



PhD Thesis
Martin Køster Rinvall, MD

Psychotic experiences in children and adolescents from the general population

Independent risk factors of psychopathology or merely epiphenomena?

Main Supervisor:

Pia Jeppesen, Associate Professor, MD, PhD

Co-supervisors:

Jim van Os, Professor, MD, PhD

Charlotte Ulrikka Rask, Professor, MD, PhD

Frank Verhulst, Professor, MD, PhD

Preface

When I started my research-year scholarship as a medical student on the Copenhagen Child Cohort 2000 (CCC2000) in 2012, little did I know that I would be peripherally involved in the project for many years to come, and that it would eventually lead to my PhD-period soon coming to an end - almost 9 years later. Before I was hired in 2012, my supervisor-to-be, Pia Jeppesen, and then-PhD student Anja Munkholm repeatedly told me about the “strenuous and tiresome” tasks that were awaiting me if I chose to come on board – today I am more than happy that I disregarded their warnings, and became a part of the team.

I owe great thanks to Pia who has been much more than a committed main supervisor of my PhD studies. Pia genuinely cares about her students, opens door and provides opportunities, and transcends from merely being a supervisor, to be an actual mentor. She has stopped me from engaging in multiple more or less hopeless ideas and projects that I have suggested throughout the years – every time with a pure intention of actually helping me in the right direction, without regard for own personal gains.

Pia, and with my co-supervisors, Jim van Os, Charlotte Ulrikka Rask and Frank Verhulst, have made my PhD period a true pleasure. They have constituted a team of supervisors that has made me a very privileged PhD student. Apart from their enthusiastic and generous approach to supervision, their good company on a personal level makes me hope for many opportunities for collaborations in the future.

I am very happy to have come across many delightful people at the Child and Adolescent Mental Health Research Unit of the Capital Region of Denmark over the years. I would like to single out the founder of the CCC2000 cohort, Anne Mette Skovgaard, as well as Else Marie Olsen, Lars Clemmensen, Anja Munkholm, Hanne Elberling, Anne Müller, Maja Gregersen and Nina Sigismund. They have been close colleagues throughout different phases of my work in the CCC2000-group and they were the ones who got me ‘hooked’ on the cohort. Also thank you to everybody else who have worked tirelessly on the CCC2000 project over the last 20 years, and also thanks the participating families, without whom the CCC2000 would never be possible. Thank you to Hanneke Wigman and Spyros Balafas for a fun and fruitful collaboration and stay in Groningen. Thank you to Rasmus Trap Wolf, Jens Søndergaard Jensen, Janne Tidselbak Larsen, Anne Sophie Oxholm, Cecilia Jespersen, Judith Rosmalen and Ernst Witt who have also all contributed directly to the studies included in the thesis.

Thank you to my Mother for careful proof-reading throughout the papers and the thesis.

Thank you to Ditte Ellersgaard for saving my ass on an airplane on the way home from a conference in Boston. Finally, I want to thank my husband, Nicolai, for reminding me to prioritize a reasonable work-life balance, and for making sure that work is never the most important thing in my life. You make me extremely happy.

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Summary

Background

Psychotic disorders, such as schizophrenia, are severe mental disorders that affect around 3% of the population throughout the lifespan. Although psychotic disorders are particularly rare among children and adolescents, psychosis can be viewed on a severity continuum, and psychotic experiences that do not conform to psychotic disorders are common in the general population in youth. However, how to understand the clinical meaning and utility of psychotic experiences is still being debated, and there is considerable controversy and mixed evidence regarding the specificity of psychotic experiences relating to the development of psychopathology transdiagnostically and psychotic disorders specifically.

Objectives

The current PhD thesis aims to assess the clinical impact and utility of psychotic experiences in the general population in late childhood and adolescence with regard to predicting healthcare service use and clinical correlates such as suicidality (*Part 1, Papers 1-3*). Furthermore, the thesis explores specific associations between psychotic experiences and aberrant bodily experiences in the form of health anxiety and functional somatic symptoms (*Part 2, Papers 4-6*).

Study Population

The population-based and prospective Copenhagen Child Cohort 2000 (CCC2000) included 6090 children born in Copenhagen County, Denmark, in the year 2000. A total of 1632 preadolescents from the cohort were assessed for psychotic experiences at age 11 years and form the core population for the studies presented in the current thesis. Psychotic experiences were assessed again at age 16 years follow-up. Various other psychological problems were assessed by clinical interviews and by questionnaires at both ages. Furthermore, all 1632 preadolescents were followed up using register-based data to examine clinical and educational outcomes following psychotic experiences at age 11.

Summary of the results

-Part 1-

Paper 1 examined the persistence of psychotic experiences between ages 11 and 16 and associations between psychotic experiences and risk behaviors (substance use, suicidality and non-suicidal self-injury) in cross-section at both ages and longitudinally. Psychotic experiences showed some continuity between age 11 and age 16 but were most often transient. Particularly persistent psychotic experiences were associated with increased risk behaviors at age 16.

Paper 2 investigated the clinical impact of psychotic experiences assessed at age 11 by examining register-based outcomes in the form of mental disorders diagnosed at child and adolescent mental health services. Compared to individuals without psychotic experiences, preadolescents with psychotic experiences had an

increased risk of incident mental illness diagnosed at child and adolescent mental health services, across diagnostic categories, and an increased use of psychotropic medications.

Paper 3 extended the findings in **Paper 2** and further examined societal impact of psychotic experiences at age 11 by examining outcomes of healthcare costs over the following 5 years as well as school performance and health-related quality of life at age 16. Psychotic experiences were associated with approximately three-fold higher total annual healthcare costs. Detailed analyses showed that costs were increased for mental healthcare services from primary to tertiary care, but not for somatic care. Psychotic experiences were only associated with slightly poorer educational attainment, but individuals with psychotic experiences more frequently reported lower quality of life.

-Part 2-

Paper 4 found associations between psychotic experiences and health anxiety and functional somatic symptoms in cross-section at age 11. The findings, that were robust after mutual adjustment and adjustment for general psychopathology, suggested a specific association between psychotic experiences and aberrant bodily symptoms.

Paper 5 extended the findings from **Paper 4** by using longitudinal data and statistical models assessing if there was an interaction between psychosis vulnerability and functional somatic symptoms on the outcome of high levels of health anxiety symptoms. Having both psychotic experiences and functional somatic symptoms increased the risk of health anxiety somewhat synergistically at both ages 11 and 16 in cross section and longitudinally between the follow-ups.

Paper 6 applied a symptom-based approach to examine associations between psychotic experiences and functional somatic symptoms at age 16 using network analyses. Although the strongest associations were found *within* the respective domains of psychotic experiences and functional somatic symptoms, specific cross domain connections between psychotic experiences and functional somatic symptoms were also found. These findings were largely replicated in a Dutch population-based sample of 15-year-olds.

Conclusions

In conclusion, although the studies in the current thesis could not test a causal relationship between psychotic experiences and a range of detrimental outcomes, psychotic experiences stood out as a robust risk marker of transdiagnostic psychopathology with potent societal impact. Hence, assessment of PE is important in the assessment of child and adolescent psychopathology. Furthermore, psychotic experiences were strongly associated with aberrant bodily symptoms, indicating that assessing bodily symptoms and anxieties should also be incorporated in an integrative fashion when considering child and adolescent mental health including psychosis vulnerability.

Dansk resumé

Baggrund

Psykoselidelser, såsom skizofreni, er alvorlige psykiske lidelser, som rammer ca. 3% af befolkningen i løbet af livet. Psykoselidelser er særligt sjældne blandt børn og unge, men psykose kan anskues på et kontinuum, og psykoseoplevelser er hyppige blandt børn og unge der ikke opfylder kriterierne for en psykoselidelse. Der er endnu ikke enighed om hvorledes psykoseoplevelser skal forstås, og hvordan de kan bruges klinisk. Evidensen vedrørende psykoseoplevelser er uligeartet med hensyn til deres rolle i udviklingen af transdiagnostisk psykopatologi og psykoselidelser specifikt.

Formål

Formålet med denne Ph.d.-afhandling er at undersøge den kliniske betydning og anvendelighed af psykoseoplevelser i normalbefolkningen henover sen barndom og i ungdommen, ved at undersøge om psykoseoplevelser kan bidrage til at forudse brugen af f.eks. sundhedsydelser og selvmordsadfærd (*Del 1, Artiklerne 1-3*). Desuden vil denne afhandling undersøge specifikke sammenhænge mellem psykoseoplevelser og afvigende kropslige oplevelser i form af helbredsangst og funktionelle fysiske symptomer (*Del 2, Artiklerne 4-6*)

Studiepopulation

Den befolkningsbaserede kohorte, Copenhagen Child Cohort 2000, omfatter 6090 børn der blev født i det tidligere Københavns Amt i år 2000, som løbende er blevet fulgt op på. 1632 af deltagerne fra kohorten blev undersøgt for psykoseoplevelser ved 11-års alderen og danner kernepopulationen for de studier der udgør denne afhandling. Deltagerne blev undersøgt for psykoseoplevelser igen ved 16-års alderen. Andre psykiske vanskeligheder blev undersøgt vha. kliniske undersøgelser og spørgeskemaer, både ved 11- og 16-års alderen. For at undersøge eventuelle konsekvenser af psykoseoplevelser ved 11-års alderen, blev alle 1632 unge desuden fulgt i de danske registre for at følge kliniske og uddannelsesmæssige udfald.

Resultater

-Del 1-

Artikel 1 undersøgte hvorledes psykoseoplevelser persisterede mellem 11- og 16-års alderen samt associationer mellem psykoseoplevelser og risikoadfærd (brug af stoffer, selvmordsadfærd og selvskade) – både i tværsnit ved 11- og 16-års alderen samt over tid. Vi fandt evidens for sammenhæng mellem psykoseoplevelser ved hhv. 11- og 16-års alderen, men de var oftest forbigående. Særligt persisterende psykoseoplevelser viste sammenhæng med senere risikoadfærd ved 16-års alderen.

Artikel 2 udforskede den kliniske betydning af psykoseoplevelser ved 11-års alderen vha. registerdata, ved at undersøge sammenhængen mellem psykoseoplevelser og senere diagnosticeret psykisk sygdom i børne- og ungdomspsykiatrisk regi. Børn der havde psykoseoplevelser, viste sig at have en øget risiko for at blive

diagnosticeret med en psykisk sygdom på tværs af diagnosekategorier i børne og ungdomspsykiatrien, og blev oftere behandlet med psykofarmaka.

Artikel 3 var en udvidelse af **Artikel 2**. Studiet undersøgte den samfundsmæssige indflydelse af psykoseoplevelser ved 11-års alderen, ved at undersøge sammenhænge mellem psykoseoplevelser og sundhedsudgifter henover de følgende fem år, samt skolepræstation og sundhedsrelateret livskvalitet ved 16-års alderen. Børn med psykoseoplevelser havde ca. 3 gange øgede sundhedsudgifter sammenlignet med børn uden. Psykoseoplevelser var associeret med øgede udgifter relateret til psykiatrisk/psykologisk behandling men ikke med somatisk behandling. Der var kun svag sammenhæng mellem psykoseoplevelser og dårligere skolepræstation, men børn med psykoseoplevelser oplevede væsentligt oftere ringere livskvalitet.

-Del 2-

Artikel 4 fandt sammenhænge mellem psykoseoplevelser og helbredsangst samt funktionelle symptomer i tværsnit ved 11-års alderen. Associationerne var til stor del uafhængige af generel psykopatologi, hvilket tyder på en specifik sammenhæng mellem psykoseoplevelser og afvigende kropslige symptomer.

Artikel 5 var en udvidelse af **Artikel 4**, som brugte data fra både 11- og 16-års opfølgningen, og undersøgte om der var interaktion mellem psykoseoplevelser og funktionelle symptomer ift. udfald af helbredsangst. Der var en vis synergistisk effekt mellem psykoseoplevelser og funktionelle symptomer ift. risikoen for helbredsangst både i tværsnitsundersøgelser ved hhv. 11- og 16-års alderen samt i længdesnit mellem de to opfølgninger.

Artikel 6 benyttede en symptom-baseret tilgang ved brug af netværksanalyser, med henblik på at undersøge sammenhænge mellem funktionelle symptomer og psykoseoplevelser ved 16-års alderen. Selvom de stærkeste sammenhænge blev fundet mellem hhv. psykoseoplevelser på den ene side og funktionelle symptomer på den anden side, var der også specifikke sammenhænge mellem de to domæner. Disse fund blev overordnet repliceret i en hollandsk population af 15-årige unge.

Konklusion

Selvom studierne i denne afhandling ikke kunne kortlægge, om der var kausal sammenhæng mellem psykoseoplevelser og en række ufordelagtige udfald, viste psykoseoplevelser sig at være en stærk risikomarkør for transdiagnostisk psykopatologi, hvilket kan have betydende samfundsmæssig og personlige omkostninger. Det er derfor vigtigt at undersøge for psykoseoplevelser når man undersøger psykopatologi hos børn og unge. Desuden var psykoseoplevelser stærkt associeret med afvigende kropslige symptomer, hvilket viser at det er vigtigt at integrere oplysninger om kropslige symptomer og angst når man undersøger psykopatologi, herunder psykosesårbarhed, hos børn og unge.

Overview of papers included in the thesis

-Part 1-

Paper 1

‘Psychotic experiences from preadolescence to adolescence: when should we be worried about adolescent risk behaviors?’ Martin K. Rimvall, Jim van Os, Charlotte Ulrikka Rask, Else Marie Olsen, Anne Mette Skovgaard, Lars Clemmensen, Janne Tidselbak Larsen, Frank Verhulst, Pia Jeppesen (2019), *European Child & Adolescent Psychiatry*, (online) doi: 10.1007/s00787-019-01439-w.

Paper 2

‘Mental health service use and psychopharmacological treatment following psychotic experiences in preadolescence’ Martin Køster Rimvall, Jim van Os, Frank Verhulst, Rasmus Trap Wolf, Janne Tidselbak Larsen, Lars Clemmensen, Anne Mette Skovgaard, Charlotte Ulrikka Rask, Pia Jeppesen (2020), *American Journal of Psychiatry*, 177(4), pp. 318–326. doi: <https://doi.org/10.1176/appi.ajp.2019.19070724>.

Paper 3

‘Healthcare costs, school performance and health-related quality of life in adolescence following psychotic experiences in preadolescence – a longitudinal cohort study’ Martin Køster Rimvall, Rasmus Trap Wolf, Else Marie Olsen, Anne Mette Skovgaard, Lars Clemmensen, Anne Sophie Oxholm, Frank Verhulst, Charlotte Ulrikka Rask, Jim van Os, Pia Jeppesen, under peer review consideration.

-Part 2-

Paper 4

‘Psychotic experiences are associated with health anxiety and functional somatic symptoms in preadolescence’ Martin K. Rimvall, Cecilia Pihl Jespersen, Lars Clemmensen, Anja Munkholm, Anne Mette Skovgaard, Frank Verhulst, Jim van Os, Charlotte Ulrikka Rask and Pia Jeppesen (2019), *Journal of Child Psychology and Psychiatry*, 60(5), pp. 524–532. doi: 10.1111/jcpp.12986.

Paper 5

‘Exploring the interplay between psychosis vulnerability, functional somatic symptoms and health anxiety in childhood and adolescence – a longitudinal cohort study’ Martin Køster Rimvall, Charlotte Ulrikka Rask, Jens Søndergaard Jensen, Else Marie Olsen, Lars Clemmensen, Anne Mette Skovgaard, Frank Verhulst, Jim van Os, Pia Jeppesen, in preparation for submission.

Paper 6

‘Symptom networks of psychotic experiences and functional somatic symptoms in adolescence: an observational study of two population-based cohorts’ Martin Køster Rimvall, Johanna T. W. Wigman, Spyros Balafas, Ernst C. Wit, Judith Rosmalen, Frank Verhulst, Jim van Os, Charlotte Ulrikka Rask, Pia Jeppesen, under peer review consideration.

Abbreviations

CAMHS = Child and adolescent mental health services.

CI = Confidence interval

DAWBA = Development and Well-Being Assessment

FSS = Functional somatic symptoms

HA = Health anxiety

OR = Odds ratio

PE = Psychotic experiences

RR = Relative risk

Introduction

Psychotic disorders across the lifespan

In modern psychiatric clinical practice, mental health problems are grouped into psychiatric disorders based on the presence of a pre-set number of phenotypic criteria and grouped into categories that are either present or absent. These disorders have been manualized and are diagnosed according to specific criteria of the Diagnostic and Statistical Manual of Mental Disorders, DSM 5 (American Psychiatric Association, 2013) or by the International Classification of Diseases 10, ICD-10 (World Health Organization, 1993). The latter classification is utilized in the majority of western countries.

The core symptoms in psychotic disorders are described within the domains of negative and positive symptoms. Negative symptoms refer to a loss of functioning and consist of symptoms such as blunted affect, marked apathy and poor and often deteriorating social performance. Positive symptoms refer to distortion, or excess, of normal functioning and include a) disorganized symptoms such as disorganized speech, bizarre behavior and inappropriate affect and b) psychotic symptoms such as hallucinations, delusions and subjective thought disturbances (i.e. passivity phenomena) (Andreasen et al., 2005; Hollis and Palaniyappan, 2015).

Psychotic disorders are rare on a population level, affecting only around 2-4% of the population throughout the lifetime (Chang et al., 2017; Pedersen et al., 2014; Perälä et al., 2007). However, there are marked geographical differences in the prevalence of psychotic disorders (Jongsma et al., 2018). Around 30% of psychotic disorders are categorized as schizophrenia (Chang et al., 2017; Pedersen et al., 2014; Perälä et al., 2007). Psychotic disorders, and especially schizophrenia, are regarded as the most severe among mental disorders. Schizophrenia is often thought to be a chronic disorder, as illustrated by the first 'key-facts' stated by the World Health Organization in its publicly available online fact-sheets on schizophrenia (World Health Organization, 2019). However, evidence suggests that approximately 50% of patients with schizophrenia have moderately good long-term outcomes (National Collaborating Centre for Mental Health, 2014), and up to 80% of first-episode psychosis patients experience prolonged periods of substantial remission (Albert et al., 2011; Morgan et al., 2014). Nonetheless, individuals with schizophrenia have markedly lower life-expectancy (Laursen et al., 2014) and the consequences of schizophrenia contribute substantially to the global burden of disease, especially for young people under age 45 (Rössler et al., 2005). Even though psychotic disorders are relatively rare on a population level, schizophrenia is estimated to be the approximately 20th leading cause of years lived with disability of all disorders, i.e. among both psychiatric and somatic conditions (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018).

Psychotic disorders in childhood and adolescence

Psychotic disorders are most often diagnosed in late adolescence or early adulthood, yet psychotic disorders in adulthood are often preceded by mental disorders across diagnostic categories, e.g. depression, anxiety, and hyperkinetic disorders, in childhood and adolescence (Kim-Cohen et al., 2003; Maibing et al., 2015). Although there is an association between diagnoses made in childhood and adolescence and later psychotic disorder in adulthood, psychotic disorders themselves are most often thought to have their onset in adulthood. High-quality epidemiological data are sparse, but it is estimated that around 10-20% of psychotic disorders are early onset psychosis, i.e. psychosis diagnosed before age 18 (Nesvåg et al., 2018; Rabinowitz et al., 2006). However, recent register-based studies from Denmark find a substantial surge in diagnosis of psychotic disorder in young people below the age of 18 over the last 40-50 years (Okkels et al., 2013), and a 2-3-fold increase between 2000-2012 (Kühl et al., 2016). A recent study found that around 0.6% of the entire population in Denmark had a register-based psychotic disorder before age 18, and of these, approximately 25% were diagnosed with schizophrenia (Dalsgaard et al., 2019). The impact of early onset psychosis might be substantial. Younger individuals are often thought to be treatment resistant, particularly with regard to negative symptoms, and to exhibit poorer outcomes compared to individuals with onset in adulthood (Clemmensen et al., 2012; Hollis and Palaniyappan, 2015; Stentebjerg-Olesen et al., 2016). However, the evidence for this is not consistent, and has recently been challenged (Vernal et al., 2020). Nonetheless, particularly in youths (Coulon et al., 2020), psychotic disorders are characterized by massive co-morbidity, which highlights the importance of an appropriate early detection and classification of psychotic disorders across all ages.

Conceptualization of mental health problems

Although systems for classification of mental disorders can be helpful in everyday clinical work in order to target specific treatments, mental disorders can be criticized for oversimplifying the complex causality that underlies psychopathology and for ignoring the overlap between disorders (Kendler, 2016; Kendler et al., 2011). Psychopathology can be conceptualized as groupings of problems that can vary in number and severity and that are multifactorial in origin rather than “diseases” that are either present or absent and that have a known etiology (Kendell, 1975). Most importantly, symptoms of mentally ill health do not ‘respect’ the boundaries of the defined categories/diagnoses, and comorbidity between symptoms and disorders is common (Plana-Ripoll et al., 2019) - e.g. anxiety often occur in patients with a diagnosis of depression, and vice-versa (Hirschfeld, 2001). The ICD-10 is built hierarchally, i.e. if an individual fulfills criteria of a psychotic disorder, such as schizophrenia, at the higher end of the hierarchy, the patient cannot be diagnosed with an anxiety disorder at the same time (World Health Organization, 1993). However, given that individual patients’ symptoms are often not sufficiently described by one singular diagnosis, this principle is often overruled in

clinical practice and multiple diagnoses can be assigned, i.e. co-morbidity is acknowledged. However, even though this practice partially remedies this weakness of diagnostic classification in psychiatry, much clinical information can still be lost, e.g. if the symptoms described within other diagnostic categories do not reach an often arbitrarily set threshold for disorder. Hence, diagnostic categories may overlook individuals that do not conform to criteria of a specific mental disorder, but still might (periodically) experience mental health difficulties that require the person to receive support.

The problem described above might at first glance appear to be primarily academic, but it illustrates a profound and significant problem with our diagnostic systems. Assignments of diagnoses are of great importance in society, since they are often necessary for individuals with mental health problems to receive healthcare benefits, sick-leave and access to treatment. However, given the description of for example schizophrenia being a “chronic mental disorder”, diagnosing schizophrenia might relay overly pessimistic predictions regarding the future for afflicted individuals, which might cause societal- as well as self-stigma (Gerlinger et al., 2013), and it has been proposed to be dropped (van Os, 2016).

Dimensional psychopathology

Given the weakness of dichotomization of ‘healthy’ vs ‘sick’ pertaining to psychiatric diagnoses, mental health problems might better be viewed in a dimensional and transdiagnostic framework. Within such a framework, symptoms can exist in a multidimensional space in which multimodal mental health problems are associated over time and place across traditional mental disorders (Kendler et al., 2011).

Several models have been suggested to help study and understand the dimensional nature of psychopathology and are continuously under development. In children and adolescents, psychopathology has long been thought of in broader terms, such as internalizing problems and externalizing problems. Internalizing problems pertain to depressive, anxious and withdrawn symptomatology and somatic complaints, whereas externalizing problems include difficulties with aggressive, delinquent and hyperactive behaviors (Achenbach and Edelbrock, 1978). The same can be seen in adults, and the suggestion of internalizing and externalizing symptomatology forms the basis of for instance a prominent, unifying model for understanding the structure of psychopathology, the general psychopathology factor ‘p’ (Caspi and Moffitt, 2018). The p-factor model goes somewhat further and suggests that a unidimensional factor of psychopathology best describes the structure of severe psychopathology, in which individuals who are prone to psychopathology have transdiagnostic symptoms that change over time (Caspi and Moffitt, 2018). Support for this idea come from sequence of being diagnosed with different mental disorders over time, showing marked comorbidity and that virtually all mental disorders are both preceded and followed by disorders within different diagnostic groups (Caspi et al., 2014; Copeland et al., 2013, 2009). Furthermore, register-

based research from Denmark shows that e.g. psychotic disorders are both preceded and succeeded by mood disorders, personality disorders, developmental disorders etc. (Plana-Ripoll et al., 2019).

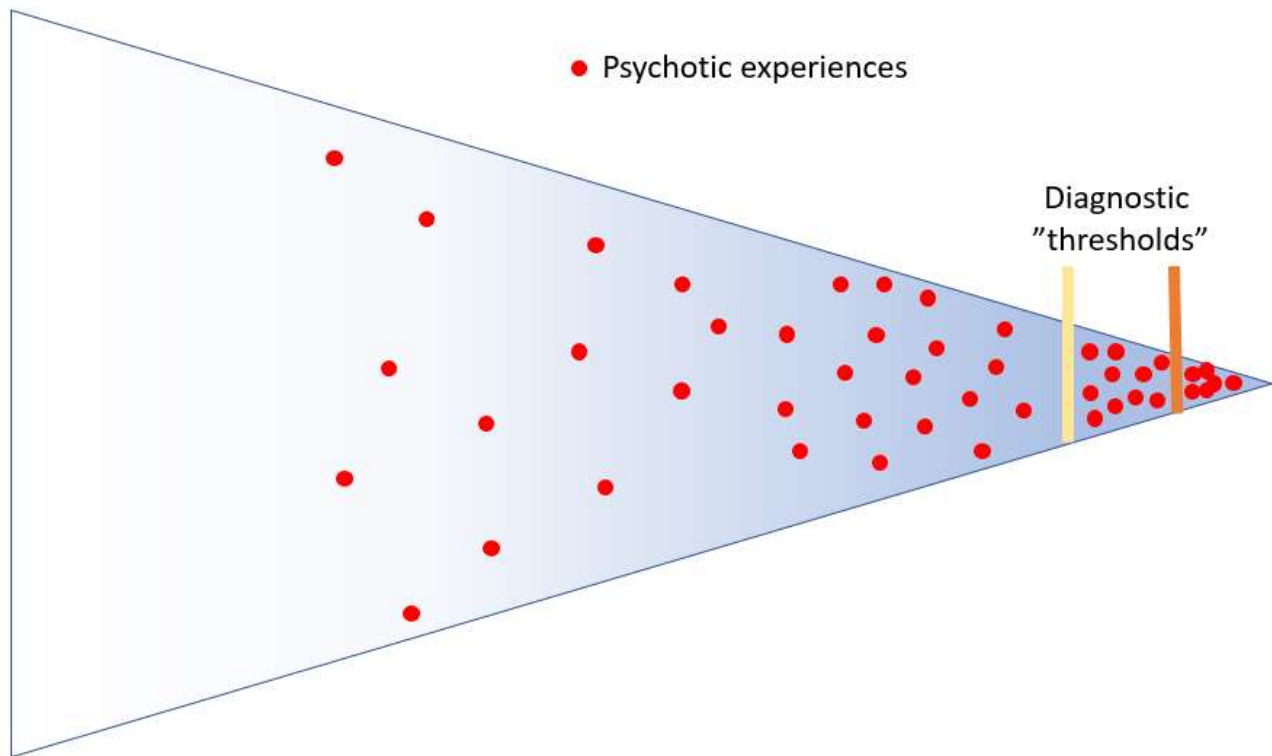
Another contemporary approach to understanding the structure of psychopathology is the network approach to psychopathology that has been widely used and developed over the past decade (Robinaugh et al., 2020). The network approach is a symptom-based approach suggesting that symptoms of psychopathology mutually impact each other and eventually lead to more severe psychopathology, potentially leading to the diagnosis of a mental disorder (Borsboom, 2017; Borsboom and Cramer, 2013). The symptoms in the network may arise and be sustained by other symptoms in the network as well as factors such as genetic vulnerabilities and external stressors, e.g. trauma and other adversities. Furthermore, once a network has been 'activated' and sustained over a longer time period, e.g. leading to diagnosis of mental disorder, such a state may become lasting/chronic (Borsboom, 2017). This agrees well with findings that for instance a lag in identification and treatment for psychotic disorders (i.e. duration of untreated psychosis) leads to a more severe course of illness (Marshall et al., 2005; Penttilä et al., 2014).

Psychosis as a continuous and transdiagnostic phenotype

Although psychotic disorders are most commonly regarded as the most severe mental health problems, features of positive psychotic symptoms still commonly occur in individuals without psychotic disorders – both in the general population and, more frequently, in individuals with non-psychotic mental illnesses (Hanssen et al., 2003; Kelleher and De Volder, 2017; Olfson et al., 2002; Wigman et al., 2012). Psychosis has generally been regarded in a bimodal fashion, in which positive psychotic features, such as auditory hallucinations, either are present to a slight (and diagnostically non-consequential) degree, or manifest as severe but rare psychotic disorder (Johns and van Os, 2001). However, such a model ignores potentially important clinical information in-between these two points, and the distribution of symptoms of psychosis has been suggested to lie on a continuum in the population (Johns and van Os, 2001).

Psychotic symptoms and the lower end of the continuum are referred to in the literature as psychotic-like experiences or psychotic experiences (van Os et al., 2009). These two terms are often used interchangeably (Seiler et al., 2020), and the term psychotic experiences (PE) will be used throughout the current thesis and in the papers. PE have an estimated meta-analytic point-prevalence of around 7% in the general population of adults (Linscott and van Os, 2013). The majority of PE, approximately 80%, remit over time, whereas 20% persist (Linscott and van Os, 2013). For some individuals, PE become sufficiently frequent, persistent and impairing and might present together with concurrent negative symptoms so that they conform to the criteria of a psychotic disorder. In some cases, such illness might become chronic, which is often labelled schizophrenia (van Os, 2016) - see [Figure 1](#) for an illustration of psychosis viewed on a spectrum.

Figure 1: A hypothesized representation of the distribution of psychotic symptoms in the population. The yellow line represents a threshold to psychotic disorders while the orange line represents the threshold to schizophrenia. Inspired by a figure from van Os and Linscott 2012.



Although the large majority of individuals who have PE are never diagnosed with a psychotic disorder, PE are associated with numerous problems including a history of psychological trauma (Sideli et al., 2020; Trotta et al., 2015), reduced health related quality of life (HRQoL) (Alonso et al., 2018), suicidality and self-harm (Honings et al., 2016; Yates et al., 2019), poorer social achievement and functioning (Rössler et al., 2007) and later development of non-psychotic psychopathology and disorders (Kaymaz et al., 2012; Kirli et al., 2019; Rössler et al., 2011; van Os and Reininghaus, 2016).

Psychosis expression at the lower end of the continuum can be viewed as a proxy for the severity of non-psychotic mental health problems (Guloksuz et al., 2015). This is supported by studies finding that PE are associated with severity and occurrence of fulfilling criteria for multiple mental disorders (Rössler et al., 2011; Wigman et al., 2012). Although evidence suggests that PE are transdiagnostic phenomena (van Os and Reininghaus, 2016), PE might still show some propensity towards reaching clinically impairing levels, i.e. psychotic disorders (Kaymaz et al., 2012; Poulton et al., 2000; Sullivan et al., 2020), and hence arguably be a 'risk marker' for psychosis. Therefore, although it might often be advantageous to view psychosis on a continuum as an extended phenotype (van Os and Linscott, 2012) with transdiagnostic implications (van Os and Reininghaus, 2016), such an approach is likely not exhaustive in explaining psychosis and schizophrenia.

It does also not preclude qualitative and quantitative differences with regard to psychosis expression between groups (e.g. schizophrenia vs. affective psychosis) (Binbay et al., 2012; van Os, 2014).

Psychotic experiences in children and adolescents

Even though psychotic disorders are uncommon in children and adolescents, PE are likely more common in childhood and adolescence compared to adulthood and can often be part of normal development (Kelleher et al., 2012a; Majjer et al., 2018). Estimated point-prevalence estimates of around 17% in children aged 9-12 and 7.5% in adolescents aged 13-17 have been reported (Kelleher et al., 2012a). The reported prevalence-estimates are subject to much uncertainty, given that the method used to assess PE, e.g. self-reports vs. clinician-conducted interviews, might have profound impact on the estimates. PE are generally more common when assessed by self-report and are likely subject to misclassification and “false positives” (Gundersen et al., 2019; Moriyama et al., 2019). Particularly delusions appear to be over-reported by respondents, whereas hallucinations are more accurately reported by self-reports, when held up against clinical interviews (Gundersen et al., 2019; Kelleher et al., 2011). However, several studies suggest that PE that are self-reported yet not interview-confirmed are still clinically relevant, since they are associated with general mental health problems and non-psychotic disorders as well as later psychotic disorders and reduced functioning, albeit to a lesser degree than interview-confirmed PE (Bak et al., 2003; Moriyama et al., 2019; Rimvall et al., 2019; van der Steen et al., 2018).

Associations with non-psychotic psychopathology

Like in adults, PE in youths are associated with a broad range of mental health problems. Ample evidence from cross-sectional, general-population studies suggest that PE are associated with mental disorders broadly, including both neurodevelopmental and emotional psychopathology and psychological distress (Hielscher et al., 2018; Jeppesen et al., 2015a; Kelleher et al., 2015, 2012b; Laurens et al., 2020). Additionally, like in adults, PE can be regarded as a severity marker of non-psychotic psychopathology, given that PE are associated with increased co-morbidity (Jeppesen et al., 2015a; Kelleher et al., 2012b, 2012d; Wigman et al., 2011). A recent review and meta-analysis of studies on PE in children and adolescents (Healy et al., 2019a) mimics meta-analytic findings in adults (Kaymaz et al., 2012): PE in youths were associated with an approximately 4-fold increased risk of psychotic disorders later in adulthood, whereas the evidence for later non-psychotic disorders such as affective and behavioral disorders was somewhat less convincing (Healy et al., 2019a). Furthermore, PE have been shown to contribute to the prediction of later mental illness over and above the predictive values of general internalizing and externalizing mental health problems (Healy et al., 2019b).

Given that suicide is one of the leading causes of death among young people (World Health Organization, 2020; Zalsman et al., 2016), it is alarming that PE are indeed strongly associated with suicidality in youths below the age of 18 (Honings et al., 2016; Kelleher et al., 2014a, 2013; Martin et al., 2015; Sullivan et al., 2015). The association between PE and such dangerous behaviors provides a strong case for unravelling the potential role of PE in the prevention of suicidality, as well as further examining the clinical impact of PE and the potential utility of assessing PEs in youths.

Functional outcomes and mental health service use

In addition to an increasingly well-established association between PE and a wide array of psychopathologies, a body of research is emerging, which examines functional correlates and outcomes of PE. Long-term follow-ups of PE in childhood and young adults have found associations between PE and problems at work and unemployment (Davies et al., 2018; Poulton et al., 2000; Rössler et al., 2007). Furthermore, a longitudinal study found that PE in a small sample of preadolescents predicted later poorer functioning in early adulthood over and above what can be explained by mental illness, and this even among individuals for whom the PE were transient (Healy et al., 2018). Additionally, studies regarding educational attainment have generally found that PE are associated with somewhat poorer academic performance (Bartels-Velthuis et al., 2011; Davies et al., 2018; Steenkamp et al., 2020; Trotta et al., 2019; Unterrassner et al., 2017), largely independently of IQ (Davies et al., 2018; Steenkamp et al., 2020; Trotta et al., 2019). However, this association is likely at least partly explained by other co-occurring psychopathology, as recently shown in studies that took into account the effect of co-occurring emotional, behavioral and attentional problems (Steenkamp et al., 2020; Trotta et al., 2019).

With regard to mental health service use, a recent meta-analysis found that adults with PE had an approximately 2-fold increased risk of being in contact with mental health services (Bhavsar et al., 2018). However, with few exceptions (Bhavsar et al., 2017; Werbeloff et al., 2012), the vast majority of the studies are either cross sectional, based on self-reported help-seeking, and most often both (Bhavsar et al., 2018). Furthermore, the findings regarding service use have not been extended to examining PE in relation to use of child and adolescent mental health services (CAMHS).

Aberrant bodily experiences in psychosis

Aberrant bodily experiences are common in individuals with psychotic disorders and take many different forms. At the most severe end of the spectrum, somatic hallucinations (e.g. tactile hallucinations or feeling that organs are burning) and somatic delusions (e.g. beliefs that organs are rotting or that facial features have changed) are described for example in the Scale for the Assessment of Positive Symptoms (Andreasen, 1984). However, less overt bodily sensations are described within the concepts of self-disturbances and basic

symptoms, and commonly occur in patients with psychotic disorder as well as in preclinical states (Sass and Parnas, 2003). Such symptoms might involve clearly aberrant manifestations such as over/underestimation of body size and loss of bodily demarcation, but a subset of these symptoms, within the subgroup of ‘cenesthopathies’, appear as vestibular sensations, numbness and moving bodily sensations/pain which in turn can be accompanied by severe illness worry (Gross et al., 1987; Parnas et al., 2005; Sass and Parnas, 2003).

Such cenesthetic experiences clinically resemble core symptoms in mental disorders characterized by physical symptoms and complaints. Mental disorders dominated by medically unexplained symptoms have previously been referred to as somatoform disorders but are now categorized as bodily distress disorder in the upcoming ICD-11 (Gureje and Reed, 2016) and somatic symptom disorder in DSM-5 (American Psychiatric Association, 2013). However, illnesses characterized by mainly health-related anxiety will be described as hypochondriasis in ICD-11 (Stein et al., 2016) and illness anxiety disorder in DSM-V. Although these defined syndromes might be described and occur independently, patients often have symptoms within both constructs and share common co-morbidity with depressive and other anxiety disorders (Leibbrand et al., 2000; Scarella et al., 2016) which is also acknowledged in the diagnosis of somatic symptom disorder in the DSM-V (American Psychiatric Association, 2013). Because aberrant bodily experiences can be quite dominating in some subgroups of patients with psychotic disorders (Jenkins and Röhricht, 2007; Röhricht and Priebe, 2002), specific subgroups of psychotic disorders have previously been suggested, such as cenesthetic schizophrenia (Huber, 1957) and hypochondriacal psychoses (Opjordsmoen, 1988). Observations that bodily symptoms are common in psychosis raise the issue of potential developmental overlaps (Simon et al., 2014).

Health anxiety and functional somatic symptoms

Like psychotic disorders, clinical levels of health anxiety (HA), i.e. hypochondriasis in the ICD-10, is relatively uncommonly diagnosed in childhood (Fritz et al., 1997; Schulte and Petermann, 2011). However, like psychosis, symptoms of HA (i.e. fears and ruminations concerning one’s physical health) can also be found as a continuum in the general population (Asmundson et al., 2010). Retrospective studies of adults have found that adults with severe HA often experienced their first symptoms in childhood and adolescence (Noyes et al., 2002), and HA symptoms are common in childhood and adolescence (Wright and Asmundson, 2003). Furthermore, prospective studies from the Copenhagen Child Cohort 2000 have found some level of continuity of HA from childhood to adolescence, and that high levels of HA are associated with increased use of somatic healthcare services, independently of physical illness (Rask et al., 2016; Rimmvall et al., 2020a). Furthermore, medically unexplained physical symptoms, often referred to as functional somatic symptoms (FSS), are common in children and adolescents (Walker et al., 2009). Symptoms described within this concept

can range from common symptoms such as pain in extremities, headaches and dizziness to more complex symptoms such as moving pains, medically unexplained seizures and pareses (Budtz-Lilly et al., 2015), the latter which are also described within the framework of cenesthopathies (Gross et al., 1987; Parnas et al., 2005; Sass and Parnas, 2003).

Common elements can be found in explanatory models underlying psychosis, HA and FSS, respectively. An important explanatory model in psychosis involves 'aberrant attribution of salience', in which the psychosis-prone individuals aberrantly augment the significance of everyday experiences and sensory input (Kapur, 2003; Nelson et al., 2014). Within this framework, these individuals are assumed to exhibit an aberrant preponderance to 'top-down' information processing, i.e. experiences arise on the basis of internal cognitive expectations, rather than primary 'bottom-up' information processing based on sensory input (Kveraga et al., 2007). Augmented top-down information processing in individuals with FSS has also been suggested as an important cognitive feature in individuals with FSS, referred to predictive processing in FSS literature (Henningsen et al., 2018; Van den Bergh et al., 2017). Furthermore, the aberrant augmentation of the significance of bodily experiences and related worries is a contemporary framework attempting to explain the occurrence and maintenance of HA (Norris and Marcus, 2014; Warwick and Salkovskis, 1990). Importantly, in clinical practice, distinguishing between cenesthopathies, FSS and HA might indeed also be difficult in adolescence. In a review by Simon and colleagues, a "cenesthopathy-hypochondriasis-psychosis spectrum" was suggested in adolescence due to the apparent overlap of symptoms, although population-based studies examining such an overlap are lacking (Simon et al., 2014).

Previous studies on psychotic experiences in the Copenhagen Child Cohort 2000

Several studies from the Copenhagen Child Cohort 2000 (CCC2000) have examined PE at age 11-12 years prior to this thesis. A total of 1632 children were examined by clinical interview at age 11 using the psychosis section of the Kiddie Schedules of Affective Disorders and Schizophrenia, along with numerous examinations and questionnaires regarding other psychopathology and clinical correlates. This is described in detail in the methods section. A cross-sectional study of PE in the CCC2000 cohort reported that a total of 10.5% of the population were rated positive for at least one lifetime PE. The prevalence-estimate of PE revealed no significant differences (10.9% [95%CI 9.1-12.7]) when weighted for sociodemographic and perinatal characteristics. PE were associated with neurodevelopmental and emotional disorders, increased co-morbidity, self-reported psychosocial difficulties and everyday functional impact of difficulties (Jeppesen et al., 2015a). Additionally, in a study linked to independently acquired register-based data, PE were associated with a family history of psychotic disorders among first degree relatives, but not with a family history of non-psychotic mental disorders, indicating a degree of specificity of PE with regard to psychosis liability (Jeppesen et al., 2015b).

Besides the interview measure of PE, PE were also independently assessed by self-report using the PE-section from the Development and Well-Being Assessment (Goodman et al., 2000; Gundersen et al., 2019), enabling studies to examine the concordance between the PE measures. The results from these CCC2000 studies (Gundersen et al., 2019; Rimvall et al., 2019) were already discussed in the “Psychotic experiences in children and adolescents”-section in relation to other literature on the subject of interview-based vs. self-reported PE on page 6.

Furthermore, PE were associated with aberrant social cognition in the form of exaggerated theory of mind, i.e. hyper theory of mind (Clemmensen et al., 2016, 2014). Finally, using an experimental test paradigm, hallucinations were associated with speech illusions, as an expression aberrant attribution of affective salience (Rimvall et al., 2016).

The papers in the current thesis extend on the PE-studies from the 11-year follow-up of the CCC2000 with further exploration of PE in relation to FSS and HA, as well as longitudinal follow-ups.

Objectives

The current thesis aimed to describe psychopathological correlates of PE in children and adolescents from the prospective general population longitudinal cohort study, Copenhagen Child Cohort 2000. The papers on which the current thesis is based, address two overall themes.

Part 1 “Investigating adolescent outcomes following psychotic experiences in preadolescence” includes **Papers 1-3**. The studies described in these papers aimed to examine hypothesized detrimental longitudinal outcomes in adolescence following presence of PE in preadolescence. The outcomes included risk behaviors and HRQoL in adolescence as well as school performance and register-based outcomes on CAMHS use and other healthcare use over a 5-year follow-up period.

Part 2 “Exploring specific developmental associations between psychotic experiences and aberrant bodily experiences” includes **Papers 4-6**. This second part attempts to describe potential specific associations between PE, FSS and HA which could contribute to denote a group of youths with particularly detrimental outcomes of psychotic and non-psychotic mental health problems.

The specific aims and hypotheses of the individual studies of the thesis are described in detail in the papers.

Methods

Study populations

The Copenhagen Child Cohort 2000 (CCC2000)

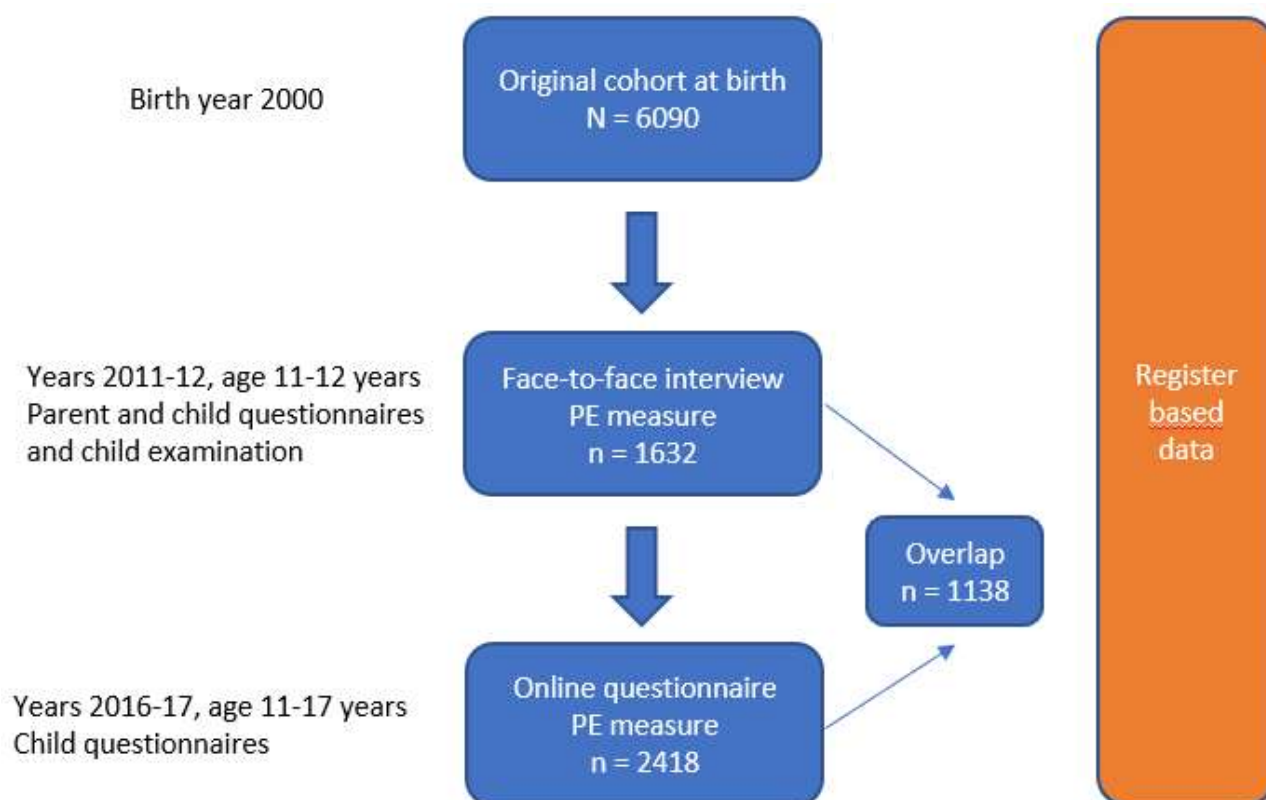
The CCC2000 consists of all 6090 children born alive by mothers residing in the former Copenhagen County (Skovgaard et al., 2005) in year 2000. The original cohort was overall representative of the Danish population born that year, except for ethnic minority parents being overrepresented due to the demographic composition of the catchment area (Olsen et al., 2007). The cohort has been followed-up at multiple points during childhood and adolescence:

- During the 1st year of life in conjunction with up to four health nurse visits.
- At age 5-7 years with parent and teacher reports of psychopathology.
- At age 11-12 years with face-to-face health examinations of the preadolescents and online questionnaires for the participants' parents, teachers and the preadolescents themselves.
- At age 16-17 years with face-to-face health examinations and online questionnaires for the youths.

Details regarding the follow-ups and attrition at the different time-points have recently been published in a cohort description (Olsen et al., 2020). Of particular interest for the current thesis are the 1632 individuals who participated in face-to-face clinician interviews of the potential occurrence of PE at age 11-12 years (hereafter age 11) between May 2011 to October 2012. Baseline sociodemographic and perinatal characteristics of the population have been described in a previous publication (Jeppesen et al., 2015b): Non-participants in the 11-year follow up were characterized by more often being male, having lower gestational age, birthweight, lower maternal age and level of education, having immigrant parent(s), coming from broken families and more often having parents with a history of a mental disorder before the birth of the child.

At age 16-17 years (hereafter age 16), a total of 2418 individuals completed full questionnaires regarding PE between August 2016 to November 2017. As described in detail in **Paper 1**, 1138 individuals (70% of those interviewed for PE at age 11) were assessed for PE by self-report at age 16, see **Figure 2** for a graphical overview. The additional attrition between the follow-ups was further characterized by disadvantageous socioeconomic characteristics (see **Paper 1**). The longitudinal analyses using register-based follow-up allowed close to 100% follow-up, with only emigration from Denmark constituting attrition. In survival analyses, all participants could contribute with data until time of emigration.

Figure 2: Graphical overview of the follow-ups of the Copenhagen Child Cohort 2000 relevant to the papers of the current thesis.



The TRacking Adolescents' Individual Lives Survey

Data from the TRacking Adolescents' Individual Lives Survey (TRAILS) was included in **Paper 6** for a collaborative study between the two cohorts. The TRAILS cohort consists of 2330 participants from the northern part of the Netherlands that were recruited in years 2001/2002 at mean age 11.1 years. They have since been re-examined multiple times in adolescence and into adulthood with high retention rates (Oldehinkel et al., 2015). Non-participation in TRAILS follow-ups was characterized by male sex and lower parental education (De Winter et al., 2005). The population used in the study of the current thesis consisted of 1665 individuals who participated at the 3rd data collection wave at mean age 15.7.

Overview of measures

Table 1 provides an overview of the questionnaire and interview-based data divided into the 11- and 16-year follow-ups of the CCC2000 cohort respectively, together with an overview of which specific measures that were used in each of the separate papers forming the basis of this thesis. **Table 2** provides an overview of the register-based data included in the majority of the studies. Furthermore, all individual measures are described shortly, with a focus on the choices made regarding their use in the individual studies. Further details regarding scoring and reliability measures etc. can be found in the separate papers.

Table 1. Overview of interview-, test- and questionnaire-based variables and measures used in the studies of current thesis. All measures are self-reported unless otherwise specified.

Interview and questionnaire data and variables		Measure	Paper in thesis					
Copenhagen Child Cohort age 11			1	2	3	4	5	6
Psychotic experiences (clinician interview)		Kiddie Schedules of Affective Disorders and Schizophrenia – present and lifetime version (Kaufman et al., 1997)	x	x	x	x	x	
Depressive symptoms (clinician interview)			x					
Suicidal ideation, suicide attempts and non-suicidal self-injury (clinician interview)			x					
Speech illusions (clinician test)								
Intelligence quotient proxy (clinician test)		White Noise Task (Galdos et al., 2011; Rimvall et al., 2016)						x
ICD-10 mental disorders (clinician-assigned disorders based on parent, child and teacher questionnaires)		Block Design Test from the Wechsler's Intelligence Scale (Wechsler, 2003)		x	x			
General psychopathology and impact of general psychopathology (parent questionnaire)		The Development and Well-Being Assessment (Goodman et al., 2000)		x		x		
General psychopathology and impact of general psychopathology (parent questionnaire)		The Strengths and Difficulties Questionnaire (Goodman, 1997) including impact supplement (Goodman, 1999).	x				x	x
Health Anxiety		Childhood Illness Attitudes Scales, self-report questionnaire (Wright and Asmundson, 2005), 21 item version (Thorisdottir et al., 2017)				x	x	
Functional Somatic Symptoms		Children's Somatization Inventory 24 revised (Walker et al., 2009)				x	x	
Copenhagen Child Cohort age 16								
Psychotic experiences		Psychosis-like Symptoms questionnaire (Horwood et al., 2008)	x				x	x
Depressive symptoms		Moods and Feelings Questionnaire (Angold et al., 1995)	x					
Suicidal ideation, suicide attempts and non-suicidal self-injury		Questionnaire from the Child and Adolescent Self-harm in Europe Study (Madge et al., 2008)	x					
Anomalous self experiences		Self-Experience Lifetime Frequency Scale - SELF (Heering et al., 2016)					x	
Substance use		The World Health Organization 'Alcohol, Smoking and Substance Involvement Screening Test' - ASSIST (Humeniuk et al., 2008)	x					
General psychopathology and impact of general psychopathology		The Strengths and Difficulties Questionnaire (Goodman, 1997) including impact supplement (Goodman, 1999).					x	x
Health Anxiety		The Whiteley 6 Index (Carstensen et al., 2020)					x	
Functional Somatic Symptoms		The Bodily Distress Syndrome Check-List (Budtz-Lilly et al., 2015)					x	x
Tracking Adolescent's Individual Lives Survey age 15 variables								
Psychotic experiences		Community Assessment of Psychotic Experiences (Hanssen et al., 2003; Stefanis et al., 2002)						x
Emotional psychopathology		Youth Self Report of the Child Behavioral Check List (Achenbach et al., 2012)						x
Functional somatic symptoms		Youth Self Report of the Child Behavioral Check List (Achenbach et al., 2012) and customized questions on musculoskeletal symptoms (Janssens et al., 2012)						x

Table 2. Overview of registers utilized in the studies of current thesis.

Register-based data and variables		Register	1	2	3	4	5	6
Sociodemographic family background characteristics		The Integrated Database for Labor Market Research (Pettersson et al., 2011) and the Danish Civil Registration System (Pedersen, 2011)	x	x	x	x		
Perinatal background characteristics		The Medical Birth Register (Bliddal et al., 2018)	x	x	x	x		
Mental disorders in tertiary care settings		Danish National Patient Register (Lyngse et al., 2011)		x	x			
Psychotropic medications		Danish National Prescription Registry (Wallach Kildemoes et al., 2011)		x	x			
Healthcare costs		Information from the Danish National Health Service Register (Sahl Andersen et al., 2011), the Danish National Patient Register (Lyngse et al., 2011), and the Danish National Prescription Registry (Wallach Kildemoes et al., 2011)				x		
School performance		The Danish Education Registers (Jensen and Rasmussen, 2011)			x			

Interview and questionnaire data

Psychotic experiences (PE)

PE at age 11 were assessed by clinician interview using the psychosis section of the Kiddie Schedules of Affective Disorders and Schizophrenia – present and lifetime version (Kaufman et al., 1997). The interviewer first screened for hallucinations and delusional ideation and subsequently inquired about a total of 22 PE, nine relating to hallucinations and 13 relating to delusions and passivity phenomena. The individual items were scored dichotomously as ‘not present’ vs ‘likely’ or ‘definitely’ present (Jeppesen et al., 2015b). The experiences were rated as ‘not present’ if the child only heard someone calling their name, if the experience was culturally acceptable or if it had only occurred in relation to fever, somatic illness or intoxication. The interviewers were psychologists and medical doctors or trained students in the corresponding professions. They were supervised every 2 weeks by a consultant child and adolescent psychiatrist (Dr. Pia Jeppesen). The interrater reliability was assessed by independent ratings of 75 videotaped interviews performed by the four raters (Lars Clemmensen, Anja Munkholm, Anne Dorothee Müller and Martin Køster Rimvall) who interviewed most of the participants. The inter-rater agreement was excellent for presence/non-presence of any PE ($\kappa=0.94$) (Jeppesen et al., 2015a). A binary variable of presence/non-presence of lifetime PE was utilized in all the studies of this thesis that included age 11 data (**Papers 1-5**).

The Psychosis-like Symptoms questionnaire (PLIKSq) (Horwood et al., 2008) was utilized at age 16 to assess self-reported PE. The measure included a total of 11 PE: 2 hallucinations, 6 delusions and 3 subjective thought disturbances. These 11 symptoms were scored as ‘not present’—‘maybe present’—‘definitely present’, and the youths were subsequently asked if they felt distress, if the PE had occurred after the age of 15, and if it had occurred solely in relation to substance use. We chose not to discard PE reported to be present solely under the influence of drugs, given that these experiences are also part of the psychosis continuum (van Os et al., 2000). Given that PE are more commonly reported using self-report measures as compared to interviews (Gundersen et al., 2019; Kelleher et al., 2011; Linscott and van Os, 2013), we chose to only include PE that were rated ‘definitely present’ for the dichotomous rating of PE used in **Paper 1** and **Paper 5**. In contrast, in **Paper 6** we chose to only use the level of distress, to make the measure as comparable as possible to the PE-measure in the TRAILS cohort. In TRAILS, PE were also measured by self-report using the Community Assessment of Psychic Experiences, consisting of questions on 20 PE and subsequent rating of distress (Hanssen et al., 2003; Stefanis et al., 2002). A total of eight items were deemed similar enough across the two cohorts to be part of the specific study, see **Paper 6**.

Speech Illusions

Speech Illusions were assessed experimentally at age 11 using the White Noise Task (Galdos et al., 2011). The speech illusions variable was utilized as a secondary psychosis vulnerability variable in **Paper 5**, as an experimental expression of preponderance to attribution of aberrant salience and top-down processing of sensory information. In the original White Noise Task, the participant is subjected to a total of 75 sound clips with white noise. The version used in the CCC2000 utilized only 36 sound clips in order to limit the strain on the young participants (Rimvall et al., 2016). Apart from the shortened version, the task was performed in the same way as the original studies in adults (Catalan et al., 2014; Galdos et al., 2011). In 24 of the sound clips (i.e. two in three), short and neutral sentences were heard over the white noise – 12 clearly audible and 12 barely audible, whereas the remaining 12 sound clips only included white noise. The respondents could select the following responses: 1='hearing positive voice', 2='hearing negative voice', 3='hearing neutral voice', 4='no speech heard' and 5 = 'uncertain'. The 24 sound clips with spoken sentences were only included to facilitate top-down information processing by creating a level of expectation. The remaining 12 sound clips were the clips of interest for assessing speech illusions. Having at least two responses of hearing a voice in white noise only, i.e. responses 1-3, were defined as speech illusions. If at least one of the speech illusions was a positive or negative voice, the speech illusion was rated as affectively salience. For **Paper 5**, a variable of presence/non presence of *affectively salient* speech illusions was utilized, since affectively salient speech illusions consistently have been shown to be more strongly associated with psychosis vulnerability than neutral speech illusions in other populations (Catalan et al., 2014; Galdos et al., 2011) and a prior CCC2000-study (Rimvall et al., 2016)

Anomalous self-experiences

Anomalous self-experiences at age 16 were also considered as an alternative psychosis vulnerability marker in **Paper 5**. To assess self-reported anomalous self-experiences at age 16, we utilized the Self-Experience Lifetime Frequency Scale – 'SELF' (Heering et al., 2016). The SELF was the only questionnaire in the studies of the current thesis that was completed in conjunction with face-to-face examinations at age 16, and is hence not part of the cohort flowchart, **Figure 2**. Given lower participation rates at the face-to-face examinations compared to the online questionnaires, we only had SELF data on 1479 individuals for **Paper 5**. The SELF includes 12 questions on frequency and distress of self-disturbance phenomena (Heering et al., 2016), based on questions from the Depersonalization Severity Scale (Simeon et al., 2001), the Examination of Anomalous Self-Experience interview (Parnas et al., 2005), and the Comprehensive Assessment of At-Risk Mental States interview (Yung et al., 2005). Compared to in the original SELF (Heering et al., 2016), only frequency and not

distress was assessed, in the CCC2000. The anomalous self-experiences score was dichotomized into predetermined top 10% vs bottom 90% scores.

Questionnaire-based ICD-10 diagnoses

Questionnaire-based ICD-10 diagnoses solely for research purposes at age 11 were assessed by parent, child, and in some cases teacher-reported information on psychopathology of the child using the Development and Well-Being Assessment (DAWBA) (Goodman et al., 2000). Highly structured questions pertaining to diagnostic categories were supplemented by open-ended questions allowing each respondent to further describe any specific problems. The information was synthesized and utilized by trained and experienced child and adolescent psychiatrists to ascribe ICD-10 diagnoses. High inter-rater reliability was found for the presence/non-presence of any diagnosis (Kappa=0.81) (Jeppesen et al., 2015a). In **Paper 2** any DAWBA-based mental disorder was utilized for stratification purposes, and in **Paper 4**, we adjusted our analyses for emotional DAWBA-disorders

General psychopathology and impact of psychopathology

The Strengths and Difficulties Questionnaire is a 25-item questionnaire scored Likert scale 0='not true', 1='somewhat true' and 2='certainly true', covering five domains with five questions each: hyperactivity-inattention, conduct problems, emotional problems, peer problems and a prosocial scale (Goodman, 2001, 1997). A total-difficulties score of 0-40 is based on all subscales except the prosocial scale (www.sdqinfo.org). The questionnaire is supplemented by a short section on everyday distress, burden and impairment of the child in different settings, forming an impact score of 0-10 (Goodman, 1999). The parents completed the parent version at age 11 and the youths themselves completed the self-report version both at age 11 and age 16. The Strengths and Difficulties Questionnaire was used in different ways across the separate papers:

Paper 1: A dichotomous measure of impact reported by the youths at age 11 and 16, respectively. This was chosen to include a measure of general impairment as a covariate. Given that a measure of depression was included in the statistical models, we chose not to utilize the total-score.

Paper 3: Another CCC2000 study found that a parent-rated SDQ-algorithm that was used in a Danish randomized controlled trial (Trial ID: NCT03535805) could identify a group with later increased healthcare utilization (Wolf et al., 2019). To encapsulate an easily reproducible group of children that was also likely to exhibit later increased healthcare utilization, a dichotomous score was created based on Danish population-based norm-scores on parent reports (Arnfred et al., 2019). Participants were scored positive if they scored *either* in the top 10% population-score on the total-difficulties scale *or* within the top 10% population-score on the impact scale.

In **Paper 4 and 5** a continuous measure of the SDQ total-difficulties score was used in both studies to adjust for general psychopathology in the models, excluding one item on physical symptoms from the emotional subscale. This item was removed to avoid overlap with the FSS variables. In the cross-sectional **Paper 4** we used the parent-rating to avoid same-informant bias. In **Paper 5** we used self-report at both age 11 and age 16 in order to homogenize the measure at both time-points (parents did not respond to questionnaires at age 16).

In **Paper 6** the emotional subscale (except the item on physical symptoms) was utilized as a measure for emotional problems. In TRAILS, the 'depressed withdrawn' and 'depressed anxious' subscales from the Youth Self-Report from the Child Behavioral Check List (Achenbach et al., 2012) were utilized to create a corresponding emotional problems subscale (similarly one item on excessive fatigue was excluded). The two emotional problems scores from the two cohorts were standardized in order to ensure similar variances across the measures.

Depressive symptoms

Depressive symptoms were assessed at both ages 11 and 16 and utilized mainly for adjustment purposes in **Paper 1**. At age 11, depressive symptoms were assessed in conjunction with the assessment of PE during the interview with selected parts of the Kiddie Schedules of Affective Disorders and Schizophrenia – present and lifetime version (Kaufman et al., 1997). Depressive symptoms were rated dichotomously as present/non-present. Presence was defined as at least one 'likely' or 'definitely' rating of the items depressed mood, irritability and anhedonia from the depressive disorders section. At age 16 a dichotomous measure of depressive symptoms was derived from the Moods and Feelings Questionnaire sum-score (Angold et al., 1995), using a cut-off at the top10% vs. bottom 90% scores. An item of suicidal ideation was removed from the sum-score to avoid overlap with the outcomes of suicidality under study in **Paper 1**.

Suicidality and non-suicidal self-harm

Suicidal ideation, suicide attempts and non-suicidal self-harm were assessed at ages 11 and 16 and utilized in **Paper 1**. At age 11 all three variables were assessed as part of the depressive disorders section of the Kiddie Schedules of Affective Disorders and Schizophrenia – present and lifetime version (Kaufman et al., 1997). Each individual lifetime symptom was rated as present (i.e. 'likely' or 'definitely' present) vs. 'not-present' in the same way as PE and depressive symptoms. For the purpose of the study, age 11 suicidal ideation and suicide attempts were combined into one variable due to few cases with suicide attempts. At age 16 the same variables were assessed by self-report based on questions from the Child and Adolescent Self-harm in Europe Study (Madge et al., 2008). Presence of each individual outcome of suicidal ideation,

suicide attempts and non-suicidal self-harm at age 16 was defined as at least one occurrence within the last year.

Substance use

Substance use was assessed by self-report at age 16 and was used as an outcome variable in **Paper 1**, using the 'Alcohol, Smoking and Substance Involvement Screening Test' (Humeniuk et al., 2008). The substance use variable was defined as having used any of the following drugs at least twice vs. only once or never: cannabis, amphetamine, ecstasy, cocaine, hallucinogens, LSD, inhalants, and non-prescription opioids or sedatives.

Health anxiety

HA was measured by self-report using the Child Illness Attitudes Scales (Wright and Asmundson, 2005, 2003), 21-item version at age 11 (**Papers 4 and 5**) (Thorisdottir et al., 2017) and the Whiteley-6 Index (Carstensen et al., 2020) at age 16 (**Paper 5**). In order to capture a group of youths who were likely to experience some impact of HA-symptoms, the HA-variables were dichotomized into a top 10% vs bottom 90% scores in both studies. The Child Illness Attitudes Scales at age 11 was chosen as an age-appropriate measure, and the Whiteley Index was chosen at age 16 to mirror data from another large Danish cohort, the Dun Fund study (Dantoft et al., 2017), and given that the measure was likely suitable as the youths approached adulthood,

Functional somatic symptoms

FSS were assessed by self-report using the Children's Somatization Inventory 24 Revised at age 11 (Walker et al., 2009) (**Papers 4 and 5**) and the Bodily Distress Syndrome Check-List (Budtz-Lilly et al., 2015) at age 16 (**Papers 5 and 6**). Like HA, the FSS variables were dichotomized into a top 10% vs bottom 90% scores for the purposes of both **Paper 4 and 5**. In **Paper 6**, to ensure comparable items between the CCC2000 and TRAILS, a total of eight items from the Bodily Distress Syndrome Check-List were deemed similar enough across the two cohorts to be part of the specific study. In TRAILS, 6 items on FSS were extracted from the Youth Self-Report from the Child Behavioral Check List (Achenbach et al., 2012) supplemented by two customized questions on musculoskeletal symptoms (Janssens et al., 2012).

Intelligence Quotient Estimate

An estimate of general cognitive ability was assessed at age 11 and was utilized for adjustment purposes in **Papers 2 and 3**. Performance on the Block-Design subtest of the Wechsler Intelligence Scale for Children III was assessed to estimate the general cognitive ability of the participants at age 11, given that the test is highly correlated with full-scale IQ Block Design Test from the Wechsler's Intelligence Scale (Wechsler, 2003).

Register-based data

Data from national registries are available for all 6090 original participants of the CCC2000 through Statistics Denmark. Data from all follow-ups of the CCC2000 have been uploaded and linked to the national registries on Statistics Denmark by use of their personal identification numbers (Pedersen, 2011), in a pseudonymized form (Olsen et al., 2020). Register-based data are available for all participants from birth until age 16-17 around 2016 or 2017 depending on the individual registers. In addition, data on the cohort-members' parents, going back until 1968, are available for some registers (Pedersen, 2011). All data analyses, except for the analyses for Paper 6, were performed on a secured online server on Statistics Denmark. Statistics Denmark's guidelines to ensure participant anonymity include that small cell sizes are never reported (rule of thumb = no less than three individuals). The register-based data utilized in the papers of the current thesis are described in brief below.

Sociodemographic family background characteristics

Sociodemographic information regarding household income, maternal and paternal age at birth, maternal and paternal level of education and unemployment, family constitution and changes in family composition, and ethnic minority status were obtained from the Danish Civil Registration System (Pedersen, 2011) and the Integrated Database for Labor Market Research (Petersson et al., 2011). In **Papers 1 and 4**, selected sociodemographic variables were used to describe attrition, i.e. to compare cohort-members who contributed data to the given studies with cohort-members who did not participate. In **Papers 2 and 3**, we used selected sociodemographic variables for adjustment purposes in the statistical models. For **Paper 2** we utilized a sociodemographic adversity index, predefined from previous work from the CCC2000 disorders (Jeppesen et al., 2015b), in order to avoid fitting too many variables in statistical models with few individuals, i.e. small cell-sizes due to rare outcomes.

Perinatal background characteristics

Perinatal background characteristics were obtained from the Medical Birth Register (Bliddal et al., 2018), including birth weight, gestational age, Apgar score, parity, singleton vs. multiple births and any registered birth complication. In the same way as the sociodemographic family background characteristics, perinatal background characteristics were used to describe attrition in **Papers 1 and 4** and for adjustment purposes in **Papers 2 and 3**.

School performance

Data on the youths' performances at the final exams of mandatory education in 9th grade were obtained through the Danish Education Registers (Jensen and Rasmussen, 2011). We constructed two variables for use

in **Paper 3**: 1) a grade point average for all individuals who had participated in at least four out of eight of the mandatory exams and 2) a variable of exam completion (i.e. participated in four or more exams) versus non-completion (participated in zero-three exams).

Mental disorders in tertiary care settings

Information on ICD-10 mental disorders diagnosed in public outpatient and inpatient tertiary mental health services were available from the Danish National Patient Register (Lynge et al., 2011). Overall good validity of the register-based diagnoses have been shown (Mors et al., 2011), including for early onset schizophrenia (Vernal et al., 2018). Diagnoses made by general practitioners or psychiatrists in private practices or at private hospitals are not available. For information on parental mental disorders in **Papers 2 and 3**, we included any non-organic mental disorder, defined as any ICD-10 codes F10–F99 or suicide attempts/self-injury defined as ICD-10 codes X60–X84, diagnosed between 1995 (5 years prior to birth of the CCC2000 participants) until 2011 (around the time of age 11 follow-up of the CCC2000). In **Paper 2** we used a parental history of mental disorders to stratify the exposure variable in survival analyses and in **Paper 3** we used the same variable for adjustment purposes. In **Paper 2**, the same above diagnoses for the youths of the CCC2000 were utilized for a variable of any mental disorder. The register also included the dates on which any given diagnosis was made. This enabled us to a) assess which children were first diagnosed with a mental disorder prior to PE-assessment at age 11 and b) to perform survival analyses assessing the first point in time at which children were diagnosed with a mental disorder over follow-up. The main outcome variable included any diagnosis, and we constructed three diagnostic subgroups of the broader variable: neurodevelopmental disorders (hyperactivity and inattention diagnoses, conduct disorders, autism spectrum disorders, and intellectual disability), emotional disorders (depressive and anxiety disorders), and other (substance-related disorders, psychotic disorders, eating disorders, and personality disorders) disorders, see the supplementary information of **Paper 2** for details. Disorders were not explored individually in the statistical analyses, given the considerations to ensure participant anonymity described previously.

Psychotropic medications

Data from Danish National Prescription Registry provided information on all prescriptions of psychotropic medications that were redeemed by the participants, including dates (Wallach Kildemoes et al., 2011). We included the following types of medications: central stimulants, antidepressants, antipsychotics, and melatonin. We did not include benzodiazepines to avoid misclassification, due to the common use of such substances for e.g. neurological conditions. In **Paper 2** this information was utilized in order to supplement data from tertiary care settings from the Danish National Patient Register to identify individuals who were treated with psychotropic medications for mental disorders through non-hospital-based settings.

Healthcare costs

Information on costs related to publicly funded healthcare was obtained from the following registers: the Danish National Health Service Register (Sahl Andersen et al., 2011), the Danish National Patient Register (Lyngé et al., 2011) and the Danish National Prescription Registry (Wallach Kildemoes et al., 2011). We constructed various variables to examine outcomes of healthcare costs related to both somatic- and mental healthcare services, as well as costs related to prescription medicines, see **Paper 3** for details. The registers did not include costs from healthcare use, which was not compensated by the state, e.g. private psychologists paid for solely by the parents themselves or private insurance. They also did not include information on costs from the municipalities, e.g. school-based psychologists or other psychosocial or educational support.

Statistical modelling

Here, the statistical models for the main analyses of the separate papers are summarized.

Part 1: Investigating adolescent outcomes following psychotic experiences in preadolescence

The majority of *Part 1* consists of longitudinal follow-up of age 11 PE using questionnaire outcomes at age 16 (**Papers 1 & 3**) and register-based outcomes over the intermediate time period between age 11 and age 16 (**Paper 2 & 3**).

In **Paper 1** we conducted binomial regression analyses with a log-link function (to convert the odds ratio [OR] to relative risk [RR]) to estimate the RR of outcomes of risk behaviors (i.e. suicidality, non-suicidal self-harm and substance use) for individuals with PE vs individuals without PE. The analyses were conducted in cross section at both ages 11 and 16, as well as in the longitudinal analyses. In the cross-sectional analyses, the RR for reporting risk behavior given the rating of 1, 2 or ≥ 3 types of PE in lifetime vs no PE was calculated, and subsequently we tested for a linear trend, i.e. if having a higher number of PE indicated a more frequent occurrence of risk behaviors. The same binomial regression analyses were used in the longitudinal analyses. Three trajectories of individuals who had experienced PE at some point were compared to individuals who reported PE at neither follow-up: i) remitting PE, i.e. reported PE at age 11 but not at age 16 ii) incident PE, i.e. reported PE at age 16 but not at age 11 iii) Persistent PE, i.e. reported PE at both ages. Finally, to examine the effect of PE at age 11 on *incident* risk behaviors at age 16, all individuals who already had expressed risk-behaviors at age 11 were excluded for the final analyses. All the above analyses were adjusted for sex, impact of general psychopathology and depression in a stepwise fashion.

In **Paper 2** we conducted survival analyses using Cox proportional hazard regression models. We compared preadolescents with/without PE at age 11 regarding the incidence of first-time register-based mental

disorders and/or treatment with psychotropic medications for over a 5-year follow-up period, i.e. individuals who had already been diagnosed with a mental disorder in CAMHS were excluded. The use of survival analyses allowed us to account for the individuals' time at risk. The participants were followed in the registers from their date of examination in year 2011/2012 until they were censored on a given date due to either a) an event of interest (diagnosis of mental disorder or redemption of a prescription of a psychotropic medication), b) emigration, c) death (none died) or d) end of follow-up on June 31st 2017. We stratified the analyses by individuals who i) concurrently fulfilled the ICD-10 criteria for one or several DAWBA-based mental disorders (solely for research purposes) at age 11 and ii) parental history of mental illness until age 11. The assumption of proportionality behind the cox regression were tested by observing Kaplan Meier survival curves and by Schoenfeld residuals. All analyses were presented a) crudely b) adjusted for sex, perinatal health index, and family adversity index and c) further adjusted for IQ-estimate.

In **Paper 3** we used logistic regression analyses to examine binary outcomes of low HRQoL and 9th grade exam non-completion at age 16, following PE at age 11. For the continuous outcomes of healthcare costs and 9th grade grade-point average, we used linear regression analyses. Because the healthcare costs variables were heavily right skewed (i.e. very few individuals had high healthcare costs, whereas the majority had low or no healthcare costs) the assumption behind the linear regression requiring a normal distribution of the outcome was not fulfilled. Hence, in order to estimate more exact 95% confidence intervals (CI), we calculated non-parametric bootstrapped 95% CIs which were further bias-corrected and accelerated.

The estimated differences between individuals with baseline PE were reported i) crudely ii) adjusted for sex, low birthweight/small for gestational age, immigrant parent(s), broken family status, parental education and unemployment, parental mental healthcare service use and parental healthcare costs iii) IQ-estimate (only school-based outcomes were adjusted for IQ). Finally, a population-based top-10 percentile score of general psychopathology and/or impact of psychopathology was added as a covariate in both the crude and adjusted models, to examine if the effect of PE on the outcomes remained robust over and above general psychopathological problems impacting the daily life of the child.

Part 2: Exploring specific developmental associations between psychotic experiences and aberrant bodily experiences.

Paper 4 is a hypothesis-generating cross-sectional study utilizing age 11 data that was performed while we conducted the follow-up at age 16. **Paper 5** cross-sectionally (at both age 11 and age 16) and longitudinally examines the same symptom dimensions as investigated in **Paper 4**. **Paper 6** is a cross-sectional study of data from the 16-year follow-up of the CCC2000 supplemented with cross-sectional data from the TRAILS using an individual symptom network-based approach.

In **Paper 4**, PE at age 11 was modelled as an outcome of high levels of FSS and HA using binomial regression analyses. The individual effects of FSS and HA on PE were first estimated in bivariate analyses and subsequently in multivariate analyses to mutually adjust for HA and FSS and further adjust for sex, puberty development, chronic physical illness and general psychopathology.

In **Paper 5**, HA was modelled as an outcome of FSS and PE in cross-section at age 11 and 16, respectively, and longitudinally from age 11 to 16. The independent associations between HA and FSS, between HA and PE, and the association between HA and the combination of FSS and PE were assessed by multiple logistic regression. A potential association with HA beyond additivity of FSS and PE was estimated by quantifying the interaction on an additive scale, using the interaction contrast ratio method (Knol et al., 2007). The above analyses were repeated in analyses replacing the PE variable with speech illusions (White Noise Task) at age 11 and with anomalous self-experiences at age 16. The models were finally adjusted stepwise for sex, chronic physical illness and general psychopathology.

In **Paper 6** we estimated symptom networks between PE and FSS using graphical models. The rationale behind the network approach is to model potential independent associations between individual data-points (here symptoms) in multivariate data sets (Whittaker, 1990). We used the mixed graphical model (Haslbeck and Waldorp, 2019) to infer symptom networks in both the CCC2000 and the TRAILS cohorts separately. First, we included only PE and FSS (8 roughly similar items on FSS and 8 on PE in each cohort), each representing a *node* in the network. Subsequently, we also including a node representing a scale score of emotional problems, to see if emotional problems substantially changed the network. We estimated the network density, i.e. the overall connectedness of the symptoms in the overall network. Many edges, i.e. connections between nodes, result in high density. Furthermore, numerous centrality indexes were reported in order to assess which nodes were most connected by different points of reference. The centrality indexes are not described in the current summary of the results, hence see **Paper 6** for more elaborated descriptions on the centrality indexes.

Summary of results

The current summary aims to provide an overview of the main results from the six separate papers constituting the basis of the current thesis. Detailed information regarding the findings are reported in the individual papers.

Part 1: Investigating adolescent outcomes following psychotic experiences in preadolescence

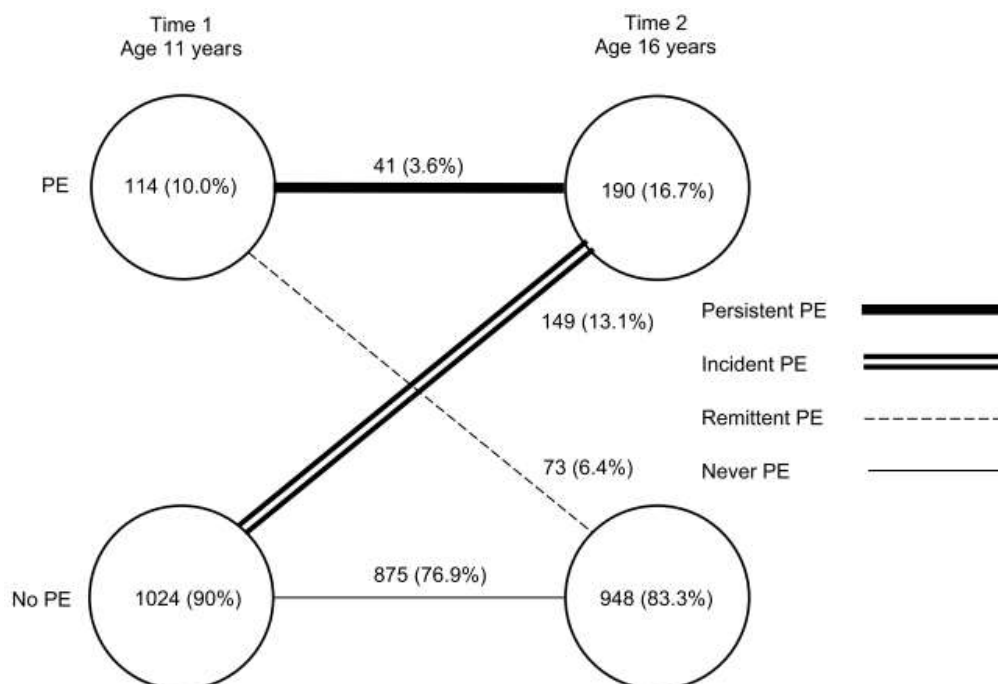
Cross-sectional correlates of psychotic experiences

In the cross-sectional analyses of **Paper 1**, we found that PE at age 11 and 16, respectively, were strongly associated with suicidality and non-suicidal self-injury in a dose-response fashion, i.e. experiencing a higher number of PE were associated with higher risks. The increased association was to a large extent, but not entirely, explained by self-reported general psychopathology and depressive symptoms in adjusted models.

Self-reported outcomes following examination of psychotic experiences

As illustrated in **Figure 3** (from **Paper 1**), among the individuals who had PE at age 11 determined in interviews ($n=114$, 10.0%), had a remitting pattern of PE from age 11 to age 16 ($n=73$, 6.4%). Individuals who had PE at age 11 had an approximately 2.5-fold increased risk of reporting PE again at age 16. Individuals with PE that persisted over time ($n=41$, 3.6%), or had incident PE ($n=149$, 13.1%), had an increased risk of suicidality, non-suicidal self-harm or substance use (risk behaviors). There was no convincing evidence that individuals with a remitting pattern of PE were associated with risk-behaviors at age 16. The statistically significant effects of incident and persistent PE on risk behaviors remained after adjustment for general psychopathology and depressive symptoms. However, when we examined only incident risk behaviors, i.e. by excluding individuals who already had reported risk behaviors at age 11, little evidence remained of an increased risk of risk behaviors following PE at age 11, particularly in the adjusted models.

Figure 3: Graphical depiction of trajectories of psychotic experiences from age 11 to age 16 in the CCC2000. From **Paper 1**.



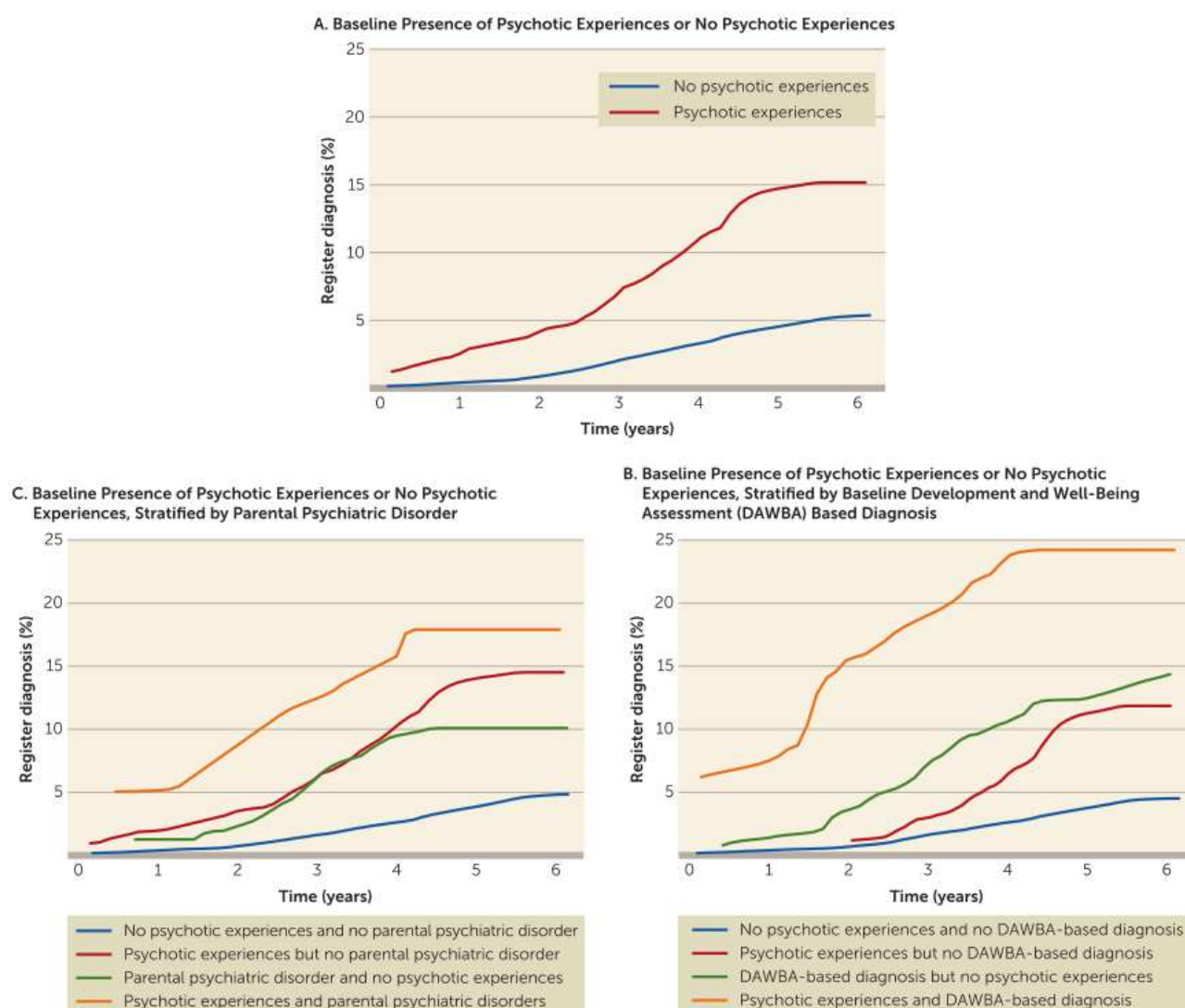
In approximately the same longitudinal sub-sample sample of the participants in **Paper 3**, we also found that PE were associated with low self-reported HRQoL. These associations were largely unaffected after adjustment for sociodemographic characteristics and general psychopathology.

Register-based adolescent outcomes of psychotic experiences

In **Paper 2**, we examined PE at age 11 as the exposure variable and future mental health disorders diagnosed in CAMHS as the outcome variable, among children with no psychiatric contacts prior to the assessment of PE at age 11. A total of 60 children were excluded due to prior contacts with CAMHS. As illustrated in **Figure 4a**, having PE at age 11 was associated with an approximately 3-fold increased risk of developing symptoms severe enough to confer contact to CAMHS and being diagnosed with a mental disorder over the following approximately 5 years. If a youth fulfilled criteria for a DAWBA-based research mental diagnosis at age 11, the risk of later mental disorder was approximately the same as for PE (**Figure 4b**). Having both PE *and* a DAWBA-based diagnosis was associated with particularly increased risk. Evidence pointed in the same direction for individuals whose parent(s) had a register-based history of mental disorder, but to a somewhat lesser degree (**Figure 4c**). Importantly, the risk of later mental disorder in individuals with PE alone at age 11 (i.e. who did not fulfill criteria for a research-based mental disorder or had a family history of mental disorder), still had a 2-3-fold increased risk of a register-based diagnosis of mental disorder. We found similar associations between PE and use of psychotropic medications as we did between PE and mental disorders. Because very few individuals were diagnosed with a psychotic disorder during the follow-up period, outcomes of psychotic disorders specifically could not be investigated in order to adhere to the ethical

guidelines of statistics Denmark to ensure participant anonymity by not reporting small cell-sizes. PE were associated with later diagnosis of both emotional disorders and neurodevelopmental disorders. Adjusting for sociodemographic characteristics, sex and IQ did not markedly change the estimated associations between PE and the outcomes.

Figure 4: Smoothed cumulative hazard plots depicting the unadjusted cumulative incidence of register diagnosis of psychiatric disorder over a 5-year follow-up period after screening for psychotic experiences at ages 11–12. From **Paper 2**.



When examining healthcare costs as outcomes of PE in **Paper 3**, we found that PE were associated with increased costs (**Table 3**), also approximately 3-fold compared to individuals without PE. The differences in healthcare costs were mainly related to mental healthcare costs, whereas there was little to no evidence of an association between PE and an excess in healthcare costs in somatic healthcare settings. The estimated differences in healthcare costs were somewhat reduced after adjustment for sociodemographic factors as

well as a parental history of mental disorder until child age 11, and finally adjusted for parent-rated general psychopathology of the child. Even in the heavily adjusted models the association between PE and increased healthcare costs remained statistically significant (Table 3).

Table 3: Annual costs in relation to multiple sectors of the public healthcare system and costs related to prescription medicine. The adjusted column was adjusted for sociodemographic factors, parental history of mental disorders until child age 11 and parent-rated general psychopathology of the child. The table modified from several tables in Paper 3.

	Psychotic experiences (n=171) Euros	No psychotic experiences (n=1436) Euros	Between group differences (crude) Euros (95% CI)	Between group differences (adjusted) Euros (95% CI)
Mental primary sector care	43	13	30 (4; 74)	20 (-6; 61)
Mental outpatient hospital care	185	74	111 (23; 284)	90 (9; 254)
Mental inpatient hospital care	2373	298	2,075 (-144; 10,463)	1,775 (-182; 8,776)
Somatic primary sector care	141	127	14 (-8; 45)	6 (-17; 37)
Somatic outpatient hospital care	254	246	8 (-83; 135)	-9 (-103; 126)
Somatic inpatient hospital care	647	338	309 (-145; 1,845)	251 (-189; 1,650)
Prescription medicine	129	66	63 (15; 141)	48 (1; 118)
<i>Total costs</i>	<i>3771</i>	<i>1161</i>	<i>2,610 (255; 11,361)</i>	<i>2,181 (52; 9,350)</i>

Furthermore, we examined an association between PE at age 11 and school performance at age 16 at the final exams at end of mandatory education in Denmark. There was evidence of a slightly decreased grade-point average among children with PE. However, the association was to a large part explained by sociodemographic adversities, general psychopathology and IQ.

Part 2: Exploring specific developmental associations between psychotic experiences and aberrant bodily experiences.

In Paper 4 we found that HA and FSS were both individually associated with PE. Subsequently, the analyses were mutually adjusted for HA and FSS, and furthermore adjusted for sex, pubertal status, chronic physical illness and parent-reported general psychopathology (Table 4). PE were still robustly associated with HA and FSS after the adjustments, although the estimated associations were attenuated.

Table 4: Associations between psychotic experiences and high scores on measures of health anxiety and functional somatic symptoms. The table is modified and shortened from **Paper 4**.

	OR of Psychotic experiences	95% CI	p-value
Health anxiety (top 10 % high score)	3.19	2.12-4.79	<0.001
Functional somatic symptoms (top 10 % high score)	4.61	3.08-6.89	<0.001
<u>Mutually adjusted (n=1572)</u>			
Health anxiety	2.26	1.46-3.50	<0.001
Functional somatic symptoms	3.72	2.43-5.68	<0.001
<u>Mutually adjusted and adjusted for all variables below (n=1503)</u>			
Health anxiety	2.15	1.36-3.41	0.001
Functional somatic symptoms	3.31	2.11-5.18	<0.001
Sex	1.00	0.69-1.44	0.992
Puberty onset	0.62	0.37-1.02	0.060
Chronic physical illness	0.89	0.54-1.46	0.649
General psychopathology	1.07	1.04-1.11	<0.001

Paper 5 extended the findings from **Paper 4** with longitudinal data, and modelled HA as the outcome instead of PE. We found that both PE and FSS were individually associated with HA at age 11 (as would be expected from based on findings from **Paper 4**). The cross-sectional findings at age 16 mimicked the findings at age 11. However, the association between FSS and HA was even more substantial at age 16. Furthermore, at age 16, there was weak evidence of a substantial synergistic effect of having both PE and FSS on the occurrence of HA that was beyond additivity, i.e. there appeared to be an interaction between the two measures. However, much of the interaction between PE and FSS on the outcome of HA, as well the individual effects of PE and FSS, were explained by general psychopathology. Consequently, the evidence of a specific association between PE and HA was reduced substantially after adjustment for general psychopathology, yet barely affected by adjustment for sex and chronic physical illness. The results when the PE variable was replaced with speech illusions at age 11 and anomalous self-experiences at age 16 respectively, essentially mirrored the findings from the models with PE. In the longitudinal analyses we found evidence of an association between having a combination PE and FSS at age 11 and later HA at age 16, but weak individual effects of PE and FSS. See **Table 5** for a summary of the results.

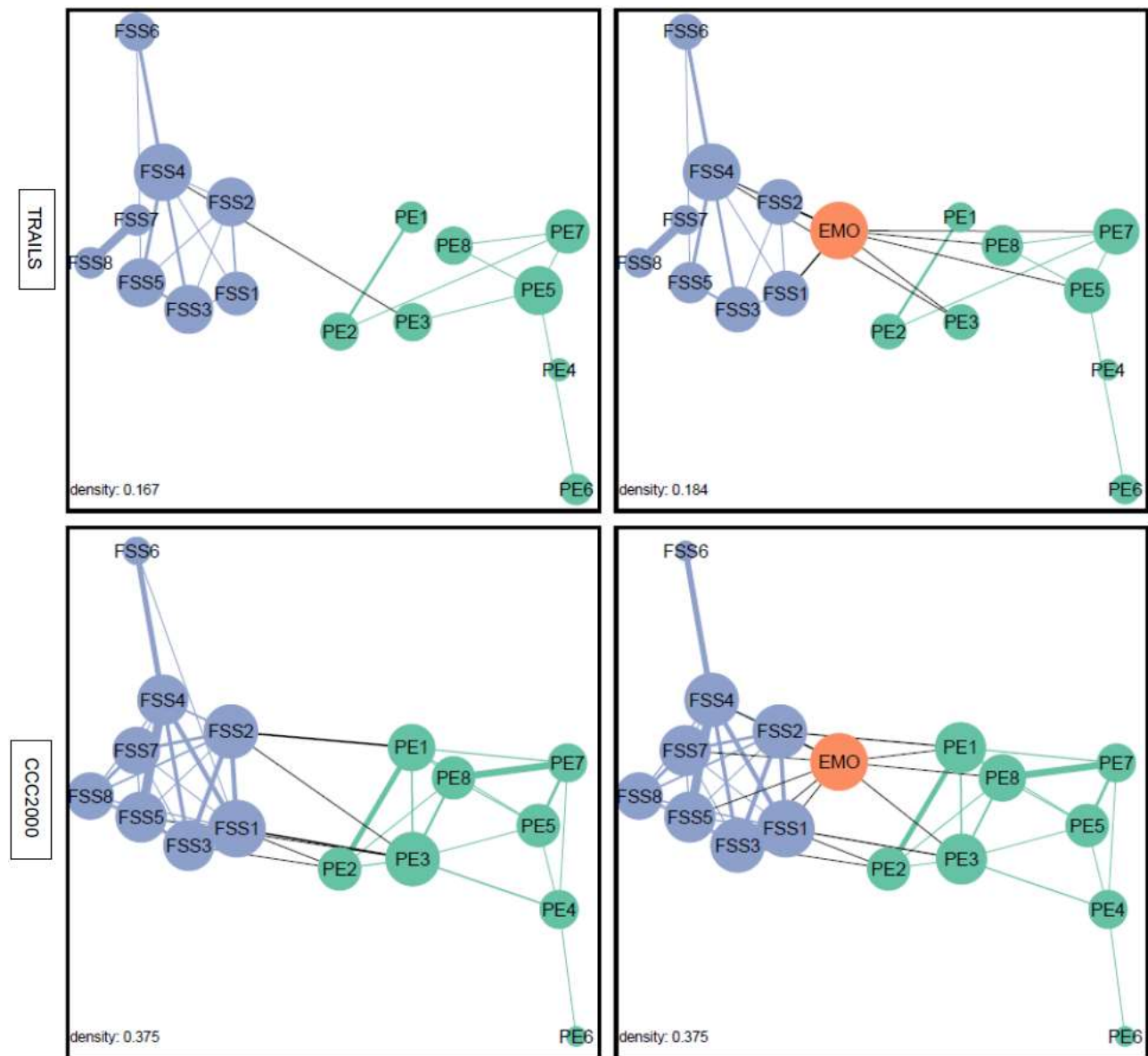
Table 5: Outcome of health anxiety (HA) as a function of psychosis vulnerability (psychotic experiences [PE], speech illusions [SI] or anomalous self-experiences [SE]) and functional somatic symptoms (FSS) in cross section and longitudinally from age 11 to age 16. ICR=Interaction contrast ratio, OR=Odds ratio, CI=Confidence Interval. Modified table from **Paper 5**.

	Unadjusted	Adjusted for sex, chronic physical illness and general psychopathology
Outcome age 11 HA (cross-section)	OR (95% CI)	OR (95% CI)
PE age 11	3.1 (1.9; 5.1)	2.7 (1.6; 4.6)
FSS age 11	6.1 (3.9; 9.6)	4.6 (2.8; 7.4)
ICR	-0.6 (-6.1; 4.8)	-1.4 (-5.4; 2.6)
PE+FSS age 11	7.6 (3.9; 14.5)	4.9 (2.4; 9.9)
Outcome age 11 HA (cross-section)		
SI age 11	2.3 (1.3; 4.3)	2.2 (1.2; 4.2)
FSS age 11	6.2 (4.0; 9.4)	4.4 (2.8; 6.9)
ICR	2.1 (-10.8; 15.1)	1.1 (-8.3; 10.6)
SI+FSS age 11	9.6 (2.5; 36.5)	6.7 (1.7; 27.1)
Outcome age 16 HA (cross-section)		
PE age 16	2.3 (1.6; 3.4)	1.6 (1.1; 2.4)
FSS age 16	13.5 (8.9; 20.6)	7.0 (4.4; 11.0)
ICR	11.2 (-0.1; 22.5)	3.5 (-1.7; 8.8)
PE+FSS age 16	26.1 (16.9; 40.2)	11.1 (6.8; 18.1)
Outcome age 16 HA (cross-section)		
SE age 16	3.6 (2.0; 6.5)	2.2 (1.2; 4.0)
FSS age 16	15.1 (9.1; 24.8)	8.7 (5.1; 14.8)
ICR	20.4 (-3.6; 44.5)	5.4 (-5.1; 15.9)
SE+FSS age 16	38.1 (20.1; 72.3)	15.2 (7.5; 30.8)
Outcome age 16 HA (longitudinal)		
PE age 11	1.4 (0.7; 3.1)	1.2 (0.6; 2.7)
FSS age 11	1.2 (0.5-2.7)	0.7 (0.3; 1.8)
ICR	2.3 (-1.1; 5.7)	1.6 (-0.8; 4.1)
PE+FSS age 11	3.9 (1.7; 8.9)	2.6 (1.0; 6.4)

In **Paper 6**, the associations between specific PE and FSS were examined using a symptom-based network approach in two cohorts (**Figure 5**). In both the CCC2000 and TRAILS cohorts, as expected, symptoms *within* the respective domains (i.e. PE and FSS) were more strongly connected compared to the connections *between* domains. However, associations were also found *between* the domains of PE and FSS. Edges from the PE domain to the FSS domain went from the node ‘persecutory ideation’ (CCC2000 and TRAILS) and the hallucinations nodes (CCC2000 only). When a scale score of emotional problems was added as a node in the network, emotional problems stood out as a central node (i.e. connected to multiple PE and FSS). However, emotional problems did not explain much of the between-domain associations, since most of the between-domain edges remained. The network was less dense (i.e. had fewer connections) in the TRAILS compared to

the CCC2000. Sensitivity analyses showed that this was to a large part explained by the smaller sample size in the TRAILS.

Figure 5) Left-hand side: Undirected networks including psychotic experiences and functional somatic symptoms without accounting for emotional problems for the TRAILS (upper panel) and CCC2000 (lower panel) cohorts respectively. Right-hand side: Undirected networks after accounting for emotional problems for the TRAILS (upper panel) and CCC2000 (lower panel) respectively. Figure from **Paper 6**.



Abbreviations: PE1=auditory hallucinations, PE2=visual hallucinations, PE3=persecutory ideation, PE4=ideas of reference, PE5=feeling controlled, PE6=grandiosity, PE7=thoughts stolen, PE8=thoughts broadcast, FSS1=dizziness, FSS2=fatigue, FSS3=headaches, FSS4=nausea, FSS5=stomach aches, FSS6=vomiting, FSS7=backaches, FSS8=pain in arms or legs, EMO=emotional problems

Discussion

Main findings and contributions

The studies in *Part 1* confirmed the hypotheses that PE in childhood are a strong risk-marker of later psychopathology and other detrimental outcomes. PE seemingly have an independent predictive value over and above general youth mental health problems. Our studies support the evidence of PE as a transdiagnostic marker of severity of psychopathology (Guloksuz et al., 2015; Kelleher et al., 2012b; Rössler et al., 2011; van Os and Reininghaus, 2016) and contribute with examinations of “real-world” outcomes of PE that supplement the current literature and underline the clinical importance of PE in children and adolescents. These clinically important outcomes, including CAMHS-use, healthcare costs and school performance, were all registered independently of the CCC2000 data collections. Furthermore, the studies support that PE are particularly important in the context of other non-psychotic psychopathology in identifying individuals at risk for future clinically impactful mental health problems, including suicidality, mental disorders and reduced quality of life.

Within the overall framework of PE as a transdiagnostic marker of psychopathology, in *Part 2* we attempted to shed light on a potential specific developmental pathways including psychosis and aberrant bodily symptoms (Simon et al., 2014). Our studies contributed with findings of strong and robust associations between the psychosis continuum and bodily symptoms in the form of both FSS and HA – something that has not previously been examined in population-based studies of youths. The strength of the associations found between the domains support the idea of possible shared underlying processes between HA, FSS and psychosis vulnerability. Furthermore, our findings underline that viewing psychosis and bodily symptoms and anxieties separately is likely not fruitful, and that symptoms from within both domains should be considered in order to provide important information in the assessment of youth mental health.

Methodological Issues

Important strengths of the studies in the current thesis include the relatively large study sample which allowed examining associations between phenomena that are relatively uncommon within the general population. In addition, detailed information regarding sociodemographic characteristics and other register-based information was available for the entire cohort, including non-participants, allowing for detailed descriptions of attrition as well as for adjusting for potential confounding effects of sociodemographic adversities. Furthermore, the youths were comprehensively assessed at both ages 11 and 16, allowing for adjusting also for the effect of general psychopathology in our analyses and thereby unravelling potential

independent effects of PE. At age 11 we had a strong interview-based measure of PE, with high inter-rater reliability (Jeppesen et al., 2015a).

Despite the strengths of the studies mentioned above, some limitations should be considered. Below, I discuss potential sources of bias pertaining to the studies that are included in the thesis.

Risk of confounding

In theory, several criteria must be met for a factor to be regarded as a confounder:

“

1. *A confounding factor must be an extraneous risk factor for the disease.*
2. *A confounding factor must be associated with the exposure under study in the source population*
3. *A confounding factor must not be affected by the exposure or the disease. In particular, it cannot be an intermediate step in the causal path between the exposure and the disease*

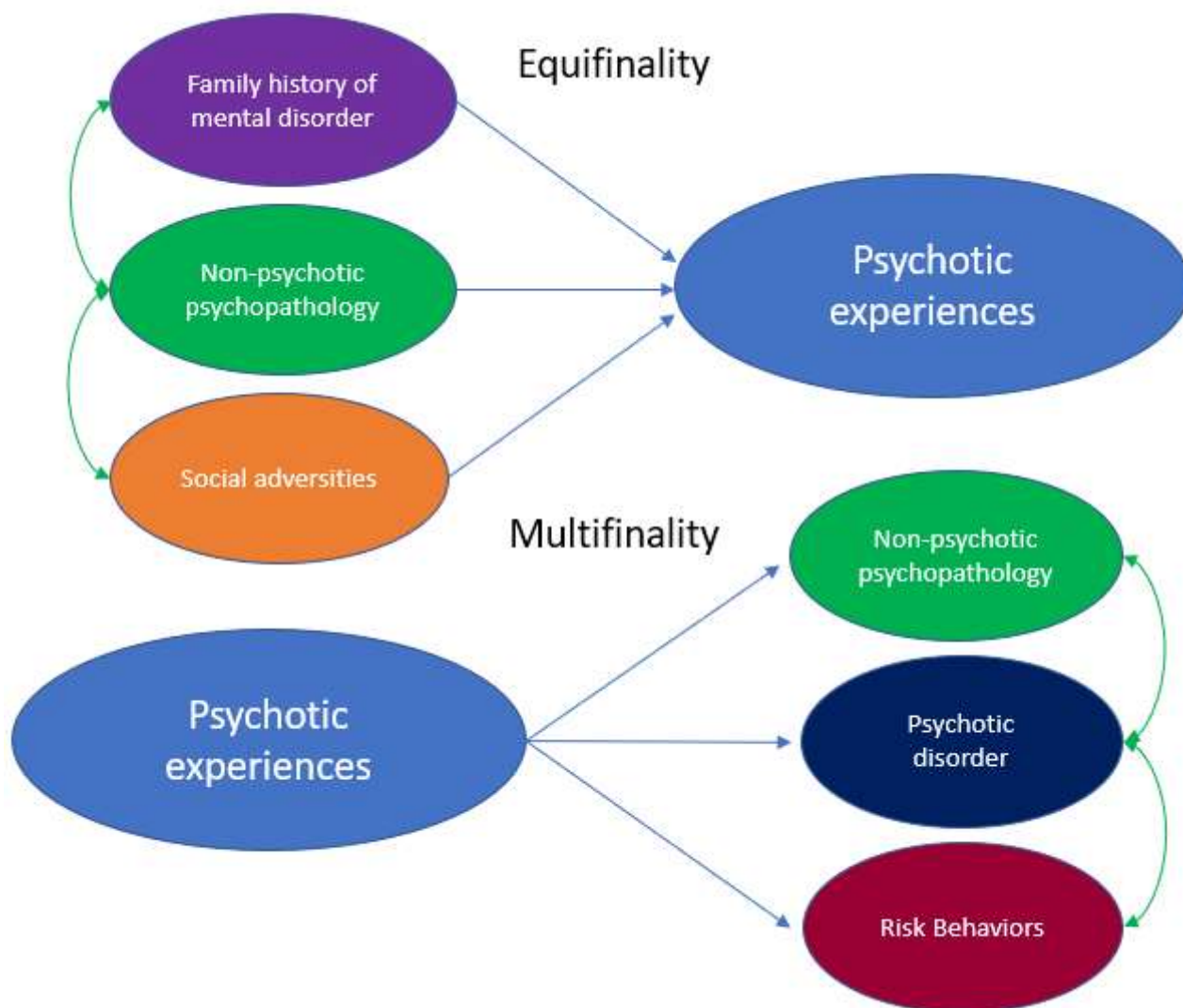
“

Quoted from Rothman, Greenland and Rash, Modern Epidemiology, 2008, third edition chapter 9

However, it is well-established that developmental psychopathology is characterized by both substantial equifinality, i.e. multiple factors lead to- or increase the risk of the same outcome, and multifinality, i.e. an exposure leads to- or increases the risk of multiple outcomes. See [Figure 6](#) for a graphical example of equifinality and multifinality involving PE.

In the majority of the studies in the current thesis we adjust, for example, for sociodemographic factors and/or general psychopathology when trying to disentangle the potential *specific* role of PE on other types of psychopathology or other outcomes. This is arguably a violation of the above criteria 1 and 3 in the definition of a confounder, since the different domains of psychopathology are intertwined and are likely on the causal pathway to each other, as illustrated by for instance in the network models of psychopathology (Borsboom, 2017; Borsboom and Cramer, 2013) and ‘P-factor’ model (Caspi et al., 2014; Caspi and Moffitt, 2018). Hence, given the pleomorphic characteristics and likely bidirectional influences of psychopathology, it is important to consider the risk of some of our models being over-adjusted. However, fulfilling all the above theoretical criteria of a confounder is rarely possible in practice, and the strategy that we have applied in the papers of the current thesis is to adjust in a stepwise fashion. This was done to a point where we perhaps over-adjusted, meaning that the best estimates may be found somewhere between the crude and the final model. It has been suggested that adjusting for a general p-factor (Caspi et al., 2014; Caspi and Moffitt, 2018) is “... *an essential covariate in studies of specific psychopathology*” (Ronald, 2019).

Figure 6. Simplified illustration of equifinality and multifinality of psychotic experiences and potential risk factors and outcomes of psychotic experiences. Furthermore, the risk factors and outcomes of psychotic experiences might also be strongly associated and interact with each other, as illustrated by the green arrows.



Nonetheless, conversely, like in all epidemiological studies, it should be expected that residual confounding might be present within the estimates presented in the current thesis – for example due to lack of high-quality assessment, and adjustment for, for instance, traumatic life-events.

Below, I specifically discuss how problems of selection- and information bias might pertain to the studies in the current thesis.

Risk of selection bias

Given that cohort-members were recruited to the cohort based on the Danish registers, and that active consent was not required from the parents, the individuals that are part of the original CCC2000 are overall representative of the Danish population, except for the over-representation of ethnic minority parents in the

catchment area (Olsen et al., 2007). Hence, self-selection bias is not an important problem in the definition of the original cohort. However, selection bias is still an important source of bias in the CCC2000 studies in the form of attrition bias. Similar to other large cohorts that study mental health such as TRAILS (Oldehinkel et al., 2015), the ALSPAC (Fraser et al., 2013; Munafò et al., 2018) and Generation R (Kooijman et al., 2016), attrition analyses of the CCC2000 have shown that the cohort-members that actually *do* participate in the face-to-face and internet-based follow-ups are characterized by fewer psychosocial and perinatal adversities than non-participants (Olsen et al. 2020). This attrition is large in the CCC2000 study (around 60-70% of eligible participants at different time-points) compared to other cohort studies (Fraser et al., 2013; Kooijman et al., 2016; Oldehinkel et al., 2015), which can likely be attributed to modest resources to retain participants, as well as the fact that the original cohort was unselected.

None-participants in the follow-up studies of CCC2000 were characterized by more adversities. This likely resulted in a reduction in variation in the dataset, i.e. participants experience less psychopathology compared to non-participants. This is likely to have attenuate the size of the associations found in the studies, i.e. bias the findings towards the null (although this direction is not guaranteed). Due to the availability of register-based data in the CCC2000 on non-participants, we have been able to show that individuals who have participated in the examinations are less likely to be diagnosed with a mental disorder in CAMHS (Olsen et al., 2020). This is particularly the case among individuals who participated in multiple follow-ups (Olsen et al., 2020). However, weighted prevalence-estimates suggest that the occurrence of PE in the sample was likely not strongly influenced by the attrition (Jeppesen et al., 2015a)

Risk of information bias

Even though all the papers in the current thesis are based on the underlying concept of dimensional psychopathology as continuous phenomena in the population, most variables in the papers of the thesis are dichotomous (e.g. PE vs no PE, HA vs. no HA). This might indeed seem contradictory to a dimensional approach, and dichotomization or categorization of continuous variables/phenomena might lead to loss of meaningful clinical information. With regard to the statistical analyses, it also results in reduced statistical strength. However, the advantages of this approach include that the outcomes are often more easily interpreted, and the estimates mirror a clinical reality, in which decisions are more often than not dichotomous, e.g. offering psychotropic medication to an individual or not, diagnosis vs. no diagnosis, etc.

Importantly, almost all psychopathology was assessed by different approaches (i.e. interview vs. self-report) and/or different measures at age 11 and age 16. Hence, it is arguably difficult to assess continuity/discontinuity of high/low levels of psychopathology over time. This can be considered an important weakness since it would likely overestimate discontinuity, particularly regarding dichotomous

variables, in that important clinical information is lost. However, the different measures at the two follow-ups can also be argued to be a strength, given that the *concepts* are being evaluated over time, rather than simply *psychometric* continuity. We similarly argue, in **Paper 6**, that it is a strength that different measures were used in the CCC2000 and TRAILS when replicating our findings.

Furthermore, the majority of psychopathology described in the papers of the current thesis relies on self-reports. This might be of particular importance to the measure of PE at age 16, as self-reported measures of PE tend to be much more inclusive compared to interview based measures (Gundersen et al., 2019; Kelleher et al., 2011). Hence, it could be considered that there is an imminent risk of the respondent classifying what a clinician would consider a “normal” phenomenon as PE, i.e. false-positives, leading to measurement error and misclassification bias. Such misclassification would likely dilute the hypothesized associations between PE and the outcomes of interest and bias the findings towards the null. However, multiple studies (Bak et al., 2003; Moriyama et al., 2019; van der Steen et al., 2018), including our prior studies of the CCC2000 at age 11 (Rimvall et al., 2019), found that even the ‘false-positive’ PE, compared to no PE, are associated with more psychopathology and detrimental outcomes, although the effects were weaker than for the interview based PE. Hence, these false-positive PE are likely not optimally considered as ‘false’, but rather symptoms at the lower end of the psychosis continuum. Another important risk of misclassification pertaining to *Part 2* of thesis, relates to the classification of functional somatic symptoms, given that some of the physical complaints might be representations of diagnosed somatic illness. We attempted to address this potential misclassification bias by adjustment for diagnosed chronic physical illness and excluding individuals with chronic physical illness in sensitivity analyses. Even though these adjustments did not change the estimates much, and absence of established somatic illness does not per definition preclude FSS (Gureje and Reed, 2016), risk of misclassification should still be considered.

Finally, an important information-related bias relates to shared-methods bias in the form of same-informant bias, as the measures of multiple domains of psychopathology were reported by the same individual. Hence, there is non-independence of observations. This bias is of course unavoidable when examining relationships between different symptoms within individuals. The risk of same-informant bias was reduced by adjusting for general psychopathology.

Psychotic experiences – specific risk-factors or merely epiphenomena?

Perspectives from Part 1

Beyond simply mapping the prevalence of mental health problems in children and adolescents, the goal of epidemiological studies of mental health in youths from the general population, is to identify early etiological factors and risk mechanisms behind the development of debilitating psychopathology, to provide potential

targets for prevention (Costello et al., 1993; Kessler, 2000; Verhulst, 2004). Over the past two decades, awareness of the occurrence of psychotic symptomatology in children and adolescents in the general population, has increased. A systematic review Kelleher and colleagues (2012a) reported a best estimate of the prevalence of PE in general population studies of 17% in children and 7% in adolescents. However, the estimates were based on studies with prevalence-estimates ranging from 5-35% (Kelleher et al., 2012a). Even higher prevalence estimates of self-reported PE of up to 60-70% have been reported in later studies (Downs et al., 2013; Karcher et al., 2020). The heterogeneity of the prevalence-estimates of PE across studies is vast and most likely well-explained by use of different measures and more or less arbitrary cut-offs. Although the psychosis field struggles with finding unifying concepts and language to describe the symptoms at all levels of the psychosis continuum (Guloksuz and Os, 2017; Seiler et al., 2020; van Os, 2016), data from multiple large cohorts of children and adolescents have documented that PE are definitely not negligible in youths. A recent review showed that PE are associated with non-psychotic mental disorders both in cross-sectional studies, and also found both homotypic and heterotypic courses towards diagnosis of later psychotic and, to a somewhat lesser degree, non-psychotic mental disorders (Healy et al., 2019a). Finally, another recent review documented a link between PE and later suicidality (Yates et al., 2019).

Part 1 of the current thesis aimed to extend the findings in the literature, and we attempted to fill some of the gaps regarding the potential clinical utility of PE. Epidemiological studies cannot simply determine firm causal interferences between PE and other psychopathology such as suicidality, and reviews have found that other psychopathology and particularly depression explain much of the association between PE and suicidality (Honings et al., 2016; Yates et al., 2019). To assess the possibility of causation between PE and suicidality, one can consider the Bradford Hill criteria of causality (Hill, 1965). These criteria are not by any means *sufficient* to determine causality, but can be considered indicative of causation (Rothman et al., 2008). As previously suggested by DeVlyder and colleagues (DeVlyder et al., 2015a), causality behind the association between PE and suicidality can be suspected due to:

1. a *strong* association, particularly in studies of youths (Honings et al., 2016),
2. relatively *consistent* findings across studies (Honings et al., 2016; Yates et al., 2019),
3. *plausibility*, e.g. distress due to PE could increase suicidality.
4. a *biological gradient*, i.e. an observed dose-response relationship between suicidality severity and PE (Cederlöf et al., 2017; DeVlyder et al., 2015b),
5. some evidence of *temporality*, i.e. PE preceding suicidality (Yates et al., 2019).

However, the fact that suicide is common in individuals with psychopathology transdiagnostically (Lönngqvist, 2009), and findings that the independent effect of PE on suicidality is negligible when considering a wide range of covariates (DeVlyder et al., 2015a), would weaken the case for a *specific* causal role of PE on

suicidality. **Paper 1** of the current thesis examined outcomes of risk-behaviors, i.e. substance use, suicidality and non-suicidal self-harm. In this discussion, I will focus on suicidality and non-suicidal self-harm in the current discussion, and regard them as a part of the same continuum (Grandclerc et al., 2016; Nock, 2010; Sveticic and Leo, 2012). The study described in Paper 1 lends some support to the notion of causality, given strong associations between PE and suicidality, and a dose-response relationship between the number of PE and increased risk of suicidality in cross-sectional analyses. However, the study has a notable strength in that PE and suicidality were considered at two time points, together with depressive symptoms and impact of general psychopathology. When the presence of suicidality at age 11 was accounted for, i.e. when individuals who expressed such behaviors already at age 11 were excluded from the analyses, there was little evidence left of a temporal relationship between PE at age 11 and suicidality at age 16. However, whether or not PE might be a specific or causal risk factor of suicidality, the strong associations do call for PE being assessed and taken seriously clinically as a risk-marker among many for suicidal ideation (Kelleher et al., 2012c). Given that suicidality rarely occurs in the absence of substantial mental health problems (Lönngqvist, 2009), and that PE can be considered as a severity marker of transdiagnostic psychopathology (Guloksuz et al., 2015), it might perhaps be feasible to consider both PE and suicidality as epiphenomena, rather than causes of, non-psychotic psychopathology?

Just like observational studies cannot unravel whether PE are causal determinants of suicidality, the same applies to the associations found between PE and both co-occurring and future mental disorders (Healy et al., 2019a). However, some studies have shown that even transient PE mark an increased risk of later functional impairment and psychopathology as a marker of underlying vulnerability to psychopathology (Calkins et al., 2017; Healy et al., 2018). Furthermore, a small study showed that PE in preadolescence contributed to the prediction of externalizing problems four years later, over and above the effect of mental disorders and functioning (Healy et al., 2019b). These conclusions are supported by the findings in **Paper 2** that PE at age 11 were associated with later diagnosed mental disorders, even if individuals with PE did not concurrently meet research-based criteria for any research-based mental disorder. Furthermore, even when adjusting for high scores of parent-reported mental health problems, PE predicted increased costs in mental health services (but not somatic care services) in **Paper 3**. The studies contribute with knowledge that the presence of PE in preadolescence is an independent risk marker of later transdiagnostic psychopathology that are not merely part of, or epiphenomena of, general mental health problems.

Our results in **Papers 2-3** correspond well with meta-analytic findings in adults of an approximately 2-3 fold increase in mental health service-use in individuals with PE compared to individuals without PE (Bhavsar et al., 2018). We further contribute with a prospective design and independently acquired data on service use,

limiting recall bias and same-informant bias. Our findings did not suggest any specificity regarding outcomes of psychotic disorders. Some specificity was expected based on the meta-analytic findings of others (Healy et al., 2019a; Kaymaz et al., 2012). This might at first glance seem somewhat contradictory, considering previous CCC2000 findings that implied quite marked specificity towards expected psychosis development, given associations with a family history of psychotic disorders and *not* a family history of non-psychotic disorders (Jeppesen et al., 2015b), using the exact same age-11 PE variable as in **Paper 2**. However, only few individuals had been diagnosed with psychotic disorders in the registers up to age ~16.5 years, and future studies should reliably determine whether a degree of specificity towards psychotic disorders can also be found in the CCC2000. Even though PE might show some level of specificity towards psychotic disorders, relying too heavily on psychotic psychopathology to screen for later psychotic disorders may not be efficient in the prevention of psychotic disorders, given low sensitivity of even clinical high risk for psychosis (CHR-P) criteria (Guloksuz et al., 2020).

When examining PE as a potential risk marker of later psychopathology, it is inevitable to touch upon the potential implications for risk-calculation and, specifically, the CHR-P paradigm. To identify help-seeking individuals who are at risk of progressing from low levels of mainly psychotic symptomatology to higher levels of severity of psychosis, numerous criteria for CHR-P have been developed (Fusar-Poli et al., 2020). Individuals who fulfill these criteria are often referred to as “prodromal”, “ultra-high risk” of psychosis (Fusar-Poli et al., 2013). Within this framework, the “transition” (versus “non-transition”) denote the crossing of the line to fulfilling the criteria for a psychotic disorder, which like all diagnoses, are arguably arbitrary (Guloksuz and Os, 2017; Kendler et al., 2011). However, clinical high-risk for psychosis criteria have shown to encompass very heterogenous populations with around 25% transitioning to psychotic disorder within the follow-up period of two years (Fusar-Poli et al., 2013). Furthermore, discouraging findings suggest intervening towards individuals with CHR-P will only minimally impact the population burden of psychotic disorders (Guloksuz et al., 2020), and only a minority of individuals who actually are diagnosed with a psychotic disorder actually made contact to specialized CHR-P mental health services (Ajnakina et al., 2019). A recent editorial from the leadership of the European Society for Child and Adolescent Psychiatry called for extending and adapting of CHR-P research and interventions to CAMHS (Armando et al., 2020). However, even though psychotic symptomatology are indeed important to identify in populations of youths in need of potential support and preventive measures (Healy and Cannon, 2020), given the caveats in the CHR-P approach described above, we have recently suggested that CAMHS focus on needs-based interventions targeting the most manifest problems, e.g. non-psychotic psychopathology or psychosocial problems, without over-emphasizing psychosis (Rimvall et al., 2020b).

Finally, findings from **Paper 3** added to the evidence that PE are associated with poor HRQoL (Alonso et al., 2018; Trotta et al., 2019). In fact, our findings suggest that PE might constitute a risk factor of poor HRQoL that persists over time, independently of general psychopathology and a large range of potential sociodemographic confounders. These finding would indicate that reducing the impact of PE in itself might reduce future healthcare needs and costs (Luyten et al., 2016; Wade and Guo, 2010). However, in the same paper we found that PE at age 11 were only weakly associated with poorer school performance at age 16, and the associations was non-independent of the overall same confounders as the outcome of HRQoL was adjusted for. These results are similar recent findings from two other large cohort studies which also took into account numerous potential confounding factors and co-occurring psychopathology (Steenkamp et al., 2020; Trotta et al., 2019). A previous CCC2000 study found that parent-rated general mental health problems were associated strongly and independently with poorer school performance (Wolf et al., 2019). Given that performing poorly in school predicts less wealth and life-satisfaction (French et al., 2015; Oreopoulos and Salvanes, 2011), our results collectively strongly suggest that assessment of PE in children *together* with (parent rated) general psychopathology is essential, since they both individually contribute with important information regarding children's future well-being and opportunities later in life.

Perspectives from Part 2

Paper 4-6 in *Part 2* of the current thesis takes a different approach as compared to *Part 1*. Where we in the papers in *Part 1* applied a broad perspective of examining outcomes of PE regarding functioning, general impairment, risk behaviors and transdiagnostic psychopathology and service use, *Part 2* takes on a narrower perspective of examining PE in relation to more specific psychopathology relating to bodily experiences and anxieties. Inspired by my own clinical experiences of patients with distressing bodily phenomena in the context of psychotic symptomatology as well as literature describing bodily experiences in psychosis (Jenkins and Röhrich, 2007; Kato and Ishiguro, 1997; Kobayashi and Kato, 2004; Simon et al., 2014), the extensive data on both PE, HA and FSS in the CCC2000 provided some unique opportunities to examine the co-occurrence of PE, FSS and HA in youths. Furthermore, although FSS, HA and particularly psychosis are generally described separately, cognitive models show striking similarities across these domains, as described in the introduction, page 9 (Henningesen et al., 2018; Kapur, 2003; Nelson et al., 2014; Norris and Marcus, 2014; Van den Bergh et al., 2017; Warwick and Salkovskis, 1990).

FSS and HA are symptom dimensions that can be impairing enough to justify diagnoses of bodily distress disorder (Gureje and Reed, 2016) and hypochondria (Stein et al., 2016) in their own right in the ICD-10, and the studies in the current study by no means aim to merely describe these symptoms as part of psychosis development. The strong associations between PE, FSS and HA described in **Paper 4-5** can be interpreted in

several directions. Within the youths who experiences both PE and HA, the strong associations can arguably lend some support to the idea of a common developmental pathway towards severe mental illness (Simon et al., 2014). However, both PE and high levels of HA are most often transitory in the current cohort (**Paper 1** and Rimvall et al. 2020a), and the associations in the longitudinal analyses of **Paper 5** were consequently relatively weak, compared to the very strong associations in cross-sectional analyses. Furthermore, although PE in the cross-sectional analyses were still associated with HA over and above both FSS and general psychopathology, much of the effect was explained by FSS and general psychopathology at ages 11 and 16. This shows that the robust associations cannot solely be interpreted as specific associations with similar underlying mechanisms, but that the associations might arise, at least in part, as a epiphenomenon of co-occurring psychopathology within a unifying factor ‘p’ (Caspi et al., 2014; Caspi and Moffitt, 2018) or common mental distress (Stochl et al., 2015). Similarly, **Paper 6** shows some specific associations between PE and FSS using a symptom-based network approach, indicating some specificity of the associations between PE and bodily experiences that cannot be accounted for simply by emotional psychopathology.

Future and clinical perspectives

Future work on the CCC2000 will allow for more extended register-based follow-up and hopefully additional questionnaire- and interview follow-ups of the current cohort. Due to the low prevalence of clinical psychosis by age 16-17 at the end of follow-up, **Paper 2** of the current thesis lacked power to study outcomes of psychotic disorders compared to non-psychotic disorders. Based on meta-analytic evidence (Healy et al., 2019a; Kaymaz et al., 2012), one could very well expect some specificity at e.g. age 25-30 years, at which age most patients who end up being diagnosed with a psychotic disorder will have received the diagnosis. Given that the register-based diagnoses reflect unbiased information on “real-life” clinical disorders and medications unlike most other studies, these future CCC2000 studies might provide unique insights. How PE might affect and interact with other psychopathology and sociodemographic variables with respect to labor market attachment, crime and socioeconomic economic register-based outcomes will also be of interest in future studies. Further assessment of the CCC2000 participants, e.g. during their early 20’ies, will also allow for examining trajectories of PE and identifying potential mediating factors in adolescence that might have positive/negative effects on outcomes following PE in preadolescence. Furthermore, although negative symptoms can be difficult to assess, delineate and distinguish from for instance depressive symptomatology (Dollfus et al., 2016; Marder and Galderisi, 2017), negative symptoms are an equally important part of psychotic disorders as positive symptoms and are often indicative of poorer prognosis (Hollis and Palaniyappan, 2015). It can be argued that negative symptoms are often overlooked in studies that examine PE, and given that negative symptoms have not been directly assessed in the CCC2000, this should be considered for future follow-ups of the cohort.

Given that persistence of PE can likely contribute to (or persist due to) detrimental development, and given that persistence is inherently associated with higher risk of psychotic disorders (Dominguez et al., 2011; van Os et al., 2009), future studies determining factors of importance for persistence/remittance of PE will be important. However, given that longitudinal studies are based on “healthy” general population-based populations, and that most PE remit (Linscott and van Os, 2013), statistical power to determine such factors is often limited. This is also the case in the CCC2000, which is further weakened by the fact that PE were measured in different ways at age 11 and age 16, respectively. A recent scoping review did not identify any consistent psychopathological or sociodemographic factors across studies that predicted persistence (Kalman et al., 2019). However, the review excluded many large studies due to low follow-up percentages, and meta-analysis was not attempted. Future meta-analysis or studies that pool data from multiple cohorts can contribute to answering this question in the future.

Although much critique has been presented in the current thesis regarding the *conceptualization* of mental disorders including psychotic disorders and schizophrenia, it is indisputable that individuals who are diagnosed with psychotic disorders include many of the individuals who are the most severely functionally impaired and suffer the most from mental health problems (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). Furthermore, they represent a group which is, even in high-income countries, often neglected when it comes to treatments beyond psychotropic medication (Patel et al., 2010). In adult populations, there is support for therapeutic interventions, pharmaceutical interventions, and particularly assertive and integrated early intervention services for individuals with first episode psychosis (Correll et al., 2018). Unfortunately, such interventions cannot readily be transferred directly to children and adolescents; for example anti-psychotic treatments might not be as tolerable nor efficacious in youths as in adults (Pagsberg et al., 2017a, 2017b). The evidence-base for interventions directed at children and adolescents are severely lacking (Anagnostopoulou et al., 2018; Armando et al., 2020). Thus, improving treatment of severe mental states as well as prevention of mental health problems at different stages of impairment in young people are both pivotal for future research and practice, and should go hand in hand (McGorry et al., 2020).

The studies of the current thesis support the growing consensus that PE, whether causal or non-causal with regard to other psychopathology and detrimental outcomes, provide important clinical information regarding current mental health problems in children and adolescents as well as future severe mental illness (Healy et al., 2019b; Healy and Cannon, 2020; Kelleher et al., 2012b; Majer et al., 2019a; van Os and Reininghaus, 2016). Hence, assessment of PE cannot be ignored when assessing and deciding which children and adolescents should be under surveillance and offered preventive transdiagnostic interventions in the

future (McGorry et al., 2018; Shah et al., 2020; van Os et al., 2019). Although PE are increasingly well-described among children and adolescents in the general population, only few, small and cross-sectional studies have examined PE in clinical populations without psychotic disorders or assigned as CHR-P, e.g. (Ames et al., 2014; Gin et al., 2018; Kelleher et al., 2014b; Pontillo et al., 2018; Wigman et al., 2014a). Examining the longitudinal correlates of having PE in clinical samples, as well as further studies examining PE as a potential moderator of treatment effects (Davies et al., 2019; Wigman et al., 2014b) are needed to illuminate and evaluate the clinical utility of assessing PE.

Interventions directed directly towards PE are currently being suggested and tested in populations without psychotic disorders or fulfilling criteria for CHR-P (Jolley et al., 2018; Majjer et al., 2019b). Furthermore, recent interesting studies from Ireland have identified improvement of self-esteem and reduction of child-parent conflict as potential targets for interventions to reduce impact and decrease persistence of PE (Coughlan et al., 2019; Dhondt et al., 2019; Healy et al., 2020), targets which one easily could imagine to have universal impact on children both with *and* without general mental health problems. Future randomized controlled studies directed at non-psychotic psychopathology could examine potential “indirect” effects on outcomes of PE. In such a study design, PE could be viewed as an epiphenomenon that is tractable through reduction of the non-psychotic psychopathology and related distress. Additionally, the role of PE in clinical samples of youths with HA and FSS should be examined, perhaps to help delineate sub-groups of individuals with different courses/treatment needs compared to individuals with FSS and HA without psychosis expression (Rask et al., 2020).

Finally, conferring knowledge of psychosis as a continuous, transdiagnostic phenotype to the general public, as well as mental health professionals, is an important and challenging task. Stigma in society, as well as self-stigma, are important issues for individuals with psychotic disorders (Gerlinger et al., 2013; Rüsch et al., 2005) as well as “at-risk” populations (Colizzi et al., 2020). Negative stigma can be regarded as a risk factor of detrimental outcomes, including suicidality, among individuals vulnerable to psychosis (Rüsch et al., 2015; Xu et al., 2016). Normalizing PE as experiences that are experienced by many, perhaps even *most*, individuals over the life-course, might contribute to reducing stigma. However, one must be cautious that describing psychosis (and non-psychotic psychopathology) as continuous variables, and describing disorders solely as social constructions, can give fodder to anti-psychiatric movements (Kendler, 2016). This, in turn, might harm individuals with severe mental illness. Apart from the potential of increasing the opportunities for individuals with severe psychosis in society, normalizing psychosis might also reduce the risk of individuals with severe mental health problems not seeking timely help (Gronholm et al., 2017), thereby reducing chronicity of mental health problems, e.g. by reducing duration of untreated psychosis (Marshall et al., 2005; Penttilä et

al., 2014). However, although PE might in some cases predict later psychotic disorder, instead of assigning CHR-P status and inducing fear of future poor prognosis, dealing with the needs and associated non-psychotic psychopathology and distress through holistic and transdiagnostic approaches (McGorry et al., 2018; Shah et al., 2020; van Os et al., 2019) will hopefully improve prognosis and wellbeing (Guloksuz and Os, 2017; Rimvall et al., 2020b; van Os and Guloksuz, 2017).

Ethical considerations

Approval for the CCC2000 study was given by the Danish Data Protection Agency (CSU-FCFS-2016-004, I-Suite 04544) and the local Committee on Health Research Ethics (protocol 16023242). Participants gave informed consent, and the Helsinki Agreement of 1975 and later amendments were followed. Furthermore, we adhered to the rules and ethical guidelines of Statistics Denmark as described on page 19.

Financial support and disclosures

I thank the Research Fund of the Mental Health Services - Capital Region of Denmark, for a PhD scholarship which has financed my work throughout the past 3 years. Additional financial support for, travel expenses, statistical support and acquirement of data related to the work on this thesis was granted by Øster-Jørgensen og Rønhild Andersen Fonden and by the Danish Society of Child and Adolescent Psychiatrists. The 11- and 16-year follow-ups of the Copenhagen Child Cohort have been made possible by the following grants: TrygFonden (J. nr. 7-10-0189, 7-11-0341 and 109903), Lundbeckfonden (J. nr. R54-A5843).

I have no financial disclosures or other potential conflicts of interest to disclose.

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