt et al., 2011). About 5% of individuals with schizophrenia will eventually commit suicide (Palmer, Pankratz & Bostwick, 2005).

## 1.3 OTHER PSYCHOTIC DISORDERS

Outside of schizophrenia, there are several other forms of psychotic disorders in the DSM-5. If sorted by severity, the disorder regarded as second most severe after schizophrenia is schizoaffective disorder, because it also requires the presentation of multiple psychopathological domains.

Two psychotic disorders are by definition limited to a single domain of psychopathology, namely catatonia, which is no longer considered a subtype of schizophrenia (as it was in the DSM-IV), and delusional disorder. Further, the DSM-5 defines two psychotic disorders based on duration of the psychotic episode; schizophreniform disorder, which is clinically very similar to schizophrenia but lasts for less than six months, and brief psychotic disorder, which may last between two days and one month. More, even though schizotypal personality disorder is part of the spectrum of schizophrenia, it is considered to lie below the diagnostic threshold for a psychotic disorder.

The "attenuated psychotic syndrome" which have been discussed extensively in the literature (e.g. Woods et al., 2010; Carpenter & van Os, 2014), apparently requires more research before it can be included in the main text as a new diagnosis in the DSM.

## 1.4 BIPOLAR DISORDER

The entity of bipolar disorder, originally called "circular madness", was developed year 1851 by Falret (Angst & Sellaro, 2000), and the term "bipolar" was used first in 1957 (Philips & Kupfer, 2013). The lifetime prevalence of the most typical form of the disorder, i.e., type 1, is about 0.6% (Merikangas et al., 2011). Due to its relatively early onset and the degree of chronicity, bipolar disorder is responsible for the loss of more disability-adjusted life years than for example all forms of cancer (WHO, 2002). The disorder is characterized by episodes of mania or hypomania, and depression, and it is currently divided into four main subtypes; type 1, which is characterized by severe depressive episodes and true manic episodes that may present with psychotic psychopathology and often require inpatient care; type 2, which is less severe than type 1 in all aspects, and very rarely include psychotic features; cyclothymic disorder, which is characterized by many hypomanic episodes and subclinical depressive symptoms, and lastly, bipolar disorder not otherwise specified, which include hypomania-like symptoms and depressive symptoms which do not meet diagnostic criteria for either hypomania or depression (Goodwin & Jamison, 2007; Phillip & Kupfer, 2013). Hence, bipolar disorder is apparently a broad and heterogeneous diagnostic construct.

### 1.4.1 Etiology and risk factors

Twin studies, adoption studies, and family studies consistently report results in congruence with a strong genetic influence in the etiology of bipolar disorder. In a recent large family study based on Swedish nation-wide registers, the heritability was estimated to 58% (Song et al., 2014), which for some unknown reason is lower than the estimate of 85% generated from twin studies (Bienvenu, Davydow & Kendler, 2011). The reminder of the etiological influences in bipolar disorder is not well known, and there are very few established non-genetic risk factors, but Mortensen et al. (2003) have reported that early maternal loss increase the risk of later bipolar disorder, although possibly representing a

"genetically influenced" environmental risk. Other factors, such as traumatic brain injury and various stressful life events, have been suggested as risk factors, but available data is inconclusive and more research is clearly needed (Tsuchiya et al., 2003).

In contrast to schizophrenia, very few studies have demonstrated premorbid neurodevelopmental aberrations in bipolar disorder, rather, some research indicates that adolescents with excellent school grades have elevated risks of later bipolar disorder, after adjusting for the potential effects of socioeconomic status and parental education (Maccabe et al., 2010). This finding is possibly restricted to males, although the interaction term between school grades and sex was not statistically significant in the study by MacCabe and colleagues.

### 1.4.2 Correlates

Just like in schizophrenia and most other psychiatric disorders, co-occurrence with other psychiatric disorder is the rule rather than the exception in bipolar disorder, even though the literature seem to be more limited than for schizophrenia. Some of the most commonly described psychiatric and somatic correlates are listed in table 1.4.2.

**Table 1.4.2. Frequently reported correlates of bipolar disorder.**

| Correlate | Reference |
|---|---|
| *Psychiatric disorders* | |
| Alcohol, and substance misuse | Cassano et al., 1998; McElroy et al., 2001; Merikangas et al., 2011; Song et al., 2014; Baethge et al., 2014; Simhandl et al., 2015. |
| Anxiety disorders | Cassano et al., 1998; McElroy et al., 2001; Merikangas et al., 2011; Song et al., 2014; O'Garro-Moore et al., 2015. |

| | |
|---|---|
| Eating disorders | McElroy et al., 2001; Krishna & Ranga, 2005; Lunde et al., 2009. |
| Obsessive-compulsive disorder | Kruger et al., 1995; Cassano et al., 1998; Angst et al., 2005; Merikangas et al., 2011; Cederlöf et al., 2014. |
| Neuropsychiatric disorder (e.g. ADHD) | Ståhlberg et al., 2004; Krishna & Ranga, 2005; Merikangas et al., 2011; Larsson et al., 2013; Song et al., 2014. |
| Personality disorders | George et al., 2003; Krishna & Ranga, 2005; Song et al., 2014. |
| Psychotic disorders | Taylor, 1992; Laursen et al., 2009; Song et al., 2014. |
| *Somatic disorders* | |
| Cardiovascular disease | Baldwin, 1979; Goldstein et al., 2009; Westman et al., 2013. |
| Darier disease | Craddock et al., 1994; Jones et al., 2001 |
| Multiple sclerosis | Joffe et al., 1987; Krishna & Ranga, 2005; Carta et al., 2015. |

The correlation between bipolar disorder and Darier disease is of particular interest for this thesis and will therefore be described in more detail in subsequent sections.

#### 1.4.2.1 *Darier disease*

Darier disease (sometimes referred to as keratosis follicularis, dyskeratosis follicularis, or Darier-White disease) was first described by James C. White and Jean Darier in 1889 (White, 1889; Darier, 1889). It is a rare, autosomal dominantly inherited skin disorder caused by mutations within the ATPase, Ca++ transporting, cardiac muscle, slow twitch (ATP2A2) gene, which encodes a sarcoplasmic/endoplasmic reticulum calcium pump (SERCA2). SERCA2 apparently plays key role for intracellular calcium signaling processes (Sakuntabhai et al., 1999).

The estimated prevalence of Darier disease ranges from 1 in 100,000 individuals in Scandinavia, to 1 in 36,000 in north-east England (Burge, 1994). The onset of Darier disease is usually between ages ten and 20 years, but may occur as early as age six and as late as age 60 (Burge & Wilkinson, 1992). The disorder is characterized by multiple focal keratotic papules, mainly on the scalp and other seborrheic regions, nail changes and palmo-plantar pits, but the phenotype is highly variable, even though the penetrance is very high (Munro, 1992). Other symptoms include itch, pain, and malodor, which patients report as a particularly socially disabling and distressing problem. Heat, sweat, and for some patients, sunlight, exacerbates the disorder. Only about a third of individuals with Darier disease experience improvement with age (Burge & Wilkinson, 1992).

The neuropsychiatric profile of Darier disease has received interest in the literature; in the earliest studies, several descriptions of mental problems reminiscent of intellectual disability crop up (Svendsen & Albrektsen, 1959; Getzler & Flint, 1966), and epilepsy seem to be overrepresented in the disorder (Burge, 1992). Psychotic episodes and schizophrenia-like syndromes have also been reported in a few cases (Medansky & Woloshin, 1961; Getzler & Flint, 1966; Hellwig, Hesslinger & Waiden, 1996).

About three decades after the first study in this field, researchers reported that Darier disease was exacerbated by lithium carbonate, the most classic psychotropic drug used for treatment of bipolar disorder (Clark, Hammer & Patterson, 1986; Milton et al., 1990). Subsequently, in an influential study, Craddock and colleagues (1994) found that Darier disease cosegregated perfectly with major affective disorder in an Irish family, meaning that all family members

with Darier disease also had a bipolar or depressive disorder, whereas none of the family members without Darier disease had bipolar disorder or major depressive disorder. This finding was later replicated in yet another Irish pedigree (Jones et al., 2001).

There are at least three apparent possible explanations of the mechanism underlying the association between Darier disease and bipolar disorder (and schizophrenia). First, there is a possibility there is no true association between the disorders. This seems highly unlikely, however, given the numerous case reports suggesting otherwise, and the perfect cosegregation with major affective disorder.

The seconds explanation can be described as follows; there is an association between Darier disease and bipolar disorder/schizophrenia in the general population. Theories surrounding this explanation posits that such an association could (hypothetically) occur either due to pleiotropic effects in the ATP2A2 gene, i.e., that mutations in this particular gene increase the risk of both Darier disease and psychiatric disorder, or because the ATP2A2 is in "linkage disequilibrium" with some susceptibility gene for affective disorder, meaning that ATP2A2 is located very near the "true" susceptibility gene that produces liability to psychiatric disorder, and that these two genes are consequently inherited together. Supporters of the theory of pleiotropic effect have argued that because skin and brain tissues are both derived from the ectoderm, it can be hypothesized that a population association with psychiatric disorder is the result of a defect in cell adhesion expressed both in the skin and brain. This intriguing yet biologically plausible hypothesis was first proposed by Medansky & Woloshin (1961).

Third, there is the possibility that social disability associated with Darier disease provoke "reactive" psychiatric illness in some patients, even though this seems unlikely, as Darier patients themselves do not attribute their psychiatric disorder to their skin disorder, and because the temporal order between disorder skin disorder and mental disorder is uncertain (Craddock et al., 1994).

### 1.4.3 Consequences

The course of illness remains unfavorable for many individuals with bipolar disorder (Merikangas et al., 2011; Keck et al., 2014). Misuse of alcohol as well as illicit drugs is highly overrepresented (Strakowski et al., 2000), and as many as 10% will eventually die from suicide (Goodwin & Jamison, 2007). Early age at onset of is associated with more comorbidity, more recurrences, and poor outcome (Perlis et al., 2004).

### 1.4.4 Juvenile mania

The disorder previously referred to as juvenile mania (Leibenluft et al., 2003) or pediatric bipolar disorder, is at the time of writing termed "disruptive mood dysregulation disorder" (DSM, 2013). Disruptive mood dysregulation disorder is one of few new diagnoses in the DSM-5, but the diagnosis clearly stems from prior descriptions juvenile mania and pediatric bipolar disorder (Pavuluri et al. 2005), and was introduced as symptoms of mania/bipolar disorder in children are not regarded as sufficiently episodic to be defined as a bipolar disorder. (www.dsm5.org). The term juvenile mania will however be used from here on and throughout this thesis. The diagnostic criteria include irritability and frequent temper tantrums combined with persistent negative mood between these tantrums, and symptoms must have an onset before age ten, be present in multiple settings for at least one year, and should not be present before age six. The prevalence in the general population have been estimated to between 0.8% to 3.3% (Copeland et al., 2013; Pavuluri et al., 2005), and around 6% in clinical samples (Leibenluft & Rich, 2008).

#### 1.4.4.1 *Risk factors, correlates, and consequences*

The etiology of juvenile mania is not well understood. Heritability estimates are lacking, but family studies suggest a genetic component, as it has been found that early-onset mania has a greater familial loading of adult-onset bipolar disorder (Neuman et al., 1997; Pavuluri et al., 2005).

Only a few studies have examined longitudinal risk factors of juvenile mania or symptoms thereof. Whereas adult onset bipolar disorder is not, juvenile mania seems to be characterized by some developmental deficits, but the evidence is inconclusive; van Os et al (1997) and Sigurdsson et al., (1999) both reported

premorbid speech problems, whereas findings of Kutcher et al. (1998) indicate a perfectly normal premorbid functioning on language-related tasks. The origins of this discrepancy is difficult to assess, but may be related to the heterogeneity of individuals diagnosed with the disorder.

Juvenile mania is highly comorbid with virtually any psychiatric disorder, especially depressive disorder, oppositional defiant disorder, anxiety disorder, conduct disorder and ADHD, but also substance misuse, psychotic disorder, language disorder, and antisocial personality disorder appear (Geller & Luby, 1997; Biederman et al., 2005; Leibenluft & Rich, 2008; Copeland et al., 2013).

Children with juvenile mania have excess risks of several adverse health outcomes, such as severely impaired psychosocial functioning (Biederman et al., 2005), self-reported general poor health, sexually transmitted diseases, slow illness recovery, and tobacco use, but also criminal behaviors, police contacts, poverty, and poor educational attainment (Copeland et al., 2014).

## 1.5 PSYCHOTIC EXPERIENCES

There is a long-standing notion that psychotic phenomena exist in individuals with clinical presentations lying well below diagnostic thresholds (Kretschmer, 1925; Meehl, 1962), and below prodromal psychosis (van Os et al., 2009). Such sub-/non-clinical psychotic symptoms are commonly referred to as psychotic experiences, but have also been called "psychotic-like experiences", "psychosis-like experiences, "psychosis proneness", "at-risk mental state", or in the earlier and more personality-based literature, "schizotypy". Moreover, the influential American psychologist and psychometrician Paul Meehl used the term "schizotaxia" (Meehl, 1962).

During the past decade, it has been demonstrated that these psychotic phenomena, who were once thought to be "the preserve of the asylum and classical psychiatry" (Murray & Jones, 2012, p.4), are common among adolescents in the general population: a meta-analysis have shown that psychotic experiences are reported by 7.5% of adolescents aged 13-18 years, and by 17% of adolescents aged 9-12 years (Kelleher et al., 2012a). As an anecdote, it is worth mentioning that these findings were initially regarded as incidental and

unexpected "byproducts" of epidemiological surveys targeting common psychiatric disorders such as depression (e.g. Kendler et al., 1996).

Just as symptoms of clinical psychosis, psychotic experiences comprise auditory and visual hallucinations and delusions, but in contrast to frank disorder, psychotic experiences are most often accompanied with intact reality testing (Kelleher et al. 2013a). Most psychotic experiences seem to be transient, and persistent experiences have been proposed to be more clinically worrisome (van Os et al., 2009). In the same vein, the clinicopathological significance of psychotic experiences, i.e., the extent to which psychotic experiences are associated with psychopathology, increases with age during adolescence. (Kelleher et al., 2012b).

### 1.5.1 Psychotic experiences in relation to a psychosis continuum, and an extended psychosis phenotype

In the early and mid-stages of psychotic experiences research, these phenomena were thought to lie on a "psychosis continuum" (e.g. van Os et al., 2000; Verdoux & van Os, 2002). Actually, this idea was formulated first by Ernst Kretschmer, who postulated that "endogenous psychoses are nothing other than marked accentuations of normal types of temperament" (Kretschmer 1925, p.118). In this dimensional model, normality is apparently the reference point and psychotic experiences occur both in normality and in clinical psychosis. Thus, as put by the Dutch psychiatrist and researcher Jim van Os:

> "Psychiatric morbidity in a population may be seen as a function of the degree to which the distribution of a continuous phenotype, measurable in both healthy and ill individuals, is shifted towards higher values" (van Os et al., 2009, p.179)".

The validity of the psychosis continuum model is supported by for example the following observations:

- ♣ There is a similar pattern of psychiatric comorbidity shared between individuals with psychotic experiences and individuals with schizophrenia (van Os et al., 2009).
- ♣ There is a clear overlap in non-genetic risk factors of psychotic experiences and schizophrenia (van Os et al., 2009; Kelleher & Cannon, 2011).
- ♣ Psychotic experiences and schizophrenia are characterized by similar neurodevelopmental risk factors (Kelleher & Cannon, 2011).
- ♣ The rates of psychotic experiences have been found to predict the rates of clinical schizophrenia in a Dutch population (van Os et al., 2001; van Os et al., 2009).
- ♣ Psychotic experiences in childhood predict psychotic disorders in adolescence (e.g. Poulton et al., 2000).

The psychosis continuum model became popular very quickly, most probably due to its moral appeal, its convergence with the orientation of modern psychiatric (and other health care) services, and because it reflects common clinical diagnostic uncertainties (David, 2010). However, Anthony David (2010) presented critique against the model, by noting that for example the distressing and hostile hallucinations that are typical for schizophrenia actually seem to never occur in general population individuals reporting psychotic experiences. Further, David (2010, p. 1940) argued that:

> "..seeing psychotic phenomena as a point on a continuum with 'normal' experience is a useful heuristic with many positive benefits. However, like viewing a Necker cube, we can also consider the same phenomena with an eye on discontinuities and these may also provide points of theoretical growth. We should use methods and statistics that, rather than inevitably leading to continua (most psychometric methods in psychology and especially composite 'severity scales'), may also uncover potential categories".

The paper by David elicited an immediate response from Nick Kaymaz and Jim van Os (2010), who first argued that there is ample evidence for a psychometric psychosis continuum, but also for a latent categorical structure in the population, underlying this continuum. What they meant was that regardless of whether a continuum exist, the population may still be divided into two kinds of people; those with psychotic experiences and associated impairment and need for care, and those with psychotic experiences without these characteristics. Further, as the word "continuum" implies some specific theory, they suggested to instead refer to an extended psychosis phenotype.

Even though several lines of evidence indicate that psychotic experiences are indeed part of an extended psychotic phenotype, it is also getting increasingly obvious that these phenomena probably are at least as correlated with other concurrent and future psychiatric disorders, such as anxiety disorders and depression, as with psychotic disorders.

This notion has been elegantly formulated by Murray & Jones (2012, p. 5):

> "It appears that during adolescent development, a substantial minority of young people will have mild psychotic experiences just as they have individual symptoms of depression and anxiety from time to time. For most, these psychotic experiences will be transitory or, at worst, persist in a trait measured as schizotypy that will never deteriorate. Yet for a proportion of these individuals, the presence of psychotic and other symptoms heralds either concomitant or later psychiatric illness. Some adolescents and young adults manifest an eruption of mixed affective, psychotic and behavioural phenomena from which more specific blends of psychopathologies may emerge, some eventually crystalising syndromes familiar from the DSM and ICD."

Much remains to be learned about psychotic experiences in adolescence, but it is clear that they no longer can be viewed as *specific* predictors of later psychotic illness. Hence, psychotic experiences do not represent "schizophrenia light", but may rather be driven by the severity of the concurrent non-psychotic symptoms, including affective symptoms (van Os, 2014).

### 1.5.2 Etiology and risk factors

According to published data, genetic factors account for about 40 % of the liability to psychotic experiences (Polanczyk et al., 2010). In addition to this moderate genetic component, longitudinal studies have identified a vast array of risk factors. These longitudinal risk factors, i.e., processes or events that occur well before psychotic experiences, are outlined in alphabetical order in Table 1.5.2. It should, however, be noted that the genetic and environmental contributions to the associations between these risk factors and later psychotic experiences rarely have been studied.

**Table 1.5.2. Longitudinal risk factors of psychotic experiences.**

| Risk factor | Reference |
|---|---|
| Atopic disorder | Khandaker et al., 2014b. |
| Autistic traits | Jones et al., 2012; Happé, 2012; Sullivan et al., 2014 |
| Cannabis use | van Os et al., 2002; Henquet et al., 2004; Wiles et al., 2006; Harley et al., 2010; Kounali et al., 2014. |
| Epstein-Barr infection | Khandaker et al., 2014c. |
| Externalizing behavior problems | Polanczyk et al., 2010; Kounali et al., 2014. |
| Family history of psychiatric disorder | Polanczyk et al., 2010. |
| Harmful drinking or tobacco use | Wiles et al., 2006. |
| Internalizing behavior problems | Wiles et al., 2006; Polanczyk et al., 2010; Kounali et al., 2014. |
| Lower IQ | Cannon et al., 2002; Horwood et al., 2008. |

| | |
|---|---|
| Maternal infection or obstetric complications | Zammit et al., 2009 |
| Motor problems | Kounali et al., 2014 |
| Night mares and terrors | Fisher et al., 2014; Thompson et al., 2015 . |
| Physical maltreatment, or negative parenting | Janssen et al., 2004; Kelleher et al., 2008; Polanczyk et al., 2010; Arseneault et al., 2014. |
| Peer victimization | Schreier et al., 2009; Harley et al., 2010; Kelleher et al., 2013b; Wolke et al., 2014; Arseneault et al., 2014; Kounali et al., 2014. |
| Small for gestational age | Polanczyk et al., 2010 |
| Speech, language, and mathematical problems | Hameed et al., 2013; Khandaker et al., 2014a. |

Of particular interest for this thesis are the effects of childhood autistic traits, speech and language problems specifically, and neuropsychiatric problems in general. Therefore, these problems will be described briefly in the subsequent sections.

#### 1.5.2.1 *Language and mathematical problems*

A disorder of language or mathematics denotes an "unexpected difficulty in one aspect of development that cannot readily be explained by such factors as low intelligence or sensorimotor impairment" (Pennington & Bishop, 2009, p.284). In study I, the not yet validated definitions of language and mathematical disorders are based on individual items from a parental screening interview. These definitions have uncertain clinical properties and therefore, the terms language and mathematical problems will used throughout the thesis.

Language problems may affect different levels and aspects of language, e.g. receptive language, syntax, semantics or pragmatics. Speech problems refer to difficulties with the production of speech sounds that has a negative impact on intelligibility, and reading problems involves difficulties with learning to read.

Even though these problems are described as separate entities in diagnostic systems, comorbidity between these three types of problems are very common (Pennington & Bishop, 2009). Disorders of language and reading are prevalent in ca 3-10% of children and can have a serious impact on educational and psychosocial outcomes (Bishop & Snowling, 2004), but also behavioral outcomes such as hyperactivity and aggression (Beitchman et al., 1996), and psychiatric outcomes such as anxiety disorders (Beitchman et al, 2001). Symptoms of these disorders (i.e., problems with speech, language and reading) are even more prevalent (Hansson et al., 2005), but may still index risk of the development of clinical neuropsychiatric disorders and other adverse outcomes (Miniscalco et al., 2006).

A clinical disorder of mathematics is often referred to as dyscalculia, although the literature is full of various terms, and has a prevalence of about 5-7% (Butterworth, Varma & Laurillard, 2011; Gross-Tsur, Manor & Shalev, 1996). Dyscalculia denotes severe difficulties with learning arithmetical skills, despite normal intelligence (Landerl, Bevan & Butterworth, 2004). As one would expect, the co-occurrence with other developmental disorders, such as dyslexia and ADHD, is considerable (Gross-Tsur, Manor & Shalev, 1996). Again, our definition of mathematical problems is not validated and relied on a single item, so the term mathematical problems will be used throughout this thesis. Longitudinal data is scarce, but mathematical problems seem to persist into adulthood (Shalev, Manor & Gross-Tsur, 2005).

Using prospectively collected data from the ALSPAC birth cohort, Hameed and colleagues (2012) found that individuals reporting psychotic experiences in early adolescence were more likely to have had childhood deficits in reading and writing skills, such as spelling and non-word reading. These effects withstood after adjustment for socio-demographic variables. In the same vein, another ALSPAC cohort study (Khandaker et al., 2014) found that a composite score of

five childhood neurodevelopmental problems (dyslexia, dyspraxia, dysgraphia, dysorthographia, and dyscalculia) predicted adolescent psychotic experiences.

#### 1.5.2.2 *Autistic traits*

The classification of autism spectrum disorder (ASD) relies on deficits in reciprocal social behavior, communication problems, and repetitive behaviors. Epidemiological, clinical and family studies have consistently suggested that symptoms of autism spectrum disorder, i.e., autistic traits, are dimensionally represented in the population (Constantino & Todd, 2000; Piven et al., 1997). Hence, the question whether ASD and autistic traits are different manifestations of the same underlying susceptibility or whether they have different etiologies has been raised by Lundström and colleagues (2012). They used data from the Child and Adolescent Twin Study in Sweden (CATSS) and found that cutoffs for ASD correlated strongly with the full variation of autistic traits, signifying an etiological link between categorical extreme-ends measures, and continuous measures of autistic phenomena. Further, through the use of twin modeling, the authors discerned that this correlation was predominantly explained by shared genetic influences. Similar results have been reported in other twin cohorts (Robinson et al., 2011).

Again based on data from the ALSPAC cohort, three studies have demonstrated prospective associations between both parent-reported autistic traits and autism spectrum disorder in childhood on one hand and psychotic experiences in adolescence on the other (Jones et al., 2012; Sullivan et al., 2013; Happé, 2012). Jones and colleagues (2012) and Happé (2012) presented the first evidence of associations between autistic traits in general, and in particular speech problems, odd rituals and unusual habits, and psychotic experiences at age 12. Children whose mothers expressed concern over odd rituals at age 7-8 years had the most pronounced risks of later psychotic experiences. In another study it was found that children with autism spectrum disorder were three times more likely to have psychotic experiences at age 12 compared with children without autism spectrum disorder (Sullivan et al., 2013).

#### 1.5.2.3 *General neuropsychiatric problems*

Fairly recently, Pettersson and colleagues (2013) conducted a genetic factor analysis based on data from CATSS and demonstrated that one general (genetic) factor accounted for a substantial proportion (34%) of the covariation among 53 symptoms of ASD, ADHD, tic disorder and learning disorder. In other words, this means that a general neuropsychiatric problems factor was responsible for the considerable phenotypic overlap between symptoms of neuropsychiatric disorders. Subsequently, it was found that this general neuropsychiatric factor was a better predictor of bully victimization than specific neuropsychiatric disorders, such as ADHD or autism spectrum disorder (Törn et al., 2015).

### 1.5.3 Correlates

Psychotic experiences may co-occur with virtually any adverse condition, characteristic or event, such as stress, alcohol dependence, poor educational qualifications (Johns et al., 2004), unemployment and relational problems (Scott et al., 2006; McGrath et al., 2015), low self-esteem and low optimism (Dolphin, Dooley & Fitzgerald, 2015), multi-morbid psychopathology, poor socio-occupational functioning (Kelleher et al., 2014), low household income level (McGrath et al., 2015), and cognitive and motor deficits (Blanchard et al., 2010).

### 1.5.4 Consequences

A few studies have examined consequences of psychotic experiences. The by far most studied consequence is suicidal behavior and several studies have shown that psychotic experiences index risk of both concurrent and subsequent suicidal ideation (Nishida et al., 2010; Kelleher, Cederlöf & Lichtenstein, 2014; DeVylder et al., 2015; Lindgren et al., 2015) and suicide attempt (Kelleher et al., 2013a; DeVylder et al., 2015; Martin et al., 2015). The second most studied outcome is apparently psychotic disorder. In a seminal study based on the Dunedin Multidisciplinary Health and Development Study, Poulton and colleagues (2000) examined if self-reported psychotic experiences at age eleven predicted schizophreniform disorder at age 26. They found that children reporting psychotic experiences had a five to 15 times elevated odds of having a schizophreniform disorder at age 26, depending on whether the psychotic experiences were categorized as" weak" or "strong". Similar results were reported 13 years later in a British cohort, where children with psychotic

experiences had six-to 13-times elevated odds of psychotic disorder at age 18, depending on whether psychotic experiences were categorized as "suspected" or "definite". Other diagnostic outcomes have rarely been explored, but Dhossche et al. (2002) reported that self-reported auditory hallucinations at ages 11 to 18 predicted depressive disorders and substance use disorders eight years later.

The excess risks of substance misuse and suicidal behavior are especially relevant for this thesis, so these phenomena will be described briefly below.

#### 1.5.4.1 *Alcohol and substance misuse*

The classifications of alcohol and substance misuse (hereafter referred to as drug use disorder) have undergone many changes over the years. In the DSM-5, which no longer separates diagnoses of misuse and dependence, at least two out of eleven diagnostic criteria covering aspects of problematic use need to be fulfilled in order for an individual to be diagnosed with a drug use disorder(APA, 2013). The prevalences of drug use disorders have been estimated to between 6 and 10% (Rehm et al., 2005; Merikangas et al., 2010). Heritability estimates vary considerably across different types of drugs and samples, but genetic effects seem to typically account for at least 30% of the liability (Ball & Collier, 2002).

#### 1.5.4.2 *Suicidal behavior*

Suicidal behavior is a major cause of death and injury and an enormous public health problem worldwide. Whereas completed suicide is more common among men, non-fatal suicidal behaviors are more prevalent in women, young persons, and individuals with psychiatric disorders. There is a significant genetic component in the etiology of suicidal behavior, accounting for about 45% of the liability (Statham et al., 1998), but stressful life events, such as romantic skirmishes, family conflicts, and legal problems, are also important risk factors (Nock et al., 2008).

Suicidal behavior can be conceptualized as a "ladder" of thoughts and behaviors starting with self-harm with unclear intent at the bottom and ending with completed suicide at the top:

- ♣ Completed suicide
- ♣ Suicide attempt
- ♣ Preparatory acts toward suicidal behavior
- ♣ Suicidal ideation
- ♣ Self-harming behavior without intent to die
- ♣ Non-deliberate self-harm
- ♣ Self-harm behavior with unclear suicidal intent

### 1.5.5 Auditory hallucinations versus other psychotic experiences

Several lines of evidence have shown that auditory hallucinations are the most important psychotic experiences. First, Dhossche and colleagues (2002) demonstrated that adolescents reported auditory hallucinations, but not visual hallucinations, had elevated risks of developing a clinical psychiatric disorder at follow-up, compared with controls. Furthermore, in two studies, it has been found that among psychotic experiences, auditory hallucinations has the highest positive predictive values when compared with clinically verifiable auditory hallucinations as well as other psychotic experiences (Horwood et al., 2008; Kelleher et al., 2011a). Moreover, in a Dutch general population sample, auditory hallucinations, but not visual hallucinations or delusions, predicted need for psychiatric care (Bak et al., 2005). Finally, Welham et al. (2010) reported that auditory hallucinations were better predictors of adult psychotic disorder than visual hallucinations and delusions. Based on these findings, we analyzed auditory hallucinations separately from the other psychotic experiences (i.e., visual hallucinations and delusions) in study I, II and IV.

# 2 AIMS

The aims of this thesis were to examine the neurodevelopmental origins of adolescent psychotic experiences, to investigate a possible population association between Darier disease and schizophrenia/bipolar disorder, and to examine consequences of adolescent psychotic experiences, namely drug use disorder and suicide attempt. Where possible, the extent to which genetic and environmental factors influenced the associations was also examined. In more detail, the specific research questions addressed in the four studies were as follows:

**Study I**:
Are childhood problems with language and mathematics associated with adolescent psychotic experiences or juvenile mania symptoms? What are the relative contributions of genetic and environmental factors in these associations?

**Study II**:
Can the alleged association between autistic traits in childhood and adolescent psychotic experiences rather be explained by general neuropsychiatric problems? If so, to what extent is this association influenced by genetic and environmental factors?

**Study III**:
Is there an association between Darier disease and schizophrenia/bipolar disorder in the general population?

**Study IV**:
Are adolescent psychotic experiences associated with later drug use disorder or suicide attempt?

# 3 MATERIALS AND METHODS

## 3.1 DATA SOURCES

### 3.1.1 The Swedish Twin Register

The Swedish Twin Registry (STR) was established in the 1950s. With its almost 200.000 members, out of which more than 150.000 have determined zygosity, it is the largest twin register in the world. The STR was established in the 1950s, and since then, it as has been an significant resource for large-scale studies of the genetic and environmental contributions to a wide range of traits and diseases (Magnusson et al., 2013). It is also possible to link data from the STR to national registers.

### 3.1.2 The Child and Adolescent Twin Study in Sweden (CATSS)

CATSS is a longitudinal study targeting all twins born in Sweden since the 1st of July 1992 (Anckarsäter et al., 2011). The study was launched in 2004 and is structured in three waves: CATSS-9/12, CATSS-15, and CATSS-18. In CATSS-9/12, parents of twins (identified via the Swedish Twin Register) are interviewed by lay interviewers over the telephone about their children's health and development, including an assessment of a range of neuropsychiatric problems (see section 3.2.1). This interview is conducted in connection with the children's ninth birthdays, but in the first three years of the study, 12-year old twins were also included. These ages were chosen because most child psychiatric conditions and very few adolescent psychiatric conditions are established by then (Anckarsäter et al., 2011).

In the CATSS-15 and CATSS-18 studies, both twins and their parents are contacted and asked to fill out separate questionnaires targeting mental, somatic and social health, including psychotic experiences and symptoms of juvenile mania. The CATSS was designed to establish a nationwide twin study appropriate for large scale epidemiological research, and is now the most comprehensive twin study on childhood and adolescent health problems in the world, including 27,500 members at the time of writing. Study participants provided informed consent and were repeatedly given the opportunity to discontinue their participation in the studies.

### 3.1.3 Swedish National Registers

Sweden collects nationwide registry data since 1749 (Ludvigsson et al., 2009), and residents have been given a unique personal identification number (personnummer) since 1947, either at birth or at their immigration to the country. The number is used by governmental agencies in their data collection. Statistics Sweden is the governmental agency that is responsible for organizing such data into registers. The personnummer thus enables Statistics Sweden to generate data sets that include data provided by multiple agencies. Researchers at Swedish universities are entitled to use de-identified data (i.e., data without the personnummer) in research following approval from an ethical review board. The following registers were used in this thesis:

- The Multi-Generation Register (MGR). The MGR enables linkage of index persons in the Total Population Register to their biological (and adoptive) parents. The coverage of data for maternal kinships is complete for individuals born in Sweden since 1950, whereas individuals born in Sweden before? 1950 can be linked to their mothers, and for 98 percent of the individuals also to their fathers (Statistics Sweden, 2013).
- The Total Population Register (TPR). This register was established in 1967 and is held by Statistics Sweden. The TPR contains demographic data such as sex, birth date, country of birth, dates of migration, and residential address, for all Swedish residents born after 1932.
- The Small Area Marketing Statistics (SAMS) Register. The SAMS register is a geographical classification system comprising more than 9,000 residential areas. SAMS is provides a definition of residential areas based on the local housing distribution. Since 1982, Statistics Sweden has assigned Swedish residents to SAMS areas based on their registered residential address annually (Statistics Sweden, 2005).

- The National Patient Register (NPR). The NPR is held by the National Board of Health and Welfare and contains diagnosis codes classified according to the World Health Organization's International Classification of Diseases; ICD-8 (1969 to 1986), ICD-9 (1987 to 1996) and ICD-10 (1997 to 2009), and data concerning admission and discharge for all psychiatric inpatient episodes since 1973. Diagnoses

are assigned by the treating medical doctor upon discharge from the hospital. Data on outpatient specialist care is available from year 2001, albeit with incomplete coverage before 2006.

## 3.2 MEASURES

### 3.2.1 The Autism-Tics AD/HD and other Comorbidities inventory (A-TAC)

The A-TAC is a comprehensive parental telephone interview developed by researchers at the Department of Child and Adolescent Psychiatry at the University of Gothenburg. The A-TAC is designed to be used in large-scale epidemiological settings to screen general populations for mental health problems. The A-TAC covers all major clinical diagnoses in child and adolescent psychiatry listed in the DSM-IV, i.e., autism spectrum disorder, ADHD, tic disorder, developmental coordination disorder and learning disorders (APA, 1994), as well as additional items targeting other psychiatric disorders (Hansson et al., 2005). The items in A-TAC are formulated to reflect symptom criteria according to the DSM-IV (APA, 1994), as well as clinical features. In addition, the A-TAC also assesses age of onset and dysfunction and suffering.

A-TAC is structured into 19 modules corresponding to diagnoses (e.g., concentration & attention, impulsiveness & activity (which together constitutes the ADHD domain), social interaction, language, flexibility (constitutes the ASD domain) that are assessed dimensionally not adhering to mutually exclusive criteria. The questions are asked in a lifetime perspective, in comparison with peers and allows four response categories; 'yes' (scored 1), 'yes, to some extent' (scored 0.5), 'no' (scored 0) , and 'do not know/do not wish to answer' (both scored as missing).

Initially the A-TAC consisted of 178 symptom questions and the first validation study compared results of children who were on the waiting list for a neuropsychiatric assessment with the results of controls (Hansson et al., 2005). The inter-rater agreements were excellent (<0.90) and test re-test reliability in the good to excellent range (<0.70). Diagnoses of autism spectrum disorder and ADHD could be predicted with excellent sensitivity and specificity, and other diagnoses with moderate to good classifications. In the pilot study of the CATSS, the A-TAC contained 227 symptom questions which were

systematically reduced. The interview was organized into a "gate structure", where all parents were asked the "gate questions" and only those who endorsed any of the gate questions were asked more detailed questions.

In a second validation study of the A-TAC, children on the waiting list for neuropsychiatric assessment were compared with children whose parents had participated in the CATSS (Larson et al., 2010). Different scores were then tested against clinical diagnoses (when eligible), and the previously reported properties (Hansson et al., 2005) were replicated and could be maintained using 96 gate questions items only. Thus, the final version of the A-TAC consisted of 96 symptom questions in addition to the items assessing age of onset as well as dysfunction and suffering. Furthermore, the A-TAC has been validated in a prospectively fashion where twins screen positive for neurodevelopmental disorders, and screen-negative controls, where invited to participate in a clinical interview three years after the A-TAC interview (Larson et al., 2013). Sensitivities and specificities for the clinical diagnoses ranged from good-excellent and confirmed that the A-TAC has an excellent ability to separate 'cases' from 'controls' in longitudinal studies. Two doctoral theses have been published concerning the validity and reliability of the A-TAC (Larson, 2013; Hansson, 2015). Although the structure of the A-TAC has changed throughout the CATSS, the questions used in this thesis has been present since the beginning. The A-TAC can be freely downloaded from www.childnps.se.

### 3.2.2 Language and mathematical problems

For purposes of study I, a scale of communication problems was constructed by adding four items targeting problems with conversations and voice use from the ASD module in the A-TAC. A cut-off of 0.5 scores was applied, which generated a prevalence of 13%. Problems with speech, reading, and mathematics were defined using one item each targeting delayed speech, reading, and mathematical development, respectively. For speech problems (prevalence 9%) and mathematical problems (prevalence 13%) a cutoff of 0.5 was used, whereas the cut-off for reading problems (prevalence 7%) was set to 1.

### 3.2.3 Autistic traits

A continuous scale of autistic traits was used in study II. This scale was created by adding all 17 items targeting different aspects of autism spectrum disorder in the relevant A-TAC modules.

### 3.2.4 General neuropsychiatric problems

A general neuropsychiatric problems factor comprising a total of 53 symptoms of ADHD, tic disorder, learning disorder and developmental coordination disorder was extracted from the A-TAC and used in study II. The factor was defined according to Pettersson and colleagues (2013) recent paper.

### 3.2.5 Psychotic experiences

Self-and parent-reported psychotic experiences were outcome measures in studies I and II, and exposure measure in study IV. The total of seven items in the CATSS-15 and CATSS-18 data collections have been used previously in community-based research (e.g. Poulton et al., 2000) and correspond very closely to the Adolescent Psychotic-Like Symptom Screener (Kelleher et al., 2011a). The individual items are listed below:

- ♣ Sometimes I thought that I was being followed or spied upon.
- ♣ Other people have read my thoughts.
- ♣ Sometimes I have thought that I was being sent special messages through the television.
- ♣ I have special powers that other people don't have.
- ♣ Sometimes I felt that I was under the control of some special power.
- ♣ Sometimes I have seen something or someone that other people couldn't see.
- ♣ Sometimes I have heard voices other people couldn't hear.

In study I and II, auditory hallucinations were analyzed separately from the other psychotic experiences, and self-reports were separated from parent-reports in all studies. Scales of self-reported (range 0-7) and parent-reported (range 0-14) other psychotic experiences in the CATSS-15 data collection were created and used in study I and IV (only self-reported). The analyses in study II and IV concerned self-reported psychotic experiences only.

### 3.2.6 Juvenile mania symptoms

Scales of self-reported and parent-reported juvenile mania symptoms were created for purposes of study I. These scales comprised nine items from The Child Mania Rating Scale Brief Version (Henry et al., 2008) targeting problems with irritability, temper tantrums, and grandiosity during the last month. All nine items are introduced with "Does it happen that you.." and are listed below.

- ♣ Have periods of feeling super happy for hours or days at a time, extremely wound up and excited, such as feeling "on top of the world".
- ♣ Feel irritable, cranky, or mad for hours or days at a time.
- ♣ Believe that I have unrealistic abilities or powers that are unusual, and may try to act upon them, which causes trouble.
- ♣ Need less sleep than usual; yet do not feel tired the next day.
- ♣ Have periods of too much energy.
- ♣ Have periods of racing thoughts that my mind cannot slow down , and it seems that my mouth cannot keep up with my mind.
- ♣ Talk so fast that I jump from topic to topic.
- ♣ Behave in a sexually inappropriate way (e.g., talks dirty, exposing, playing with private parts, masturbating, making sex phone calls, humping on dogs, playing sex games, touches others sexually).
- ♣ Have rage attacks, intense and prolonged temper tantrums.

Similarly as for psychotic experiences, self-reports and parent-reports were separated in the analyses. In study I, scales of self-reported (ranges 0-27 and 0-8, respectively) and parent-reported (ranges 0-27 and 0-8, respectively) juvenile mania symptoms in CATSS-15 and CATSS-18 studies were used.

### 3.2.7 Darier disease

Darier disease was defined as at least one diagnosis of 757D (ICD-9) or Q82.8E (ICD-10). Owing to the poor specificity of the ICD-8 code for Darier disease, which includes several other congenital malformations of skin, this particular code was excluded.

### 3.2.8 Schizophrenia and bipolar disorder

Schizophrenia was defined as at least one inpatient episode in the NPR according to the following diagnosis codes: 295.0-295.6 (ICD-8), 295A-295G (ICD-9), F20 (ICD-10).

Bipolar disorder was defined according to a validated algorithm (Sellgren et al., 2011) including the following diagnosis codes: 296 (ICD-8, ICD-9), F30, F31 (ICD-10), excluding those whose diagnoses relied only on 296.2 or 296B. This definition relies on at least two discharge diagnoses in the NPR.

Diagnoses of chronic or severe disorders in the NPR are generally valid (Ludvigsson et al., 2011), and the diagnosis codes for schizophrenia and bipolar disorder have more than 90% agreement when compared with research diagnoses (Ekholm et al., 2005; Sellgren et al., 2011). The definition by Ekholm and colleagues is based on two discharge diagnoses in the NPR, but due to issues pertaining to statistical power, the definition used in study III relied on one diagnosis instead of two. However, extensive sensitivity analyses using one vs. two diagnoses have failed to reveal any meaningful differences in other nation-wide Swedish studies (Sariaslan et al., 2015). A recently published validation study showed the same pattern in Danish register data (Sörensen et al., 2015).

### 3.2.9 Drug use disorder

Drug use disorder was defined as an inpatient or outpatient diagnosis of F10-F16, and F18-F19 in the ICD-10.

### 3.2.10 Suicide attempt

A suicide attempt was defined as at least one inpatient or outpatient ICD-10 diagnosis of X60-X84, or Y10-Y34.

## 3.3 STUDY DESIGNS

### 3.3.1 Prospective cohort study

Studies I, II, and IV are all prospective cohort studies. A cohort can be defined as a group of individuals who share some characteristics and are followed up over some period of time. Individuals at risk is typically defined according to their status on a given exposure (risk factor) and followed-up with the aim of comparing their outcome status with individuals with a different status with regards to the exposure. The word prospective means that the outcome status is unknown at baseline and that the study "peaks into the future", in contrast to retrospective studies. When follow-up is completed, relative risks can be estimated by comparing the outcome status in the exposed vs. unexposed group, typically involving some kind of regression modeling (Rothman, 2002).

### 3.3.2 Matched cohort study

Study III is a matched cohort study, and in this study design, unexposed subjects are matched to exposed subjects on a set of potential confounders such as age, sex and residential area. Matched cohort studies are getting increasingly popular and are useful for researchers with access to large population data sets with information about potential confounders (Sjölander et al., 2012). For example, a cohort matched 1:10 contains pairs of observations (1 exposed and 10 unexposed subjects) with the same level of the matching variables, typically the same sex and age. The exposed subjects are identified first, and unexposed subjects are subsequently matched with randomly selected unexposed subjects. Thus, the matching scheme in matched cohort studies is by definition completely "exposure driven" (Sjölander et al., 2012, p.4). The statistical analyses in matched cohort studies usually involve conditional logistic regression models.

### 3.3.3 Family study

In addition to being a matched cohort study, study III is also a (matched) family study. They key assumption that family studies rely on is that similarity is greater within families than between families. Family studies are commonly used to examine the "phenotypic signal" and the familial, i.e., genetic and shared environmental, causes of comorbidity between two disorders. The extent of shared pathophysiology can then be estimated by comparing the occurrence of

the comorbid disorder in relatives of individuals with only the index disorder and not the comorbidity, versus in unaffected relatives to matched comparison individuals without the index disorder. (Szatmari, White & Merikangas, 2007).

The rationale for the use of the family study method in study III was based on the fact that if the occurrence of the comorbid disorder (i.e., schizophrenia or bipolar disorder) is increased only when coupled with the index disorder (Darier disease), this would suggest that the index disorder promotes the comorbid disorder (Merikangas, 1990).

## 3.4 STATISTICAL ANALYSES

### 3.4.1 Logistic regression

Logistic regression analyses are widely used in epidemiological research. Such analyses describe the association between a categorical (binary or ordinal) outcome and one or more predictor variables (categorical or continuous). The output from logistic regressions are odds ratios (OR), which denotes the probability of having the outcome divided by the probability of not having the outcome if you are in the exposed group, compared with the probability of having the outcome, divided by the probability of not having the outcome if you are in the unexposed group. If the outcome is rare, the OR can be regarded as a risk ratio. In situations where controls (in case-control studies) or unexposed subjects (in cohort studies) are individually matched to cases or exposed subjects, i.e., stratified data as in study III, the conditional logistic regression model is preferred (Rothman, 2002). Logistic regression models are used in study I, and conditional logistic regression models are used in study III.

### 3.4.2 Cox regression

The Cox regression model is a model often used in epidemiological follow-up studies, as it enables modeling of survival data. Survival models such as the Cox regression aim to measure the risk of an event but also the quantity of time it takes for the event to happen. Importantly, survival models also take right censoring, i.e., that study participants exit the study before the event occur or before the end of the follow-up, into account. The model estimates relative hazard rates and the magnitude of the effects are stated as hazard ratios (HR).

An assumption of the Cox regression model is that the hazard rates are proportional (Cleves, 2008). A Cox regression model is used in study IV.

### 3.4.3 Twin modeling

Twin models are used in studies I and II. The extent to which a trait is influenced by genetic factors, the phenotypic similarity correlates with the degree of genetic relatedness. Using monozygotic (MZ; who are genetically identical) and dizygotic (DZ; who share in average 50% of their segregating genes) twins, this principle can be used to estimate the relative contribution of genetic and environmental factors in the variation or covariation of one or more traits. Thus, the existence of these two types of twin pairs with differing genetic relatedness provides a powerful "natural experiment" for unraveling genetic from environmental factors in a given trait or for associations (Rijsdisjk & Sham, 2002; Verweij et al., 2012).

It is possible to partition trait variation into three source, or components: A, which denotes additive genetic factors, i.e., the sum of all influencing genes, C, which denotes shared environmental factors (factors shared between family members), and E, which denotes unique environmental factors (factors not shared between members of a family). The E component also includes measurement errors. The total (phenotypic) variation in a trait is the sum of these variance components (A+C+E). Given that 100% of the variation in a trait is due to variation in genetics, a correlation of 1 for MZ twin pairs and 0.5 for DZ twin pairs would be expected.

Hypothetically, because both MZ and DZ twin pairs share environmental influences, we would expect a correlation of 1 for both types of pairs if the C component was the only source of variation in a trait. Furthermore, unique environmental influences (E) are not shared between individuals, so if the variance in a trait was solely influenced by E, a correlation of 0 would be expected for both MZ and DZ pairs. The MZ twin pair correlation can thus be summarized as A + C, and the DZ twin pair correlation as 0.5A + C. By using the formulas below, it is thus possible to estimate the proportion of variation that is influenced by A, C and E, using observed phenotypic correlations for MZ ($r$MZ) and DZ ($r$DZ) twin pair correlations.

Formulas solving for the A and C components:

$^{r}MZ = A + C.$

$^{r}DZ = 0.5A + C.$

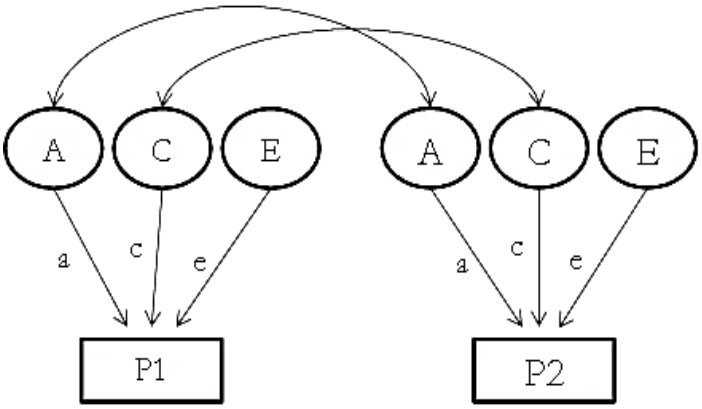
$A = 2 (^{r}MZ-^{r}DZ)$, commonly referred to as ”Falconer´s formula”.

$C = 2\ ^{r}DZ-^{r}MZ.$

We know that A + C + E equals 1, so E must be equal to $1 - ^{r}MZ.$

Rather than using these formulas for calculation of the A, C and E components, structural equation modeling is generally employed to generate more precise estimates, including corresponding confidence intervals. In Figure 3.4.3, the classic twin model is depicted as a path diagram.

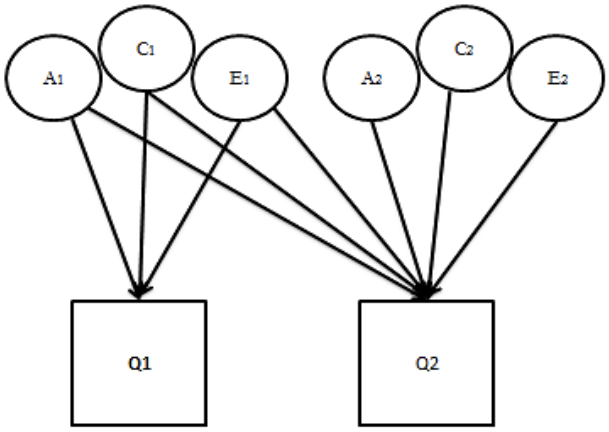
**Figure 3.4.3** Path diagram of the classical twin model.




In this model, P1 and P2 refer to the observed phenotype of twin 1 and 2 in a pair, for example auditory hallucinations as in study I. The circles refer to the variance components that measure the contributions of A (additive genetics), C (shared environments), and E (unique environments) to the studied phenotype. The standardized regression coefficients (lowercase a, c, and e) mirror the magnitude of the associations between the variance components and the phenotypes.

This basic univariate model can relatively easily be extended to include two (or more) traits, in order to partition the covariance between two traits. Hence, bivariate models can be used to answer questions like "to what extent is the correlation between height and weight due to overlapping genetic and/or environmental factors?". An example of a bivariate twin model is illustrated in Figure 3.4.4.

**Figure 3.4.4**. The bivariate twin model as a path diagram.




Here, Q1 and Q2 refer to the observed phenotypes for one of the twins in a pair. For example, C1 is a latent shared environmental factor that influences both measured phenotypes, and A2 is a latent shared environmental factor that influences only phenotype 2. The same structure applies for the A and E factors.

# 4 STUDY SUMMARIES AND RESULTS

## 4.1 STUDY I – LANGUAGE PROBLEMS AND LATER PSYCHOTIC EXPERIENCES, AND JUVENILE MANIA SYMPTOMS

Study I is a prospective cohort study based on data from the CATSS-9/12, CATSS-15, and CATSS-18 studies. The sample comprised 5,812 twins and one of their parents (their mother where possible). The main aim of this study was to examine if children with language or mathematical problems in childhood, assessed in CATSS-9/12 with the A-TAC, would have elevated risks of having self-reported or parent-reported psychotic experiences in adolescence (assessed in the CATSS-15 and 18 studies) after adjusting for a set of possible demographic confounders. Risks of juvenile mania symptoms were also estimated in the same children. Based on the literature suggesting important differences between auditory hallucinations and other psychotic experiences (see section 1.5.5), we analyzed auditory hallucinations separately from the other psychotic experiences, i.e., visual hallucinations and delusions. Associations were examined with logistic regression models. As statistically dependent twin pairs were used in the analyses, a robust sandwich estimator was used to adjust for the correlated data when calculating the confidence intervals. In addition, we examined the genetic and environmental contributions to the possible associations, using bivariate twin analyses based on structural equation modeling.

### 4.1.1 Results

After adjusting for demographic factors, the most consistent finding was that children with communication problems had elevated risks of having auditory hallucinations at ages 15 and 18 years (self-reported), other psychotic experiences at age 15 (self-and parent-reported), and juvenile mania symptoms at ages 15 and 18 (parent-reported). Further, reading problems also predicted psychotic experiences and mathematical problems predicted juvenile mania symptoms (Table 4.1.1). In the analyses concerning psychotic experiences, statistically significant odds ratios ranged from 1.3 to 7.3, and associations were generally more prominent between childhood language and mathematical problems and auditory hallucinations than between childhood problems and the scale of other psychotic experiences.

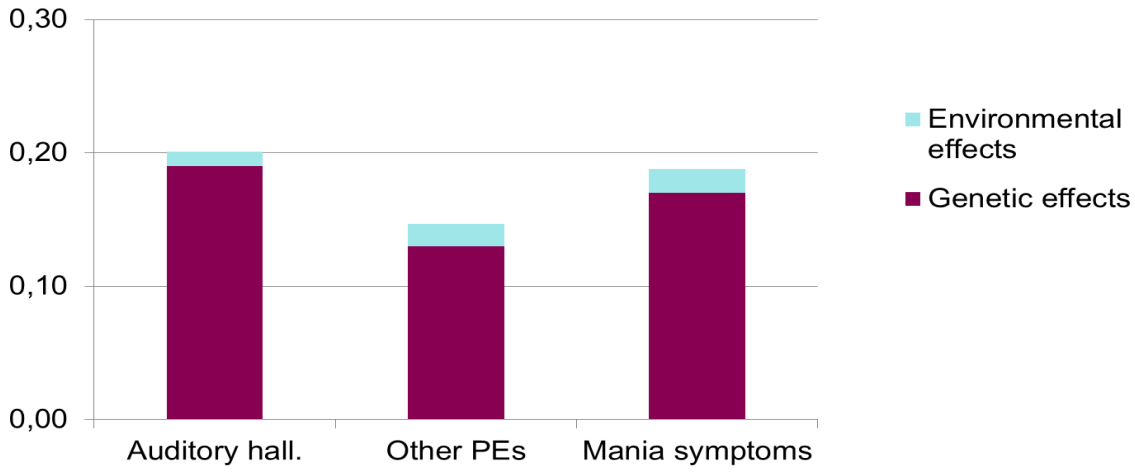
**Table 4.1.1. Associations between childhood problems and later adolescent auditory hallucinations, other psychotic experiences (PE), and juvenile mania symptoms. Significant associations are denoted with a X.**

| | Auditory hallucinations | | | | Other PE | | Juvenile mania symptoms | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Age 15 | | Age 18 | | Age 15 | | Age 15 | | Age 18 | |
| Rater | Child | Parent | Child | Parent | Child | Parent | Child | Parent | Child | Parent |
| **Communication problems** | **X** | | **X** | | **X** | **X** | | **X** | | **X** |
| **Reading problems** | | | | **X** | | | | | | |
| **Mathematical problems** | | | | | | | | **X** | | **X** |
| **Speech problems** | | | | | | | | | | |

Due to insufficient statistical power and/or distributional problems, bivariate twin analyses were employed only on the associations between communication problems and self-reported auditory hallucinations, parent-reported other psychotic experiences, and parent-reported juvenile mania symptoms at age 15 years.

These analyses revealed that genetic effects explained essentially the entire association between communication problems and the studied adolescent psychiatric symptoms, whereas unique environmental effects where non-significant and of considerably less importance (Figure 4.1.1).

**Figure 4.1.1.** Genetic and environmental contributions to the associations between childhood communication problems and adolescent auditory hallucinations, other psychotic experiences, and juvenile mania symptoms. The Y axis shows phenotypic correlations. The shades of the graphs indicate the proportion of the phenotypic associations explained by genetic and environmental effects, respectively.




**Note:** auditory hall. = auditory hallucinations, other PEs = other psychotic experiences.

## 4.2 STUDY II – GENERAL NEUROPSYCHIATRIC PROBLEMS, AUTISTIC TRAITS, AND LATER PSYCHOTIC EXPERIENCES

This prospective cohort study was based on 9,282 twins who were members of the CATSS-9/12 and the CATSS-15 and/or the CATSS-18 studies. Here, we examined if the alleged association between autistic traits in childhood and self-reported psychotic experiences in adolescence would rather be explained by a general neuropsychiatric problems factor, comprising symptoms of ADHD, tic disorder, developmental coordination disorder and learning disorder. Both autistic traits and general neuropsychiatric problems were assessed with the A-TAC in the CATSS-9/12 study. First, auditory hallucinations were regressed on autistic traits. Second, the general neuropsychiatric problems factor was added to the model. We also disentangled the genetic from environmental influences in the associations. As in study I, auditory hallucinations were analyzed separately from the other psychotic experiences, which were further divided into visual hallucinations and delusions.

### 4.2.1 Results

Replicating prior studies, associations were found between childhood autistic traits and adolescent psychotic experiences at ages 15 and 18 years, but only for auditory and visual hallucinations (Table 4.2.1, crude model). Beta coefficients were moderate and ranged from 0.05 to 0.09. When the general neuropsychiatric problems factor was included in the model, all significant associations in the univariate model disappeared (Table 4.2.1, full model). However, the association between the general neuropsychiatric problems factor and auditory (but not visual) hallucinations remained after adjustment for the effect of autistic traits (Table 4.2.1, full model).

**Table 4.2.1. Crude and adjusted associations between childhood autistic traits, a general neuropsychiatric problems factor, and adolescent hallucinations. Associations are expressed as β coefficients and 95% confidence intervals (CI).**

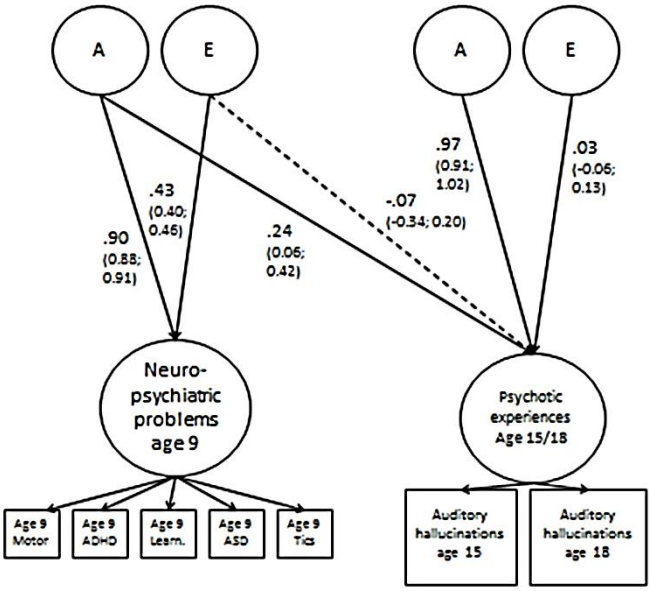
| | **Crude model** | | **Full model** | | | |
|---|---|---|---|---|---|---|
| | **Exposure** | | **Exposures** | | | |
| | Autistic traits | | Autistic traits | | General neuropsychiatric problems factor | |
| **Outcomes** | β | (CI) | β | (CI) | β | (CI) |
| Age 15 auditory hallucinations | **0.07** | **(0.03-0.11)** | -0.08 | (-0.18-0.02) | **0.24** | **(0.10-0.38)** |
| Age 18 auditory hallucinations | **0.09** | **(0.05-0.13)** | -0.04 | (-0.16-0.10) | **0.21** | **(0.03-0.39)** |
| Age 15 visual hallucinations | **0.05** | **(0.02-0.10)** | -0.01 | (-0.08-0.06) | 0.10 | (-0.01-0.20) |
| Age 18 visual hallucinations | **0.07** | **(0.01-0.13)** | 0.01 | (-0.13-0.15) | 0.11 | (-0.11-0.32) |

**Note:** statistically significant associations are shown in bold.

We continued with twin modeling on the association between the general neuropsychiatric factor and auditory hallucinations, i.e., the significant associations in the full model presented in Table 4.2.1. To increase statistical power, a latent factor comprising auditory hallucinations at both ages was used, as these two variables correlated highly ($r$ =0.64). The results from these twin analyses are illustrated in Figure 4.2.1. It was found that the association

between the general neuropsychiatric problems factor and auditory hallucinations was influenced in essence only by genetic factors, whereas influences from unique environmental factors were negligible.

**Figure 4.2.1.** Standardized regression weights for genetic and unique environmental components of the association between a general neuropsychiatric problems factor, and auditory hallucinations at ages 15/18.




**Note:** DCD = developmental coordination disorder, LD = earning disorder, AT = autistic traits, TD = tic disorder. A = additive genetic factor, E = unique environmental factor. The bolded line denotes $p<0.05$, and the dotted line denotes $p>0.05$.

## 4.3 STUDY III – DARIER DISEASE AND SCHIZOPHRENIA, AND BIPOLAR DISORDER

In this matched cohort study and family study, we used data from the National Registers to investigate if individuals with Darier disease (n=788), or their first-degree relatives (n=3,288), would have an increased risk of being diagnosed with schizophrenia or bipolar disorder compared with matched comparison individuals (ratio 1:10). Matching criteria were age, sex and county of residence for the analyses concerning individuals with Darier disease, and age and sex for the analyses concerning relatives to individuals with Darier disease. Associations were examined with conditional logistic regression models.

When assessing shared familial risks between two disorders, a common method is to exclude relatives who have the index disorder, i.e., Darier disease, themselves. Therefore, we conducted an additional analyses specified accordingly and expected that the associations to schizophrenia and bipolar disorder would disappear, due to the virtually complete penetrance of the Darier-causing mutations.

### 4.3.1 Results

Results from the conditional logistic regressions showed that individuals with Darier disease had a 4.3-fold elevated risk of being diagnosed with bipolar disorder, and a 2.3-fold elevated risk of being diagnosed with schizophrenia, compared with matched comparison subjects without Darier disease.

In the family analysis, first-degree relatives to individuals with Darier disease had a 1.6-fold elevated risk of bipolar disorder, but there were less evidence of an excess risk of schizophrenia (Table 4.3.1).

The additional family analyses, where only relatives without Darier disease were included, yielded expected results; there were no associations with neither schizophrenia (risk ratio 0.7, 95% confidence interval 0.3-1.6) nor bipolar disorder (risk ratio 1.1, 95% confidence interval 0.6-1.9).

**Table 4.3.1. Risks of bipolar disorder/schizophrenia in individuals with (exposed) vs. without (unexposed) Darier disease, and their first-degree relatives.**

| | **Bipolar disorder** | | | **Schizophrenia** | | |
|---|---|---|---|---|---|---|
| | Exposed *n* (%) | Unexposed *n* (%) | RR (CI) | Exposed *n* (%) | Unexposed *n* (%) | RR (CI) |
| Individuals | 15 (2.0) | 351 (0.5) | **4.3 (2.6-7.3)** | 6 (0.8) | 261 (0.3) | **2.3 (1.1-5.2)** |
| 1st degree relatives | 21 (0.7) | 1 028 (0.4) | **1.6 (1.1-2.5)** | 7 (0.2) | 657 (0.2) | 0.8 (0.4-1.8) |

**Note:** statistically significant risk ratios are shown in bold. RR = risk ratios, CI = 95% confidence intervals.

## 4.4 STUDY IV – CONSEQUENCES OF PSYCHOTIC EXPERIENCES

Study IV is a prospective cohort study, just like study I and II. The study is based on 8,407 twins who were members of the CATSS-15 and/or the CATSS-18 studies. The study participants were linked to the NPR to retrieve information about diagnoses of drug use disorder and suicide attempt, assigned after the CATSS-15 or CATSS-18 questionnaires were completed. Hazard rates of these adverse outcomes were then compared between adolescents who did versus did not report distinct psychotic experiences at ages 15 or 18 years. The psychotic experiences were auditory and visual hallucinations and delusions of persecution, reference, control, special powers, and thought broadcasting. We further examined the relationship between the number of reported psychotic experiences in relation to risk of later diagnoses of drug use disorder. Because distributional problems prohibited this analysis for suicide attempt, we instead used a composite score as a predictor variable. There were different response alternatives for different items, so answers were dichotomized so that 1 score equaled 1 one psychotic experience. Participants were followed from the date they completed the CATSS-15 or 18 questionnaires; those who participated in both studies were followed from the CATSS-15 study. Because of the survival data structure, associations were examined with Cox proportional hazard regression models. As correlated twin pairs were used in the analyses, a robust sandwich estimator was applied to control for the correlated data structure when calculating the confidence intervals.

### 4.4.1 Results

After adjusting for the potential confounding effect of sex and low parental education level, adolescents who reported psychotic experiences had excess hazards of later drug use disorder or suicide attempt (Table 4.4.1). Further, there was a dose-response relationship between the number of psychotic experiences and later drug use disorder (Table 4.4.2). When the composite score was used as a predictor variable, the hazard of later drug use disorder and suicide attempt increased by 1.4 and 1.2 times respectively, for each psychotic experience (Table 4.4.2).

**Table 4.4.1. Hazard ratios and 95% confidence intervals (CI) of drug use disorder and suicide attempts in adolescents with distinct psychotic experiences at ages 15 or 18 years.**

| | Later drug use disorder | | Later suicide attempt | |
|---|---|---|---|---|
| **Ages 15 or 18 years psychotic experiences** | CHR (CI) | AHR (CI) | CHR (CI) | AHR (CI) |
| Auditory hallucinations | **3.2 (1.3-7.6)** | **3.3 (1.4-7.9)** | **2.9 (1.8-4.7)** | **3.0 (1.8-4.9)** |
| Visual hallucinations | **2.6 (1.4-4.9)** | **2.6 (1.4-5.0)** | **2.1 (1.4-3.4)** | **2.1 (1.3-3.3)** |
| Being spied upon | **3.1 (1.5-6.4)** | **3.3 (1.7-6.4)** | 1.3 (0.8-2.0) | 1.4 (0.9-2.1) |
| Thought broadcasting | **2.0 (1.1-4.0)** | **2.0 (1.1-4.0)** | 1.5 (0.9-2.3) | 1.5 (0.9-2.3) |
| Being sent special messages through TV | 1.5 (0.4-4.9) | 1.5 (0.4-4.9) | 1.9 (0.9-3.8) | 1.8 (0.9-3.7) |
| Having special powers | **2.4 (1.1-5.4)** | **2.4 (1.1-5.5)** | **2.0 (1.1-3.6)** | **1.9 (1.1-3.5)** |
| Being controlled by some special power | 1.7 (0.7-3.9) | 1.7 (0.7-3.8) | **2.3 (1.4-3.8)** | **2.3 (1.4-3.9)** |

**Note:** Statistically significant associations are bolded. CHR= crude hazard ratio, AHR= adjusted hazard ratio.

**Table 4.4.2. Associations between the number of psychotic experiences and later drug use disorder, and suicide attempt.**

| | Later drug use disorder | Later suicide attempt |
|---|---|---|
| **Age 15/18 years psychotic experiences** | HR (CI) | HR (CI) |
| 0 (reference) | | |
| 1 | 0.9 (0.4-2.4) | n/a |
| 2 | 2.0 (0.8-5.1) | n/a |
| 3 | **3.3 (1.3-8.4)** | n/a |
| 4 | **6.6 (2.6-16.8)** | n/a |
| 5 | **9.3 (3.2-27.3)** | n/a |
| 6 | n/a | n/a |
| 7 | n/a | n/a |
| Composite score | **1.4 (1.2-1.6)** | **1.2 (1.1-1.3)** |

**Note:** Statistically significant associations are bolded. A total of 100 individuals were excluded from the analysis due to missing data.

# 5 DISCUSSION

## 5.1 PSYCHOTIC EXPERIENCES AS NEURODEVELOPMENTAL PHENOMENA

The findings from studies I and II clearly indicate that adolescent psychotic experiences are neurodevelopmental phenomena. This is because childhood problems widely accepted as neurodevelopmental in origin, i.e., communication problems, reading problems, autistic traits, and a general neuropsychiatric problems factor, were associated with adolescent psychotic experiences. In the same vein, it was observed that the crude association between childhood autistic traits and adolescent psychotic experiences was better explained by the general neuropsychiatric problems factor.

These results are generally in keeping with prior studies (Jones et al., 2012; Happé et al. 2012; Sullivan et al., 2013; Hameed et al., 2013; Khandaker et al., 2014) and provide evidence for a neurodevelopmental continuity between adolescent psychotic experiences and clinical schizophrenia, for which the studied childhood problems are established risk factors (e.g. Kolvin et al., 1971; Crow et al., 1995; Hollis, 1995; Cannon et al., 2002; Rapoport et al., 2009). As far as I am aware, the association between a broad, general factor of childhood neuropsychiatric problems comprising symptoms of ADHD, developmental coordination disorder, tic disorder, and learning disorder, and adolescent auditory hallucinations has not been demonstrated before. Hence, findings from this thesis suggest that the heuristically important neurodevelopmental model of schizophrenia (Murray & Lewis, 1987; Weinberger, 1987; Rapoport et al., 2005) can be applied also on psychotic experiences in the general adolescent population. Further, the findings also suggest that adolescents reporting psychotic experiences, which is a considerably larger group than clinical cases, is a potentially valuable population for research into the etiology of schizophrenia. For example, longitudinal neuroscience research based on adolescents reporting psychotic experiences might provide important clues to the pathogenesis of schizophrenia, as the vast majority of these adolescents are not treated with psychotropic drugs (Rössler et al., 2011), are typically years before a possible prodrome (Polanczyk et al., 2010), and considerably easier to access than individuals with schizophrenia, which enables population-based studies.

I studied a genetically informative sample of twins, and through the use of structural equation modeling, findings from both studies I and II showed that the associations between neuropsychiatric problems and adolescent psychotic experiences were essentially only due to genetic factors, whereas environmental factors were negligible. In other words, the same set of genes seems to be involved in the pathogenesis of a broad spectrum of neuropsychiatric problems in childhood, as well as in susceptibility to psychotic experiences in mid-and late adolescence. To my best knowledge, this was the first demonstration of the importance of shared genetic factors for associations between these childhood and adolescent problems. Further, these genetic correlations are consistent with the overarching trend in molecular psychiatry research, namely that risk alleles confer liability for a range of psychiatric disorders (Cross Disorder Group of the Psychiatric Genomics Consortium, 2013).

## 5.2 THE POPULATION ASSOCIATION BETWEEN DARIER DISEASE AND BIPOLAR DISORDER, AND SCHIZOPHRENIA

Findings from study II document that the risk of bipolar disorder and schizophrenia is markedly elevated in individuals with diagnosed Darier disease in Sweden. Further, the risk of bipolar disorder was increased also in individuals with a first-degree relative who had Darier disease, but not when relatives who had Darier disease themselves were excluded from the analysis.

Earlier studies have demonstrated a familial co-segregation of Darier disease and bipolar disorder, and schizophrenia (Getzler & Flint, 1966; Craddock et al., 1994; Jones et al., 2002). The findings observed in this study extends these findings which were observed in occasional pedigrees, and provides evidence for an tendency towards a familial co-segregation of Darier disease and bipolar disorder in the Swedish general population.

Several splicing, frame shift, missense, and nonsense mutations have been documented in the Darier-causing ATP2A2 gene (Jacobsen et al., 1999; Sakuntabhai et al., 1999; Ruiz-Perez et al., 1999).This gene is involved in synaptic plasticity and neurotransmission (Berridge, Bootman, and Lipp, 1998), and is important in intracellular calcium signaling (Lytton & MacLennan, 1988). Genome-wide association studies have shown that calcium channels are involved

in psychopathology, especially bipolar disorder and schizophrenia (Cross Disorder Group of the Psychiatric Genomics Consortium, 2013; Ripke et al., 2013). Further, calcium homeostasis defects seem to be involved in bipolar disorder, and pharmacological treatment for the disorder might be elicited through intracellular calcium changes (Emamghoreishi et al., 1997). Hence, the ATP2A2 gene is a robust functional candidate gene for bipolar disorder, but also for schizophrenia. Interestingly, this was recently confirmed in a large genome-wide association study (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

Taken together, the results in this study strongly suggest that the ATP2A2 gene produce liability for bipolar disorder in particular, but also for schizophrenia. The Darier-causing mutations merit in-depth attention in molecular genetic studies of psychiatric disorders.

## 5.3 ADOLESCENT PSYCHOTIC EXPERIENCES AS PREDICTORS OF LATER DRUG USE DISORDER, AND SUICIDE ATTEMPT

The findings from study IV showed that adolescent psychotic experiences were associated with elevated risks of later development of two particularly adverse outcomes, namely diagnosed drug use disorder and diagnosed suicide attempt.

Prior studies have shown that adolescents who report auditory hallucinations, but not visual hallucinations, have 8-fold elevated risks of later substance misuse in early adulthood (Dhossche et al., 2002). Suicidal behaviors like self-reported suicidal ideations (Kelleher, Cederlöf, and Lichtenstein 2014b), self-reported suicide attempts (Kelleher et al., 2013a), and diagnosed suicide attempt (Fisher et al., 2013) have also been reported in adolescents with auditory hallucinations or a composite of auditory hallucinations and four delusions.

Our results are generally congruent with previous research, and additionally show that longitudinal risks of drug use disorder and suicide attempt are not confined to auditory hallucinations or to psychotic experiences above some arbitrary, distribution-based cutoff level, as in a prior study based on data from the Dunedin cohort (Fisher et al., 2013). Our data is also consistent with a recent study, in which psychotic experiences were categorized into hallucinations,

delusions, and both hallucinations and delusions, and where no meaningful differences were detected regarding the effect on subsequent self-reported suicide attempt (Sullivan et al., 2015). In the current dataset, all distinct psychotic experiences were associated with later diagnosed drug use disorder and/or suicide attempt. Further, for the first time, evidence for a dose-response relationship between the number of reported psychotic experiences and drug use disorder was presented.

Suicide attempts were measured with diagnoses assigned by physicians at discharge from a hospital ward, or at a visit at a specialist psychiatric clinic. This particular measure might have more severe clinical properties than self-reported suicide attempt. This is because, most probably, only a fraction of all suicide attempts are registered in the National Patient Register. Hence, we could here show that psychotic experiences are predictive of severe suicide attempt, which have clinical implications.

## 5.4 METHODOLOGICAL CONSIDERATIONS

### 5.4.1 Surveillance bias

Surveillance bias, or detection bias, is a form of non-random misclassification bias that refers to a situation where one group is more closely monitored than another group. The results in study III may have been affected by such bias to an extent that cannot be estimated. This is because individuals with Darier disease probably are more likely to be diagnosed with schizophrenia or bipolar disorder than the comparison individuals due to their interactions with health care. Because of the ample evidence suggesting true associations between these disorders, and because of the plausible underlying biological mechanism, the magnitude of the possible influence of surveillance bias in the observed associations between Darier disease and schizophrenia and bipolar disorder, was probably marginal.

### 5.4.2 Assumptions of the twin method

The twin method relies on a number of assumptions, for example that 1) MZ and DZ twin pairs share their environment equally (the "equal environments assumption"). Other assumptions include that 2), there is no correlation between genes and environments in the trait/traits under study, 3), there are no differences between twins and singletons in the trait, 4), mating occur randomly in the population (the "assortative mating assumption") and DZ twins pairs therefore share 50% of their segregating genes.

#### 5.4.2.1 *Violations of assumptions of the twin method*

Violation of assumption 1), for example in a situation where MZ twin pairs are treated more similarly by their caregivers than DZ twin pairs, will consequently result in an incorrect inflation of the estimate of A.

Violation of assumption 3) may bias the estimates of either A, C or E, depending on how singletons differ from twins in the trait/traits under study. If assumption 4) is violated and the genetic relatedness of DZ twins exceeds 0.5, this results in an inflation of the C estimate. These assumptions may, or may not, be realistic and can have important implications for the interpretation of the results, depending on the studied trait/traits and the research question (Rijsdijk & Sham, 2002, Verweij et al., 2012).

Empirical evidence has shown that the influence of the equal environments assumptions is minimal (Felson, 2014), I am not aware of any data suggesting any differences between twins and singletons regarding psychotic experiences, and simulations have shown that the influence of assortative mating bias is modest (Barnes et al., 2014). Hence, bias from twin methodology is not likely to be a major problem in this thesis.

## 5.5 ETHICAL CONSIDERATIONS

All studies in this thesis were approved by the Regional Ethics Review Board in Stockholm. In medical research, researchers have to weigh the benefits of the research against the welfare of the study participants. Observational register-based studies, such as all studies in this thesis, are generally less ethically challenging than experimental studies, because data is collected without intervention. However, is it still possible that some questions to both children

and parents in the CATSS studies may have elicited a negative reaction, such as shame, anxiety or worry. Therefore, both parents and children, who gave informed consent to participate, were offered contact with a licensed psychologist. Further, all studies used sensitive personal information that potentially can detriment the personal integrity of the participants. Therefore, and in accordance with Swedish law (Swedish parliament, 2003), the identity of the participants (i.e., personnummer) was protected by the use of a unique identification code number (löpnummer and/or tvillingnummer).

### 5.6 CLINICAL IMPLICATIONS

As researchers have noted, answering questions about psychotic experiences may identify several perceptual phenomena with highly varying degrees of clinical relevance, which makes research findings potentially problematic to translate into practice (e.g. Garralda, 2016). However, validation studies have shown that endorsement of auditory hallucinations predict clinically verifiable psychotic experiences (Horwood et al., 2008; Kelleher et al., 2011a). Still, robust and replicated results are needed before changes in the clinical management of adolescents with psychotic experiences are considered.

Findings from studies I and II suggests that clinical practice may indeed be enhanced through consideration of childhood, but also co-existing, problems with communication, reading and mathematics, as well as general neuropsychiatric problems, in adolescents with psychotic experiences, as they likely have a negative impact on broad patient function. Further, it is conceivable that the monitoring of children with these childhood neurodevelopmental problems may facilitate early identification of psychotic experiences (as well as juvenile mania symptoms), which may reduce their possible negative consequences.

Regarding individuals with Darier disease: in our cohort, 2.0 % had a diagnosis of bipolar disorder and 0.8% had a diagnosis of schizophrenia. These psychiatric disorders rarely escape detection. Nevertheless, a much larger proportion of individuals with Darier disease might very well have subclinical affective and/or psychotic symptoms. More research is needed, but dermatologists and other health care professionals who meet patients with this disorder should be alert to changes in the behavior and mental states of their patients.

The findings from the thesis suggest that psychotic experiences should be enquired in psychiatric examinations of children and adolescents. Careful and ethically considered monitoring of adolescents reporting psychotic experiences may at best reduce their risk of developing a psychotic disorder, a drug use disorder, or a suicidal attempt. At least, such prevention strategies would likely facilitate early detection of these adverse conditions. Hence, results from studies I, II and IV might have bearing for both primary prevention (prevention of disorder occurrence) and secondary prevention (minimizing time to detection and treatment of disorder) strategies in clinical psychiatry. Finally, clinicians should include both hallucinations and delusions when assessing psychotic experiences in adolescents.

## 5.7 CONCLUDING REMARKS

The population-based, genetically sensitive designs, and bi-directional approach to research into the risk, correlates and consequences of the extended psychosis phenotype yielded replications of prior research as well as a number of novel findings: adolescent psychotic experiences (and to some extent juvenile mania symptoms) are characterized by developmental deviations in areas of communication, reading, mathematics, and neuropsychiatric problems in general. Further, these associations between childhood and adolescent problems share a common etiology of a primarily genetic origin. It can also be concluded that there is a population association between Darier disease and schizophrenia and bipolar disorder. Finally, adolescent psychotic experiences are associated with elevated risks of later diagnoses of drug use disorder, and suicide attempt.

# 6 SVENSK SAMMANFATTNING

Psykossjukdomar innebär ett avsevärt lidande för de drabbade och deras familjer. Av hävd betraktas dessa sjukdomar som diagnosticerbara ”ting” som man antingen har eller inte har. Denna syn på psykossjukdomar har dock börjat ifrågasättas, eftersom forskning har visat att psykosliknande upplevelser är vanliga, speciellt bland ungdomar. Trots en hel del forskning vet man fortfarande relativt lite om orsaker, korrelat och konsekvenser av psykossjukdomar och psykosliknande upplevelser. Målet med denna avhandling var därför att vidare undersöka möjliga riskfaktorer, korrelat och konsekvenser av dessa fenomen.

I studie I och II användes tvillingstudien The Child and Adolescent Twin Study in Sweden (CATSS) för att undersöka om neuropsykiatriska problem i barndomen ökar risken för psykosliknande upplevelser i tonåren. Genom tvillinganalyser kartlades de genetiska och miljömässiga influenserna bakom sambanden. Vi fann att problem med språk och matematik ökade risken för psykosliknande upplevelser i tonåren. Vi fann också ett samband mellan autistiska drag och psykosliknande upplevelser, men detta specifika samband visade sig kunna förklaras av generella neuropsykiatriska problem snarare än autistiska drag i sig. Tvillinganalyserna visade att sambanden mellan barndomsproblemen och psykosliknande upplevelser till största delen influerades av genetiska faktorer.

I studie III använde vi Patientregistret för att undersöka om Dariers sjukdom, en ovanlig hudsjukdom, är kopplat till risk för schizofreni och bipolär sjukdom. Denna hypotes grundar sig i att hud och hjärna bildas ur samma groddblad i embryots tidiga utveckling. Vi fann att personer med Dariers sjukdom hade en fördubblad risk att bli diagnosticerade med schizofreni, och en fyrfaldigt förhöjd risk att bli diagnosticerade med bipolär sjukdom.

I den fjärde och sista studien länkade vi CATSS-studien mot Patientregistret för att undersöka konsekvenser av psykosliknande upplevelser i tonåren. Det visade sig att tonåring som rapporterat dessa upplevelser löpte en förhöjd risk att senare bli diagnosticerade med missbruksproblem eller självmordsförsök.

Sammanfattningsvis fann vi att psykosliknande upplevelser i tonåren präglas av utvecklingsmässiga problem i barndomen och att dessa två typer av problem delar en gemensam genetisk grund. Vidare fann vi ett samband mellan Dariers sjukdom och schizofreni och bipolär sjukdom i befolkningen. Slutligen fann vi att psykosliknande upplevelser i tonåren är associerade med senare missbruk och suicidförsök. Dessa resultat stöder ledande förklaringsmodeller för orsakerna bakom psykossjukdomar och betonar vikten av att följa upp tonåringar med psykosliknande upplevelser.

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