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THE RISK FACTORS, CLINICAL CHARACTERISTICS AND OUTCOMES OF PSYCHOTIC DEPRESSION

The Northern Finland Birth Cohort 1966

Miika Nietola



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The originality of this publication has been checked in accordance with the University of Turku quality assurance system using the Turnitin OriginalityCheck service.

ISBN 978-951-29-8165-6 (PRINT)
ISBN 978-951-29-8166-3 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama Oy, Turku, Finland 2020

UNIVERSITY OF TURKU

Faculty of Medicine

Department of Psychiatry

MIIKA NIETOLA: The Risk Factors, Clinical Characteristics and Outcomes of Psychotic Depression

Doctoral Dissertation, 127 pp.

Doctoral Programme in Clinical Research

August 2020

ABSTRACT

Major depression with psychotic features (psychotic depression, PD) is a severe mental disorder characterized by depression and psychotic symptoms. Despite grave symptoms and high mortality, PD has remained under-researched. Furthermore, the majority of research has focused on the acute phase of the illness or included only a short follow-up. Few studies have focused on the risk factors or long-term outcomes of PD.

In this thesis, the aim was to examine the risk factors, clinical characteristics and outcomes of PD. Firstly, a systematic review and meta-analysis were performed to analyze existing literature. Secondly, an original study in the Northern Finland Birth Cohort 1966 (NFBC 1966) was conducted. The NFBC 1966 is a naturalistic and prospective birth cohort study that includes 12058 subjects who had an estimated date of birth in 1966. The participants have been followed since mid-pregnancy for over 50 years. Data about study subjects were acquired from several different sources including national registers, clinical measurements and questionnaires. PD (n=55 in Study III; n=58 in Studies II and IV) was compared to other severe mental disorders and, regarding risk factors, to healthy controls (HC).

Both in the meta-analysis and the study in the NFBC 1966, PD was found to have a worse clinical picture and prognosis than non-psychotic depression, comparable to psychotic bipolar disorder but better than in schizophrenia. The majority of PD patients were females. In the NFBC 1966, only a few significant risk factors for PD were found. These included mental illness in the family and low school sports grade in adolescence. The original study showed that, also in the long term, PD patients have negative outcomes such as impaired functioning and recurrent hospitalizations. Furthermore, male gender predicted worse outcomes. Psychiatric comorbidity was especially common in PD in the NFBC 1966 and associated with poor outcomes.

To conclude, PD has similar outcomes than psychotic bipolar disorder and should be treated accordingly with a proper long-term focus. Due to a lack of research, more prospective studies with a long follow-up are urgently needed.

KEYWORDS: Psychotic depression, risk factors, outcome, symptoms, gender, prospective

TURUN YLIOPISTO

Lääketieteellinen tiedekunta

Psykiatrian oppiaine

MIIKA NIETOLA: Psykoottisen masennuksen riskitekijät, kliiniset piirteet ja ennuste

Väitöskirja, 127 s.

Turun kliininen tohtoriohjelma

Elokuu 2020

TIIVISTELMÄ

Psykoottinen masennus tarkoittaa vakavaa masennusta, jonka yhteydessä ilmenee myös psykoottisia oireita kuten harhaluuloja tai hallusinaatioita. Siitä huolimatta, että psykoottiseen masennukseen liittyy vaikea oirekuva ja korkea kuolleisuus, sitä on tutkittu vain vähän. Suuri osa tutkimuksesta on myös keskittynyt sairauden akuuttivaiheeseen tai sisältänyt vain lyhyen seuranta-ajan eikä riskitekijöistä tai pitkän aikavälin ennusteesta ole kovin merkittävästi tietoa.

Tämän väitöskirjatyön tavoitteena oli selvittää psykoottisen masennuksen riskitekijöitä, kliinisiä ominaispiirteitä ja ennustetta. Ensiksi tehtiin systemaattinen kirjallisuuskatsaus sekä meta-analyysi. Tämän jälkeen suoritettiin alkuperäistutkimus, jonka aineistona oli Pohjois-Suomen syntymäkohortti 1966. Kohortin jäseniä on seurattu raskausajasta asti yli 50 vuoden ajan. Tutkimusaineisto kerättiin kansallisista rekistereistä, kliinisistä mittauksista ja kohortissa kerätyistä kyselylomakkeista. Psykoottista masennusta (n=55 osatyössä III; N=58 osatyössä II ja IV) verrattiin muihin vakaviin mielenterveyden häiriöihin. Lisäksi riskitekijöiden osalta käytettiin vertailuryhmänä myös terveitä verrokkeja.

Sekä meta-analyysin että alkuperäistutkimuksen tuloksena oli, että psykoottisen masennuksen kliininen kuva ja ennuste ovat vaikeampia kuin ei-psykoottisessa masennuksessa, vastaavia kuin psykoottisessa kaksisuuntaisessa mielialahäiriössä ja parempia kuin skitsofreniassa. Enemmistö psykoottista masennusta sairastavista oli naisia. Pohjois-Suomen kohortissa vanhempien mielenterveysongelmat ja matala liikunnan kouluarvosana murrosiässä lisäsivät psykoottisen masennuksen riskiä. Alkuperäistutkimus osoitti sen, että psykoottiseen masennukseen liittyy heikko pitkäaikaisennuste. Psykiatrinen oheissairastavuus oli psykoottisessa masennuksessa yleistä ja se ennusti vaikeampaa sairaudenkulkua, kuten myös miessukupuoli.

Pitkällä aikavälillä psykoottiseen masennukseen liittyy toimintakyvyn lasku ja toistuvia sairaalahoitoja, jotka ovat vastaavia kuin psykoottisessa kaksisuuntaisessa mielialahäiriössä. Tämän vuoksi hoidon tulee olla pitkäjänteistä. Lisää prospektiivisiä seurantatutkimuksia psykoottisesta masennuksesta tarvitaan.

AVAINSANAT: Psykoottinen masennus, riskitekijät, ennuste, oireet, sukupuoli, prospektiivinen

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Abbreviations

AESOP	Aetiology and Ethnicity in Schizophrenia and Other Psychoses
BD	Bipolar Disorder
BMI	Body Mass Index
CINAHL	Cumulative Index of Nursing and Allied Health Literature
DBH	Dopamine-beta-hydroxylase
DMN	Default Mode Network
DSM-5	The 5 th version of the Diagnostic and Statistical Manual of Mental Disorders
DST	Dexamethasone suppression test
ECT	Electroconvulsive therapy
GAF	Global Assessment of Functioning Scale
GAS	Global Assessment Scale
HC	Healthy Control
HR	Hazard Ratio
HPA	Hypothalamus-pituitary-adrenal
ICD-8	The 8 th version of the International Classification of Diseases
ICD-9	The 9 th version of the International Classification of Diseases
ICD-10	The 10 th version of the International Classification of Diseases
NFBC 1966	The Northern Finland Birth Cohort 1966
NPD	Non-Psychotic Depression
PBD	Psychotic Bipolar Disorder
PD	Psychotic Depression
PDAS	Psychotic Depression Assessment Scale
PNOS	Other Psychoses
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-analyses
REM	Rapid Eye Movement
scACC	Subcallosal Region of the Anterior Cingulate Cortex
SOFAS	Social and Occupational Functioning Assessment Scale
SPSS	Statistical Package for the Social Sciences
SZ	Schizophrenia

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

- I Jääskeläinen E, Juola T, Korpela H, Lehtiniemi H, Nietola M, Korkeila J, Miettunen J. Epidemiology of psychotic depression - systematic review and meta-analysis. *Psychological Medicine*, 2018, Apr 48(6): 905-918.
- II Nietola M, Huovinen H, Heiskala A, Nordström T, Miettunen J, Korkeila J, Jääskeläinen E. Early childhood and adolescent risk factors for psychotic depression in a general population birth cohort sample. *Social Psychiatry and Psychiatric Epidemiology*, 2020, Feb 13: 1-8.
- III Nietola M, Heiskala A, Nordström T, Miettunen J, Korkeila J, Jääskeläinen E. Clinical characteristics and outcomes of Psychotic Depression in the Northern Finland Birth Cohort 1966. *European Psychiatry*, 2018, Sep 53: 23-30.
- IV Nietola M, Nordström T, Miettunen J, Korkeila J, Jääskeläinen E. Effects of gender and psychiatric comorbidity on the age of illness onset and the outcome of psychotic depression – a birth cohort study. *Manuscript*.

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1 Introduction

In 2012 Rebecca Lawrence, a practicing doctor from Scotland, wrote in the BMJ (Lawrence et al. 2012) about her history with mental illness: *“Quite suddenly my life fell apart. I don’t remember feeling depressed, but I became terrified of everything, afraid to eat, and convinced the baby would die... What was my diagnosis? How to classify the feelings of fear, terrible fatigue, anxiety, and blackness? Depression was what I was told, but I formed an unshakeable conviction that everyone thought I had a personality disorder... When I read a textbook description of psychotic depression, my diagnosis, I can’t marry it with how I feel. I do feel low, but also agitated and frightened, and simply very ill.”*

Psychotic Depression (PD hereafter) is a severe and under-researched disorder characterized by the combination of depression and psychosis. The illness has been associated with specific clinical and biological findings. Therefore, it has been argued that PD should be considered a distinct illness (Schatzberg & Rothschild 1992). Recommended and evidence-based treatments of PD include either combination therapy with an antidepressant and an antipsychotic medication (Flint et al. 2019) or electroconvulsive therapy (van Diermen et al. 2018). However, only a small number of studies have been conducted on the treatment of PD. Because PD sits in the middle of psychotic and affective disorders, it has been difficult for the science of psychiatry to find a stance on it.

Kraepelin divided mental illness into two main categories in 1899 in his influential textbook of psychiatry (Kraepelin 1899). Dementia Praecox was a deteriorating continuous illness mostly affecting intellectual functioning while manic-depressive illness had an episodic course and affected mostly mood (Falkai et al. 2015). Psychiatry in the 20th and 21st centuries has been heavily influenced by this categorization and the paradigm shift away from the psychoanalytic tradition has sometimes been referred to as the “neo-Kraepelinian revolution” (Compton & Guze 1995). The abovementioned categories are still found in current diagnostic classifications renamed as schizophrenia (SZ) and bipolar disorder (BD), even though the validity of this dichotomy has often been criticized (Craddock & Owen 2010). These disorders have also been targets of a thorough investigation while other

clinical presentations such as PD have remained under-researched (Crebbin et al. 2008).

Despite the multi-categorical nature of the prevailing diagnostic classifications, psychotic illness is currently understood differently. Psychotic symptoms are reasoned to appear on a continuum from mild and transient to severe and deteriorating, while also presenting themselves with almost all other symptom clusters across the diagnostic spectrum (Kelleher & Cannon 2016). Psychotic symptoms are conceptualized dimensionally, and schizophrenia is considered to include the 30% of people with the most severe symptoms (Guloksuz & Van Os 2018). Schizophrenia has also been the main focus of research perhaps hiding the large variation of psychotic phenomena. Psychotic depression is an example of these other symptom clusters that have been largely ignored in the scientific literature. Almost as if they did not even exist (van Os 2016).

It is important to remember that already Kraepelin believed a complete categorization of mental illness will prove impossible but still thought that clinical work needed diagnostic grouping (Kendler & Jablensky 2011). While research is revealing the dimensional nature of psychiatric illness and pragmatic categories are needed in the clinic, combining dimensional and categorical models may be a beneficial way forward (Chamberlain et al. 2018).

Regardless of any debates concerning diagnostic systems, patients with depression and psychotic symptoms will continue to be a clinical reality. This study is an effort to increase knowledge about this disorder, of which very little is known about. This thesis includes a systematic review and meta-analysis of epidemiology and a naturalistic birth cohort study in the Northern Finland Birth Cohort 1966.

2 Review of the Literature

2.1 Characteristics of Psychotic Depression

2.1.1 Diagnosis of Psychotic Depression

The diagnosis of PD (major depressive disorder with psychotic features or psychotic depression) and its nosological status have been debated for decades (Schatzberg & Rothschild 1992). Primary controversy has been about whether PD should be handled as a separate psychotic illness or as simply one type of severe depression. A vast amount of research has been published showing differences between PD and non-psychotic depression (NPD) to try to confirm that PD is a distinct illness and that it should be categorized as such (Rotschild 2013).

Currently, PD is defined slightly differently in the 10th version of the International Classification of Diseases (ICD-10) and the most recent version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). In Finland, the ICD-10 system is currently in use. ICD-10 diagnostic criteria (Table 1; World Health Organisation 1992) dictate that a patient must exhibit symptoms of severe depression accompanied by psychotic symptoms and the psychotic symptoms are also required to be other than typically schizophrenic. DSM-5 (American Psychiatric Association 2013) separates affective and psychotic symptom dimensions in the way that PD may be diagnosed in a person with mild or moderate depressive symptoms.

In clinical settings, the diagnosis of PD is often missed. Rothschild et al. conducted a study (2008) in 4 academic medical centers to examine how accurate the diagnosis of PD is in naturalistic environments. They found that in 27% of diagnostic evaluations the diagnosis of PD was missed. Failure to correctly diagnose PD was especially common in emergency room settings (39%) and it was also more common among attending psychiatrists (34%) than among psychiatry residents (10%). In this study, it was the psychotic symptoms that were missed and not the mood disorder. The authors note that the actual symptoms, such as guilt, were often in these cases noticed but they were not interpreted to be psychotic. This underlines the difficulty in separating psychotic and non-psychotic feelings of guilt.

Table 1. Diagnostic criteria for PD according to ICD-10 (The ICD-10 Classification of Mental and Behavioural disorders – Diagnostic criteria for research).

<p><u>F32.3 Severe depressive episode with psychotic symptoms</u></p> <p>A. The general criteria for depressive episode (F32) must be met.</p> <p>B. The criteria for severe depressive episode without psychotic symptoms (F32.2) must be met with the exception of criterion D.</p> <p>C. The criteria for schizophrenia (F20.-) or schizoaffective disorder, depressive type (F25.1) are not met.</p> <p>D. Either of the following must be present:</p> <p style="padding-left: 40px;">(1) delusions or hallucinations, other than those listed as typically schizophrenic in F20, criterion G1(1)b, c, and d (i.e. delusions other than those that completely impossible or culturally inappropriate and hallucinations that are not in the third person or giving a running commentary); the commonest examples are those with depressive, guilty, hypochondriacal, nihilistic, self-referential, or persecutory content;</p> <p style="padding-left: 40px;">(2) depressive stupor.</p> <p>A fifth character may be used to specify whether the psychotic symptoms are congruent or incongruent with mood:</p> <p style="padding-left: 40px;">F32.30 With mood-congruent psychotic symptoms (i.e. delusions of guilt, worthlessness, bodily disease, or impending disaster, derisive or condemnatory auditory hallucinations)</p> <p style="padding-left: 40px;">F32.31 With mood-incongruent psychotic symptoms (i.e. persecutory or self-referential delusions and hallucinations without an affective content)</p> <p><u>F33.3 Recurrent depressive disorder, current episode severe with psychotic symptoms</u></p> <p>A. The general criteria for recurrent depressive disorders (F33) are met.</p> <p>B. The current episode meets the criteria for severe depressive episode with psychotic symptoms (F32.3).</p> <p>A fifth character may be used to specify whether the psychotic symptoms are congruent or incongruent with the mood:</p> <p style="padding-left: 40px;">F33.30 with mood congruent psychotic symptoms</p> <p style="padding-left: 40px;">F33.31 with mood incongruent psychotic symptoms</p>

Different measurement scales are routinely used to assess psychiatric disorders. The Psychotic Depression Assessment scale (PDAS) is the only empirically validated measurement scale for PD (Østergaard et al. 2015). The scale has been developed in 2014 and it combines six items of the Hamilton Melancholia Subscale with relevant items from the Brief Psychiatric Rating Scale (Østergaard et al. 2014a). PDAS can be used to screen for PD among patients with depression (Park et al. 2014a) and in the measurement of response to treatment (Østergaard et al. 2014a).

2.1.2 Symptoms of Psychotic Depression

The symptoms of PD are in many ways like those of severe NPD, such as lowered mood, anhedonia, loss of appetite and problems with concentration, but there are also certain important separating differences. First, the depressive symptoms must be accompanied by psychotic symptoms: either hallucinations, delusions or psychomotor retardation (World Health Organization 1992). Characteristic psychotic symptoms in PD are overwhelming feelings of guilt during which the patient may, for instance, have delusions about having committed a crime or being responsible for a pending disaster. Secondly, patients with PD often exhibit a different clinical picture concerning symptom severity than patients with NPD.

According to literature, the depressive symptoms in PD are more difficult than in severe NPD both in younger samples (Rush et al. 2006; Zaninotto et al. 2013) and in older age (Gournellis et al. 2001). Therefore, psychotic symptoms in severe depression indicate that also the depressive symptomatology is more likely to be harsh. In a large European multicenter study (Dold et al. 2019) PD patients were also more likely to have melancholic characteristics than patients with severe NPD, in addition to having more severe depressive symptoms.

Depressive symptoms of PD patients have also been compared to depressive symptoms in SZ. The results of these studies have been conflicting (Craig et al. 2000; Hill et al. 2004) and currently, it is not known whether there is a difference between depressive symptom severity in PD and SZ. It is known that depression is common at different stages of SZ (Upthegrove et al. 2017) and this causes a challenge to diagnostic categorization and clinical practice. However, psychotic symptoms in SZ are more severe than in PD (Taiminen et al. 2000; Jäger et al. 2005) and this applies to both positive (Craig et al. 2000; Hill et al. 2004) and negative (Craig et al. 2000; Owoeye et al. 2013) symptoms.

The comparison of PD and psychotic bipolar disorder (PBD) is also of great interest. It seems that PD patients have more negative symptoms but at the same time exhibit fewer positive symptoms than patients with PBD (Craig et al. 2000; Dell’Osso et al. 2002; Owoeye et al. 2013). The results concerning depressive symptoms have been more mixed (Benazzi 1999; Dell’Osso et al. 2002).

2.1.3 Diagnostic instability

The validity of psychiatric diagnosis is in part evaluated by how stable the diagnosis is over a long period. Many factors are affecting this level of consistency during recurring diagnostic assessments such as the changes in the symptom presentation over time, the diagnostic process and the reliability and validity of diagnostic classification (Nietola et al. 2017). Descriptive diagnoses need to reach a certain level of stability to be clinically useful.

There are two central aspects to the question of diagnostic stability in PD. Firstly, it is important to know how often PD diagnosis converts to other diagnoses such as schizophrenia or bipolar disorder. Secondly, psychotic symptoms may accompany depression only once or recur during every depressive episode. The latter affects our understanding of the diagnostic stability of PD even though there is no conversion away from the diagnosis of depression.

The diagnostic stability in PD has been criticized to be low and, due to this, it has been suggested that the diagnosis of PD should be regarded as provisional (Ruggero et al 2011). However, there has been much variation between studies and different studies have shown diagnostic consistency (no change in diagnosis) from 24% (Forrester et al. 2001) to 100% (Schimmelmann et al. 2005). There are many components in the studies that may have affected this such as length of the follow-up, diagnostic tools that were used and the age of the sample. Also, study design including only first-episode cases as opposed to other samples is likely to influence diagnostic stability since first-episode diagnoses may often change while non-first-episode samples consist of patients who are more ill (Heslin & Young 2018). In the studies with the longest duration of follow-up, approximately 45% of patients diagnosed with PD at baseline had the same diagnosis ten years afterward (Ruggero et al. 2011; Heslin et al. 2015). Both of these studies included young adults with the median age at baseline being roughly thirty years.

The results of a large systematic review and meta-analysis conducted at The University of California supported the diagnostic consistency of PD over longer periods (Nelson et al. 2018). The researchers compared patients with an index episode of PD to those with NPD. They found PD patients to have nearly a ten-fold risk of having had prior or subsequent episodes of PD compared to patients with NPD. They also compared the risk of the patient having had all depressive episodes accompanied by psychotic symptoms and found that patients with PD had over seven times bigger risk for this to have happened.

The age of the sample is especially important in PD when analyzing diagnostic stability. Depression of old age may be a prodromal phase of dementia (Singh-Manoux et al. 2017) and PD may be even more common in old age than among younger population (Kivelä & Pakkala 1989; Perälä et al. 2007). Also, younger onset age of PD is a probable risk factor for conversion to BD (Østergaard et al. 2014b) and it is likely to predict conversion from unipolar depression to SZ (Musliner et al. 2017). Therefore, it seems that the relationship between the age of the sample and diagnostic stability is complex and needs to be taken into account when planning and interpreting all studies conducted on PD.

It is also important to remember that PD is not the only psychiatric disorder undergoing debates about diagnostic validity due to relatively low diagnostic stability, causing vague boundaries between disorders. NPD and BD have also

shown quite low rates, like PD, in diagnostic consistency (Baca-Garcia et al. 2007). Although there are many limitations to the current categorical diagnostic system, and therefore it may be legitimately criticized, the lack of research concerning PD cannot be justified based on a uniquely low diagnostic consistency.

However different study designs may produce different results if the diagnostic change is not considered. Different diagnostic shifts do not only affect the validity of the diagnostic group of PD but potentially lower the validity of comparison groups that also may drift to other diagnoses, including PD (Figure 1).

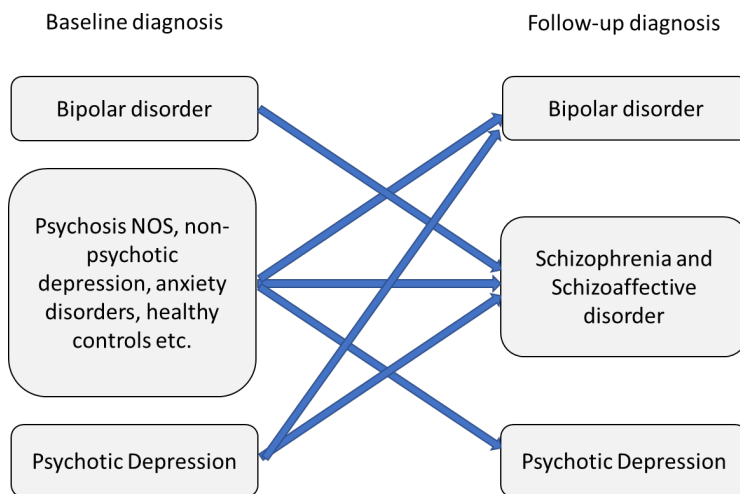


Figure 1. Illustration of potential diagnostic changes during follow-up studies.

2.1.4 Onset age

Studies on the onset age (first episode of PD) show a great variation in results. For example, in samples with first-episode psychosis the youngest mean onset age has been 25.2 years (Hill et al. 2004) and the oldest 51.5 years (Nakamura et al. 2015). In other samples, the variation has been even more significant. In two studies from the USA, Gaudiano et al. (2009) reported a mean onset age of 20.7 years while in the study by Meyers et al. (1999) it was 67.5 years. These major differences naturally reflect on the other hand methodological differences but also give information about the different courses of illness in PD: the first episode of PD may appear in early adulthood or at a significantly older age. Different age groups have been analyzed in different studies and this selection of the sample also affects the differences between the onset age in PD compared to other disorders. Variation in onset age, in addition to diagnostic instability, causes challenges to the research of PD. No previous meta-analyses have analyzed the onset age in PD.

2.1.5 Cognitive changes in Psychotic Depression

Cognitive symptoms have been long recognized to exist in different psychotic disorders and their more specific characteristics and possible differences have been examined. PD has been associated with significant cognitive disturbances. A review and meta-analysis from 2004 discovered cognitive domains where there was a decrease in performance and these changes were more prominent among PD patients than in NPD (Fleming et al. 2004). Most affected cognitive domains were verbal memory, executive functioning and psychomotor speed. However, the authors mention several limitations especially due to the lack of relevant studies.

Another meta-analysis found significant cognitive impairments in affective psychoses as a group and did not report a significant difference between PD and BD (Bora et al. 2010). The interpretation of these results also had a limitation of a relatively small amount of studies about PD.

Most recent evidence is examined in the meta-analysis by Zaninotto et al. (2015). They analyzed studies that compared PD to NPD. Significantly more cognitive deficits were found in patients with PD and the largest impairments were found in verbal learning, visual learning and processing speed. The effect sizes were larger in unmedicated patients, which implicates a potential benefit of pharmacological treatment on cognition in PD. Cognitive deficits appeared to be qualitatively similar to those reported in SZ and worse than those in BD (Zaninotto et al 2015).

2.1.6 Biological findings

2.1.6.1 Neuroanatomy and neurobiology

There is a clear lack of studies focusing on the neuroanatomy of PD and the results so far have been mostly heterogeneous. Reduced volume of the posterior subgenual cingulate cortex has previously been reported in PD (Coryell et al. 2005). Structural changes were also analyzed in a newer study that compared PD patients to HC (Bijanki et al. 2014). The results showed a significant reduction of hippocampal volume bilaterally in PD, perhaps a consequence of hypercortisolism. Another finding in the study was that the subcallosal region of the anterior cingulate cortex (scACC) was smaller among those PD patients with a family history of depression, which may indicate genetic vulnerability. Also, according to a review by Busatto (2013), most studies have not found neuroanatomical differences between PD and NPD, which can be seen to posit PD close to NPD in regard to these biological findings. However, some studies show that PD may be associated with additional structural and functional brain abnormalities in comparison to NPD, while these changes are still not as significant as in SZ (Busatto 2013).

A more recent study using resting-state functional magnetic resonance imaging (fMRI) investigated the functional connectivity between the hypothalamus and the subgenual cortex and found a clear reduction in the PD group compared to HC (Sudheimer et al. 2015). The authors discuss that decreased connectivity may be causing often observed HPA (hypothalamus-pituitary-adrenal) axis functional abnormalities, such as cortisol dysregulation, or be the consequence of these changes. Another study utilizing resting-state fMRI compared remitted PD patients with HC and found specific changes in the default mode network (DMN) (Neufeld et al. 2018).

Other interesting findings have also been made. Sapru et al. (1989) analyzed serum dopamine-beta-hydroxylase (DBH) levels and discovered decreased activity in the PD group compared to HC. Patients with NPD, manic symptoms or SZ did not show this deviation. Abnormalities in the sleep patterns of PD patients have also been detected. Thase et al. (1986) found decreased rapid eye movement (REM) sleep in PD patients compared to NPD.

2.1.6.2 Hypothalamus-pituitary-adrenal (HPA) axis

The functioning of the hypothalamus-pituitary-adrenal (HPA) axis and the cortisol hormone have been studied in many psychiatric disorders since they are essential in the regulation of stress. Especially the stress responses in a variety of psychiatric disorders have been found to exhibit physiological deviations from HC (Zorn et al. 2017). These changes are prominent in depression (Viinamäki et al. 2012). Disturbances of the HPA axis have been studied for decades and these abnormalities seem to be more common in PD than in NPD or among HC (Nelson & Davis 1997; Belanoff et al. 2001). These documented aberrations include elevated cortisol levels both in the afternoon and in the evening. In addition, a blunted response to fludrocortisone and non-suppression in the dexamethasone-test have been found (Keller et al. 2017). These changes are likely to have implications for somatic health and may partly explain the increased mortality reported in PD (Coryell et al. 2008).

Along with direct physiological influence, hypercortisolism is likely to have a significant negative effect not only on the cognitive functioning of PD patients but on HC as well, and cortisol levels seem to correlate with cognitive functioning (Belanoff et al. 2001).

There has also been an effort to localize potential genetic predispositions to cortisol dysfunction in PD and researchers found that variation in the glucocorticoid receptor gene explains a significant amount of differences in cortisol levels (Schatzberg et al. 2014). A recent interesting and high-quality study conducted at Stanford University aimed to investigate in combination the roles of HPA axis activity, clinical symptoms, HPA genetic variation and cognition in HC and patients

with PD and NPD (Keller et al. 2017). High cortisol levels were associated with lower cognitive functioning and PD patients had both lower cognitive functioning and higher cortisol levels than other groups. The study also found that genetic variation in glucocorticoid and mineralocorticoid receptor genes predicted specific cognitive functions and paralleled the estimated density of those receptors in the areas of the brain responsible for those cognitive functions.

Studies analyzing the HPA-axis function in SZ have been heterogeneous indicating the possibility of both hypo- and hyperfunction (Bradley & Dinan 2010). A recent study compared PD and SZ regarding HPA axis function and cognition and their results showed higher evening cortisol levels in PD, while there was no significant difference in cognitive functioning (Cherian et al. 2019). However, as discussed in the article, these results may be affected by the SZ group consisting of less acutely ill patients, and cortisol functioning is likely to be different at different phases of the illness in both SZ and PD.

2.2 Treatment of Psychotic Depression

2.2.1 Standard pharmacological treatments

The effects of different pharmacological agents in the treatment of PD are heavily understudied (Wijkstra et al. 2015). A meta-analysis by Farahani & Correll (2012) analyzed 8 randomized studies with placebo-control that were conducted in the acute phase of the illness. They found that combination treatment with both an antidepressant and an antipsychotic was more effective than monotherapy with either medication alone. Cochrane Database review from 2015 (Wijkstra et al. 2015) reached similar conclusions although they alerted the reader of considerable risk of bias and a low quantity of studies that lowers the reliability of results. The Finnish guidelines for the treatment of depression recommend combination treatment with an antidepressant and an antipsychotic medication in PD (Depression: Current Care Guidelines, 2020).

Until recently, there has been little evidence to support any particular method of continuation therapy after remission. Since antidepressants have for long been recognized to be effective in preventing relapses of depression, a major question has been about how long antipsychotic medication should be used in PD. A recent study (Flint et al. 2019) examined the effect of discontinuing the antipsychotic medication after remission on the relapse rate during a 36-week follow-up. Patients were treated to remission with sertraline plus olanzapine. After 36 weeks, 20.3% of patients still using olanzapine had experienced a relapse compared to 54.8% of those who had switched to placebo. There was a significant difference ($p < 0.001$) favoring the usefulness of continuing antipsychotic medication after remission. However, olanzapine was associated with adverse effects such as weight gain.

2.2.2 Electroconvulsive therapy

Electroconvulsive therapy (ECT) has been used for nearly a hundred years and remains to be considered the most effective treatment for mood disorders, while it is underused and there is great geographical variation in ECT availability (Sackeim 2017). In 2002, ECT was estimated to be used for 1 million patients globally (Abrams 2002). A meta-analysis published in the *British Journal of Psychiatry* (van Diermen et al. 2018) confirmed that ECT is especially effective with patients suffering from PD. Efficacy of ECT has been confirmed in studies that included a sham ECT as a control group (Buchan et al. 1992). ECT is recommended for the treatment of PD in the Finnish depression guidelines (Depression: Current Care Guidelines, 2020).

Cognitive side-effects have been a significant concern when using ECT. It is known that ECT causes brief confusion immediately after the procedure, transient anterograde amnesia and a varying amount of retrograde amnesia (Kellner & Farber 2016) but most cognitive side effects are limited to first three days and ECT may also improve cognitive functioning in depressed patients (Semkovska & McLoughlin 2010). Technical advances concerning the administration of the treatment are also decreasing the effect of these side effects (Sackeim 2017). ECT is associated with an extremely low mortality rate (Tørring et al. 2017).

A high relapse rate has also been limiting the use of ECT previously (Sackeim 2017). A meta-analysis examining relapse rates post-ECT discovered that despite continuation pharmacotherapy following ECT, approximately half of the patients are likely to relapse within a year and most of these within 6 months. Also, without continuation medication, the relapse rates were as high as 80% (Jelovac et al. 2013).

The mechanism of action causing the beneficial effects of ECT is currently unknown, but several changes have been found to accompany ECT treatment involving, for example, functional connectivity, gene expression and immune system (Singh & Kar 2017). According to a recent meta-analysis, it seems that ECT increases the size of the hippocampal regions and the amygdala (Takamiya et al. 2018) but hippocampal growth is not a marker for clinical outcome (Oltedal et al. 2018).

There is a shortage of studies on the continuation and maintenance ECT treatment of PD. When combined with nortriptyline, continuation and maintenance ECT was more effective than medication alone in preventing relapse in old age PD over a 2-year follow-up (Navarro et al. 2008). Additionally, in NPD samples, continuation ECT treatment has shown promise when combined with medication (Gagné et al. 2000; Kellner et al. 2016). However, in one study conducted on NPD patients, continuation ECT was not more effective than the combination of nortriptyline and lithium in preventing relapse (Kellner et al. 2006).

2.2.3 Other treatments

Psychotherapeutic treatments of PD have not been studied almost at all. Preliminary results have shown that PD patients may benefit from acceptance-based behavioural treatment combined with pharmacotherapy and the treatment is likely to be acceptable by patients (Gaudiano et al. 2013). As noted in the study mentioned above, cognitive behavioural therapy has not been previously studied in PD samples but some studies have included PD patients and shown encouraging results. However, subclinical psychotic symptoms have been shown to predict worse psychotherapy outcomes in depression (Wigman et al. 2014). Also, in patients with depression and post-traumatic stress disorder, the presence of psychotic symptoms predicted worse outcomes (Gottlieb et al. 2011).

HPA axis disturbance and hypercortisolism have been found to be common in PD and to associate with cognitive disturbances. These results have added motivation to find ways to safely and effectively pharmacologically regulate cortisol levels in PD. A glucocorticoid receptor antagonist mifepristone has been studied the most and has shown promise in the treatment of PD but is not currently in standard clinical use (Block et al. 2018). There are also some case reports favoring the use of ketoconazole in PD (Kling et al. 2009). Unfortunately, no studies have investigated the effectiveness of ketoconazole in PD, despite the fact, that ketoconazole seems to be most effective in NPD when the patient presents with hypercortisolemia (Lombardo et al. 2009).

2.3 Epidemiology of Psychotic Depression

2.3.1 Prevalence, incidence and proportion of psychosis in depression

A Finnish nationally representative study with a sample of people over 30 years of age showed a lifetime prevalence of 0.35% in PD (Perälä et al. 2007). Other studies have found higher prevalence rates. In an American community sample (the Epidemiological Catchment Area study), the lifetime prevalence was 0.6% (Johnson et al. 1991) and in a telephone survey conducted in several European countries, there was a 0.5% point prevalence in PD (Ohayon & Schatzberg 2002). In the latter study, there was also variation between different countries and social groups.

The annual incidence of PD has been studied in a few studies. Reay et al. (2010) found an annual incidence of 6.0 per 100 000 persons in a sample of patients 16 years old or older. In the Cavan-Monaghan First Episode Study conducted in Ireland the annual incidence was similar (6.4 per 100 000) (Baldwin et al. 2005). In the UK, Farquhar et al (2007) reported a lower annual incidence of 3.0 per 100 000 in 1995.

A study in Northern Finland reported a significant growth in cumulative incidence until age 27 years from 0.02% in 1966 to 0.27% in 1986 (Filatova et al. 2016).

Psychotic symptoms are present in a minority of patients with depression. Currently, it is estimated that 11-25% of patients with depression exhibit psychotic symptoms (Coryell et al. 1984a; Johnson et al. 1991; Ohayon & Schatzberg 2002; Gaudiano et al. 2016; Dold et al. 2019). This proportion is likely to be higher in inpatient than outpatient samples (Rothschild 2013).

The lifetime prevalence rate of major depressive disorder is estimated to be 15-18% (Malhi & Mann 2018), and, therefore, higher lifetime prevalence rates of PD should be found if psychotic symptoms are genuinely as common in depression as described in previous studies. It is possible that PD is especially difficult to detect in epidemiological studies investigating the lifetime prevalence or the studies focusing on the prevalence of psychotic symptoms in depression may have had more ill patients leading to a biased sample.

In a Finnish study, 26% of inpatients diagnosed with depression had psychotic symptoms, compared to 5% of secondary care outpatients and 1% of primary care patients (Vuorilehto et al. 2007). When investigating the prevalence of psychotic symptoms in depression, it is especially important to pay attention to the characteristics of the sample, since there is significant variation between different patient populations.

2.3.2 Risk factors and sociodemographic findings

The risk factors of PD have not been studied as much as in other severe mental disorders and especially the early risk factors are mostly unknown with only one previous study analyzing risk factors since birth (Østergaard et al. 2013). This Danish study utilized extensive national registers to analyze a large PD sample (n=2183) but gestational age, birth weight and maternal or paternal age were not found to associate with an increased risk for PD.

Childhood traumas are likely to be a risk factor for PD, but the results on the studies that have analyzed childhood traumatic events in PD have been slightly contradicting. In an outpatient study, childhood traumatic events were more common in PD than in NPD (Gaudiano & Zimmerman 2010), but this difference was not significant in an inpatient sample (Gaudiano et al. 2016). This may be due to more severe cases of NPD in the inpatient sample. In the AESOP study, conducted in defined catchment areas in the UK, PD patients more often had experienced childhood adversity (Heslin et al. 2016b). In the same study, certain social factors were found to associate with PD. Unemployment, living alone, having few contacts with friends and having no close confidants were more common in patients with PD.

Østergaard et al. (2013) found in their study that those who had suffered the loss of a mother due to unnatural causes after the age of 15 had an elevated risk of PD. This effect was not significant if this event had taken place when the person was under 15 years old, possibly due to sample size. However, based on this study, it is likely that the loss of a relative, in general, is a risk factor for PD also, as it is for NPD.

The educational background of PD patients has been looked at in quite many studies but there has been no specific observable educational profile. In some studies PD patients have had lower education than in PBD (Breslau & Meltzer 1988) and in NPD (Gaudiano et al. 2009). Johnson et al. (1991) found PD to be associated with a lower socioeconomic status than NPD. Most studies analyzing marital status in PD and comparing it to other disorders have found differences to be nonsignificant. Few studies reported significant differences. PD patients were found to be more often single than patients with NPD in an elderly sample (Baldwin 1995) and among inpatients (Gaudiano et al. 2016).

Several studies have analyzed the ethnicity of patients diagnosed with PD. The most common finding has been that PD patients were more often non-Caucasian (Goldberg & Harrow 2005, Gaudiano et al. 2016). In a British study, minor physical anomalies were not more common in patients with PD but neurological soft signs were (Heslin et al. 2016b).

2.3.2.1 Gender differences

Very little research has been carried out to examine gender differences in PD (Park et al. 2015). However, studies indicate that the prevalence of PD among females is higher than among males comparably to NPD (Kessing et al. 2005; Østergaard et al. 2013). Therefore, this finding of the different prevalence of PD between genders differs from SZ where the majority of affected persons are male (Perälä et al. 2007).

Female PD patients have been reported to have more often disorganized (Deligiannidis et al. (2013), systematized and mood-incongruent psychotic symptoms in addition to increased fatigue and psychomotor agitation (Fennig et al. 1993). Park et al. (2015) analyzed gender differences in a different sample where they included all patients with depression and psychotic symptoms into the PD group, including also patients with mild or moderate depression symptoms. Their inclusion criteria were, therefore, more in line with the current DSM-5 diagnostic criteria. The results of the study showed a higher prevalence of hallucinatory behavior among men after adjusting for the effects of marital status. Park et al. consider that the confounding effect of marital status in a previous study by Deligiannidis et al. (2013) may have explained the opposite results regarding gender difference.

Current evidence suggests that male PD patients are at a higher risk of committing suicide than female patients (Leadholm et al. 2014). This finding is in line with other psychiatric illnesses, in which male gender is recognized as a significant risk factor for suicide (Large et al. 2011). Several reasons for this gender difference have been suggested including the use of more violent methods and cultural factors such as reluctance towards help-seeking and maladaptive coping strategies caused by traditional masculinity (Möller-Leimkühler et al. 2003).

Regarding comorbidity, male PD patients seem to have more often a comorbid alcohol use disorder (Fennig et al. 1993, Isometsä et al. 1994). Studies about the prevalence of comorbid anxiety symptoms have shown contradicting results (Fennig et al. 1993; Deligiannidis et al. (2013), possibly due to methodological differences discussed above.

2.3.2.2 Family history of mental illness

It is well known that parental mental illness confers a clearly increased risk of several mental disorders among offspring. The increased risk of mental disorders caused by parental mental illness is likely to be at least partly transdiagnostic in nature, so that for example also non-affective psychotic illness among parents increases the risk of affective psychotic illness among offspring, and the risk is cumulative in the way that 2 affected parents cause a greater risk than 1 affected parent (Dean et al. 2010).

Mental illness in the family has been shown to be a risk factor for PD (Heslin et al 2016). Depression in the family has not been found to be more common in PD than in NPD (Park et al. 2014b) but maternal mental illness was more common in PD in a large Danish register-study (Østergaard et al. 2013). A family history of BD seems to be more common in PD than in nonpsychotic depression (Maj et al. 2007; Østergaard et al. 2013). These studies do not separate the genetic and environmental factors affecting this increased risk, but both likely have a significant role.

According to clinical genetics studies, there is significant familial aggregation and heritability (39%) in PD (Domschke 2013). This heritability is partly shared with other severe mental illnesses such as schizoaffective disorder, schizophrenia and affective disorders.

2.4 The outcome of Psychotic Depression

2.4.1 Hospitalization

Due to severe symptomatology, PD patients are often hospitalized during the course of their illness. Four different studies have analyzed the difference between PD and NPD in the amount of hospitalization. All these studies have investigated only

inpatients. A 15-year follow-up study in Germany found a significantly higher number of rehospitalizations in the PD group (n=2.8) than in NPD (n=1.3) (Jäger et al. 2005). In a small Italian study PD was associated with a longer duration of current hospital stay (33.7 days in PD and 15.1 days in NPD) but with less previous hospitalizations (n=2.9 in PD and n=4.1 in NPD), although the latter difference was non-significant (Buoli et al. 2013). Further research is needed to clarify whether there are significant differences between PD and NPD.

When comparing SZ and PD, during a ten-year follow-up in the AESOP study conducted in the UK, patients with PD had spent significantly fewer days (63.5) in the hospital than patients with SZ (107) (Heslin et al. 2016a). In this study, there was no significant difference in hospitalization rates between PBD and PD. Contradictingly, Jäger et al. (2005) did not find a significant difference in the frequency of rehospitalizations between PD (n=2.8) and SZ (n=2.9). In addition, no difference was detected in another study with first-episode psychosis patients conducted in England (Crebbin et al. 2008), although there was a rather large absolute difference in hospitalization days between PD and SZ during the follow-up (mean days: 124 in PD and 231 in SZ). PBD was not examined in these two latter studies. In light of these studies, SZ is likely associated with more hospitalization than PD. The potential differences between PD and PBD remain unclear.

2.4.2 Symptomatic remission, relapse rate and functional outcome

There are some mostly old studies addressing the symptomatic remission and relapse rate in PD. In one inpatient study with a mean follow-up period of 2.4 years, remission rates were very low and lower in PD (19% for depressive symptoms and 35% for psychotic symptoms) than in NPD (29% for depressive symptoms) (Sands & Harrow 1994), while another study with a sample of over 65-year-olds showed no significant difference between these two (Baldwin 1988). The relapse rate during 48 months follow-up in PD (46%) appears to be higher than in NPD (25%) when analyzing relapses based on hospital readmissions (Baldwin 1988). However, when out-patient relapses were added, there was no difference between PD and NPD (50% for both).

Considering the fact, that PD has been estimated to be especially severe regarding symptoms and clinical course (Keller et al. 2007), studies focusing on the functional outcome have been somewhat inconclusive. When comparing to NPD, PD patients' global outcome has been somewhat poorer (Gaudiano et al. 2009; Jäger et al. 2005) but there are also contradicting results (Coryell et al. 1986). Same heterogeneity of results applies for the occupational outcome, where some studies show worse occupational outcome for PD (work impairment:70.8%) than NPD

(34.2%) (Coryell et al. 1984b), while some studies show no difference between these two (Rush et al. 2006).

Global clinical outcome in PD appears to be better (Craig et al. 2000; Jäger et al. 2005) and the relapse rate lower (Craig et al. 2000) than in schizophrenia. Also, occupational functioning is better in PD during follow-up (Coryell & Tsuang 1985; Jäger et al. 2005) and full recovery seems to be more common (Coryell & Tsuang 1982). Compared to PBD, results on global clinical outcomes have been conflicting (Craig et al. 2000; Dell’Osso et al 2002), but the functional outcome in PD and PBD is likely to be similar (Kingston et al. 2018). Meanwhile, rehospitalization rates during a 24-month follow-up (31.4% for PD and 33.6% for PBD) (Craig et al. 2000) and functional recovery rates after a six-month follow-up (31.8% for PD and 32.6% for PBD) (Tohen et al. 2000) were similar in PD and PBD. Results on the occupational outcome also reflect comparable outcomes (Dell’Osso et al. 2002).

2.4.3 Comorbidity

According to an extensive Danish register-study, psychiatric comorbidity seems to be extensive throughout the spectrum of mental illness in the way that most psychiatric disorders cause an increased risk to most other psychiatric disorders, regardless of which of them occurs first (Plana-Ripoll et al. 2019). However, certain pairs of disorders carry a more significant risk of co-occurrence than others.

PD has been associated with certain psychiatric disorders and also general medical illness. In the McLean-Harvard first-episode project 37.5% of PD patients had any comorbid Axis 1 disorder (excluding substance use disorders) (Tohen et al. 2012). A large European multicenter study examined the prevalence of comorbid anxiety disorders in PD and found 13.6% to have any current anxiety disorder, out of which generalized anxiety disorder was the most common (8.4%) (Dold et al. 2019). In an inpatient sample, Gaudiano et al. (2016) reported a much higher comorbidity of anxiety disorders (58.6%). When analyzing the lifetime prevalence of anxiety disorders in an outpatient sample, the same research group reported high prevalence rates for different anxiety disorders (8.3-56.7%) (Gaudiano et al. 2009). In this study, opposite to the study by Dold et al. (2019), the most infrequent disorder was generalized anxiety disorder. The most frequent was posttraumatic stress disorder.

The prevalence of comorbid personality disorders in PD has been looked at in a few studies. Especially comorbid A cluster personality disorders have been found to be common (Serretti et al. 1999; Gaudiano et al. 2009). Previously, borderline personality disorder has not been shown to be more prevalent among PD patients. The differential diagnosis may also be sometimes difficult between PD and

borderline personality disorder, if the patient exhibits minor and transient or otherwise “false” psychotic symptoms (Gaudiano et al. 2009).

Harmful use of psychoactive substances is a major comorbidity affecting the clinical course in different psychiatric illnesses. In PD the prevalence of comorbid substance use disorders is very high. Tohen et al. (2012) reported that a stunning 89.3% of PD patients had either alcohol or drug abuse or dependence at the beginning of the study, and in the case of 62.5% of the patients, the substance of use was alcohol. In the inpatient sample by Gaudiano et al. (2016) 41.4% had a comorbid substance use disorder while in the outpatient sample this prevalence was 55.0%.

General medical comorbidity has also been shown to be high in PD. In an inpatient sample, those diagnosed with PD had more medical comorbidities than patients with NPD (Gaudiano et al. 2016). High medical comorbidity may also predict diagnostic stability in PD. In a study by Tohen et al. (2012) 86.2% of patients who held their diagnosis of PD in a two-year follow-up had general medical comorbidity, while only 40.0% of those whose diagnosis had changed ($p=0.002$).

2.4.4 Mortality and suicide

The most influential study about mortality in PD was published in 2003 (Vythilingam et al. 2003). The authors compared mortality rates in PD (61 patients, 59% female) and NPD (59 patients, 64% female) over a follow-up period of 15 years. After age and medical comorbidity were controlled, PD patients had a twofold mortality rate in comparison to NPD. This increased mortality was not explained with more suicides either. General medical illness was the cause of death in most cases in the whole sample (30/34 in total). The patients also underwent a dexamethasone suppression test (DST) to examine for hypercortisolism. PD subjects more often had a positive test result indicating hypercortisolism, but this did not predict mortality autonomously, in spite of the well-known detrimental effects of hypercortisolism on physical health. In light of the results of the previous study, it is interesting that in a large nationally representative Finnish study of over 8000 persons affective psychoses as a group were not associated with increased mortality (Suvisaari et al. 2013). More evidence for the increased mortality in PD brings the study by Murphy et al. (1983), which found very high mortality in a sample of old age PD patients.

Different studies that have been carried out over the years have had conflicting results about whether PD is associated with more suicides than NPD, but a systematic review indicated that particularly in the acute phase of the illness PD patients are more likely to die of suicide (Zalpuri & Rothschild 2016). Also, another recent systematic review and meta-analysis found psychosis to be a risk factor for suicide in major depression during the acute phase but also over the lifetime

(Gournellis et al. 2018a). In Finland, a study of over 56 000 first-hospitalized patients with up to 24-year follow-up demonstrated an increased risk of suicide caused by PD (Aaltonen et al. 2019). Suicide attempts have also been examined in PD. According to a systematic review and meta-analysis by Gournellis et al. (2018b), suicide attempts are more common in PD than in NPD (OR 2.11, 1.81-2.47) and the results also showed that the elevated risk was present in all age groups.

2.5 Summary of the literature

The literature review on psychotic depression shows a great deficit in knowledge about the etiology, risk factors, clinical characteristics and outcomes of PD. There is also quite a high variability in results possibly due to different study designs using dissimilar methodologies or subjects from incomparable age groups. The crucial finding is the near absence of prospective long-term follow-up studies carried out in naturalistic designs. Due to intermediate diagnostic stability, significant methodological differences between studies are the length of follow-up and the use of either baseline or follow-up diagnosis. Since not many studies have controlled for diagnostic change, most studies have used baseline diagnoses. This means that the PD samples included many subjects whose diagnosis would later change to for example SZ or BD.

The major implication of diagnostic instability in PD on research is that studies should address this question, especially when analyzing the validity and utility of results for clinical practice. Studies should be preferably carried out in incidence samples and diagnostic conversion should be controlled using a sufficient follow-up (Heslin & Young). Considering the clinical usefulness of research, simply controlling for diagnostic change is not enough because clinical decisions need to be made at baseline. A deeper understanding of the interplay between psychotic and depressive symptomatology is needed to identify beforehand those patients whose illness is likely to develop into other symptom constellations.

The prevalence rate in PD is relatively high compared to other psychotic disorders and it is worth wondering why PD has remained so under-researched. The knowledge base regarding risk factors of PD is especially thin. Consistent finding throughout the literature review is the severe course of illness in PD that negatively exceeds outcomes in NPD. Mortality and suicide rates are likely to be elevated in PD. Previous research also indicates a clear neurobiological disturbance in PD that affects at least the HPA axis and related neurophysiology. To summarize, the results of the previous studies depict a grave disorder with unique characteristics and poor outcomes and emphasize the need for more prospective and representative studies to be carried out.

3 Aims

The objective of this thesis was to study the risk factors, clinical characteristics and outcomes of PD. Regarding these factors, the intention was to investigate whether there are significant differences between PD and other severe mental disorders. Firstly, a systematic literature review and meta-analysis on the subject was carried out. Secondly, a study was conducted in a naturalistic birth cohort using lifetime diagnoses.

The research questions were:

- Study I According to previous literature, what are the risk factors of PD and does PD differ from other severe mental disorders (SZ, PBD, NPD, PNOS) in the clinical characteristics and outcomes?
- Study II Are there significant early life and adolescent risk factors for PD and are there differences between PD and other severe mental disorders (SZ, PBD, NPD, PNOS) concerning these factors?
- Study III Are there differences between PD and other severe mental disorders (SZ, PBD, NPD, PNOS) in the clinical characteristics and outcomes based on a naturalistic birth cohort sample?
- Study IV Does gender or psychiatric comorbidity affect the clinical picture or outcome of PD and in what way?

4 Materials and Methods

4.1 Meta-analysis and systematic review (Study I)

4.1.1 Meta-analysis as a research method

Meta-analysis refers to the statistical technique with which the results from many resembling studies of a certain subject can be combined (Glass 1976). The data from the primary studies are analyzed together to create an estimate of an effect. Also, the between-study heterogeneity and the impact of biases can be evaluated (Sutton & Higgins 2008).

The rapid growth of published research literature and the need for fast and scientifically justified decisions in medicine have made meta-analyses a frequently applied method to synthesize knowledge from individual studies (Stroup et al. 2000). In the past, medical research was summarized in narrative reviews that lacked a systematic approach and quantitative analysis of combined data (Thacker 1988). These are important characteristics that form the basis of meta-analysis.

When conducting a meta-analysis, numerous factors need to be taken into consideration to avoid errors that may lead to invalid or misleading results. A meta-analysis is often an effort to retrospectively integrate studies that have been conducted with varying methodologies and potential biases. Therefore, meta-analyses should address these questions in detail and, also, exclude flawed studies (Ioannidis 2017). A systematic assessment of primary studies is essential to achieve this.

4.1.2 Data collection

The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) guidelines were followed in the design of the systematic review and meta-analyses (Moher et al. 2009).

Relevant studies were located by conducting a systematic database search in May 2016. Four different electronic databases were used (PubMed, Scopus, Web of Science and CINAHL). The used search string was as follows: (“psychotic depression” OR “delusional depression” OR “depression with psychotic features”)

AND (epidemiology OR “risk factor” OR outcome OR employment OR occupational OR progression OR course OR stability OR relapse OR remission OR prevalence OR incidence OR “onset age” OR “diagnostic stability” OR mortality OR mortality OR suicide OR physical OR somatic OR comorbidity OR “early intervention” OR prevention). There were no exclusions made based on publication date. In addition, reference lists of previous reviews were used to do a manual search.

The analysis of all abstracts was made by two independent authors. Following the exclusion of inapplicable articles, the remaining ones were inspected by two authors (one of whom was the same as in the primary analysis). A third author extracted the data out of those articles that met inclusion criteria. After this, the collected data was again checked by two authors. In case of disagreement concerning the extraction of data, a resolution was approved by reaching consensus.

4.1.3 Study selection

For a study on prevalence and incidence of PD to be included, it needed to use estimates from population surveys or include both inpatient and outpatient data. As for risk factor and outcome studies, the following inclusion criteria were used: A) Sample of PD was included in the original study. The sample needed to include at least 80% of PD (delusional depressions were included). Episodes of psychotic depression in SZ or PBD and postpartum PD were excluded. B) The sample size of PD was at least 15. C) The majority of subjects had an onset age of over 16 years. D) The results of the studies included risk factors, sociodemographic factors or outcomes of PD. E) Diagnoses of PD were done using a common diagnostic system or otherwise properly reported. F) Studies had to include a comparison group of at least 15 subjects and the comparison group needed to include a minimum of 80% of either NPD, PBD, SZ, schizoaffective disorder or HC.

Intervention studies were excluded due to variation in representativeness, so the meta-analysis only included observational studies. In addition, only studies published in English were included. Furthermore, studies focusing on treatment, neurobiology, somatic comorbidities, mortality and suicide were excluded due to being outside of the scope of this meta-analysis.

4.1.4 Incidence, prevalence and risk factor studies

A systematic review was used to report studies concerning incidence and prevalence. Most risk factors were also reported using a narrative approach and results were presented in a literature table. Risk factors in this study included both early risk factors and cross-sectional sociodemographic factors. A meta-analysis was able to be conducted on gender distribution and onset age.

4.1.5 Outcome studies

The following outcome variables reported in the studies were included: the number of hospitalizations during prospective follow-up, occupational functioning, symptomatic remission, global outcome, global clinical outcome, the severity of psychotic symptoms (positive, negative and total symptoms were evaluated separately), the severity of depression symptoms. Global clinical outcome refers to outcomes measured without specific instruments. Global outcome refers to an outcome that is measured with a specific instrument such as GAF (Global Assessment of Functioning scale), GAS (Global Assessment Scale) or SOFAS (Social and Occupational Functioning Assessment Scale).

Meta-analysis was performed on those outcomes that were reported in at least three studies from different samples. These included depression symptoms, total psychotic symptoms, positive symptoms, negative symptoms, symptomatic remission, hospitalization, global outcome and poor global clinical outcome. For symptom measurements, the most common time of assessment was the baseline, and this was used in the meta-analysis. PD was compared to NPD, SZ and PBD when there was sufficient data available. The occupational outcome was reported narratively.

4.1.6 Statistical analyses

Meta-analyses were conducted if there were a minimum of three studies investigating a specific variable. In case there were multiple studies with partly or completely same samples, the article with the largest sample size or the one using more valid instruments was chosen. Pooled estimates of effect sizes between PD and comparison groups were created using random-effects models in the meta-analyses, based on associations' expected heterogeneity. Every study was weighted by the inverse of its variance and the between-study variance. Hedges' g was used to describe the effect sizes of the between-group standardized mean differences. Hedges' g is analogous to Cohen's d but better suited for the analysis of small samples. Hedges' g values above zero indicate more symptoms or later onset age in PD. Regarding categorical variables, Relative Risk (RR) with a 95% confidence interval (CI) was used to estimate pooled effect size.

Subgroups of studies were analyzed separately when there were enough studies. The division into subgroups was made based on mean study age (below 45, 45-55, over 55 years), publication year (1973-1991, 1993-2003, 2004-2016) and mean age of illness onset (below 45 years, 45 years or over). Sensitivity analyses were also conducted based on sample size ($n < 50$ vs. $n \geq 50$).

The degree of heterogeneity was examined with I^2 statistics in which values range from 0 to 100% describing the total variation of studies (Higgins et al. 2003). The

significance of this heterogeneity was evaluated by using the chi-square test. Metan command of the 13th version of Stata (Statacorp 2013) was used in all the analyses.

4.2 The Northern Finland Birth Cohort 1966

The Studies II-IV were conducted in the Northern Finland Birth Cohort 1966 (NFBC 1966; <https://www.oulu.fi/nfbc/>), which is a general-population birth cohort study consisting of 12068 pregnant women and their 12058 live-born children who had an expected delivery date in 1966. The study takes place in the North of Finland covering the provinces of Lapland and Oulu. Professor Paula Rantakallio originally launched the study with an interest in the somatic health of infants. Later in 1990, Professor Matti Isohanni started psychiatric research in the NFBC 1966 focusing on long-term perspectives on SZ. The study design is prospective in nature and the sample is unselected.

The NFBC 1966 utilizes a wide range of data collection methods including register-data from several national registers, questionnaires and clinical measurements. This birth cohort design enables long-term follow-up of study subjects starting from pregnancy. It also makes possible the collection of a vast quantity of biological, psychosocial and environmental data about potential risk factors and acquirement of occupational, functional and treatment-user information about outcomes.

4.2.1 Psychiatric diagnoses and study groups

Several data sources were used to obtain information on all psychiatric diagnoses that the study subjects had received during their lifetime. The Care Register for Health Care is a nationwide register including all somatic and psychiatric inpatient hospital discharges with relevant ICD-diagnosis information from 1969 (Sund 2012). Information concerning outpatient diagnoses in specialized care starts from 1998 and in primary care from 2011. In Study III Care Register for Health Care information until the end of 2013 was used and in Studies II and IV until the end of 2016.

Additional information was gathered from Finnish Social Insurance Institute registers of those subjects with a psychotic illness that granted them a right to reimbursable medication. This information was available from 1974-2005. Prescription data for antipsychotics from 1997 and data about diagnoses leading to pension and sick leaves were also able to be obtained. The data was supplemented with diagnoses from a diagnostic validation study carried out in 1997 and a subgroup study performed when the NFBC 1966 cohort members were 43 years old.

Many study subjects were diagnosed with several different psychiatric disorders during their lifetime according to registers. This imposes challenges to the definition of diagnostic groups when these groups should be observed over a long follow-up

period. It is especially important for PD, which is shown to have a higher diagnostic instability than many other disorders. The formation of these diagnostic groups may have a significant impact on study results. In other words, it is crucial how lifetime diagnosis is defined.

A hierarchical method was used to form diagnostic groups based on the most severe lifetime diagnosis. All lifetime diagnoses of each subject were acknowledged and the diagnosis which had the highest position in the hierarchy determined the group (Table 2) the subject was positioned into. The hierarchy is described in Figure 2. An exception to the hierarchy is that subjects with both PD and delusional disorder or both PD and non-psychotic bipolar disorder diagnoses were excluded. Implementation of the methods means that none of the PD group subjects had been diagnosed with SZ, BD or delusional disorder during their life. All PD group subjects' lifetime diagnoses were additionally manually checked to make sure there were no diagnoses that would invalidate the PD diagnosis. As previously mentioned, in Study III, the diagnostic information was available until the end of 2013 and in Studies II and IV until the end of 2016. This resulted in small differences in the PD sample. In Study III there were 55 PD subjects, whereas 58 subjects in Studies II and IV. Between the beginning of 2014 and the end of 2016, 5 new subjects were diagnosed with PD while two subjects exited the group due to a diagnosis of schizophrenia or bipolar disorder.

Since the 1960s, the diagnostic system in Finland has changed from ICD-8 (used in Finland from 1968 to 1986) first to ICD-9 (from 1987-1995) and then to ICD-10 (from 1996). To form the lifetime diagnostic groups, the diagnoses from previous diagnostic systems that described up-to-date diagnostic categories in the best possible way were selected. These diagnoses are presented in Table 2. Diagnostic groups of SZ, PBD, PNOS (Other Psychoses) and NPD were used as comparison groups for PD in Study III. In study II, HC, who did not have any lifetime psychiatric diagnoses, were used as a comparison, in addition to the abovementioned groups.

Table 2. Diagnostic categories based on ICD-8-10 used in the current study (Study III).

	ICD-8	ICD-9	ICD-10
PSYCHOTIC DEPRESSION (PD)	2960, 2980	2961E	F32.3, F33.3
NON-PSYCHOTIC DEPRESSION (NPD)	3004, 7902	2961A-D, 3004	F32.0-32.2, F32.8-F33.2, F33.4-F33.9, F34.1, F38.10
SCHIZOPHRENIA (SZ)	295, 2954, 2957	295, 2954, 2957	F20, F25
PSYCHOTIC BIPOLAR DISORDER (PBD)	2961-2969	2962E, 2963E, 2964E, 2967	F30.2, F31.2, F31.5
OTHER PSYCHOSES (PNOS)	297, 298 (except 2980), 299	297, 2988, 2989	F22, F23, F24, F28, F29

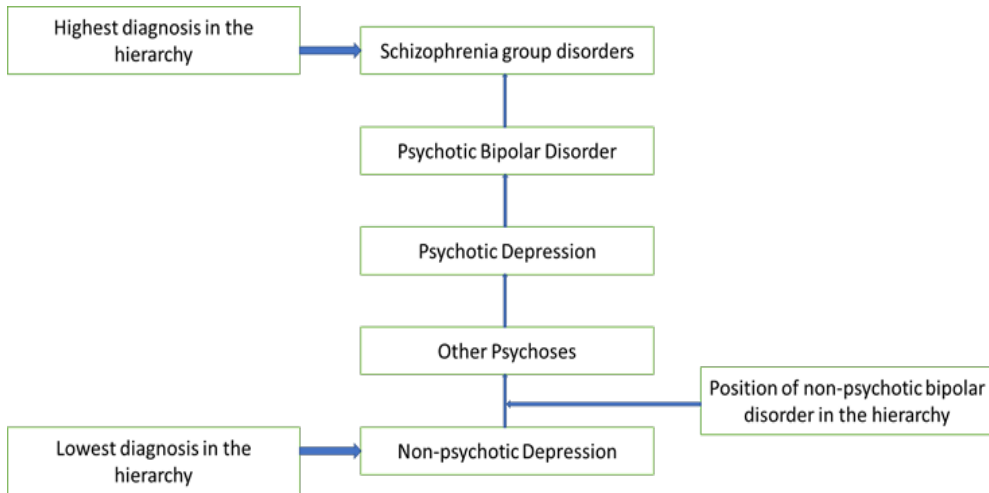


Figure 2. Illustration of the diagnostic hierarchy. Highest diagnosis in the hierarchy during a subject's lifetime defined the diagnostic category. Patients with both PD and delusional disorder or non-psychotic bipolar disorder were excluded from the PD group. Other diagnostic groups concerning Other Psychoses or higher include subjects with non-psychotic bipolar disorder diagnosis.

4.2.2 Early childhood and adolescent risk factors (Study II)

In Study II the early and adolescent risk factors of PD were analyzed. First, PD was compared to HC, and then PD was compared to all other disorder groups. The study was designed, in addition to presenting risk factors of PD, to reveal the differences in risk factors in different disorder groups. Relevant and available potential risk factors from birth until the age of 16 were examined.

4.2.2.1 Data acquisition

Several sources were used to obtain data about potential risk factors. There was some variation in the amount of missing data (0-32.8%). The average proportion of missing data in the PD group was 9.2%. *Psychiatric and somatic illness of the parents* was examined using the same registers as with study group formation. In addition to mental illness in the family, parents' somatic illness (hospitalizations ≥ 30 days) was analyzed as a marker of childhood traumatic event (Keskinen et al. 2015). Concerning somatic illness, those hospitalizations that took place before the end of 1982 were included, and for psychiatric illness (any psychiatric illness, psychosis, SZ, depression, BD and alcohol use disorder), those diagnoses that were registered before the study subjects turned 16.

For psychosocial risk factors, risk factors during birth and risk factors at the age of 14 were separately looked into. A questionnaire (filled in 1965-1966) was used to

examine risk factors at birth. These included *mother's antenatal mood, unwantedness of pregnancy, mother's education, urbanicity and social class in 1966* (determined by father's occupation) (Myhrman et al. 1996, Keskinen et al. 2013). Another questionnaire was filled by the study subjects at the age of 14 and the variables based on this were: *moving hometown in 1966-1980, mother's work status, family type, social class in 1980* (determined by father's occupation) and *deceased siblings*.

The early biological risk factors of *paternal and maternal age, mother's antenatal smoking, perinatal complications, birth weight, gestational age, birth weight/gestational age and parity* were gathered from the questionnaire of 1965-66 (Mäki et al. 2009, Keskinen et al. 2013), that was filled by a nurse at the antenatal clinic or birth. Motor development was observed, and parents interviewed at the Finnish welfare clinics routinely and this data was used to form the variables of *age when the child learns to walk without support and age when the child learns to stand without support* (Keskinen et al. 2015).

Information about the *school level*, at which the subjects were when they were 14 years old, was obtained from the National Board of Education and combined with the information from the postal questionnaire of 1980. *School grades at age 16* were acquired from the Finnish national application system for upper secondary education register (Isohanni et al. 1999).

Alcohol and smoking consumption, BMI and frequency of sport hobbies data came from the questionnaire that the study subjects filled in 1980. This same questionnaire was also used for psychosocial risk factors in adolescence, mentioned above.

4.2.2.2 Statistical analyses

Contingency tables were used to analyze different variables in all the diagnostic groups focusing on frequency distributions. Then PD was compared to HC using the Cox Proportional-Hazards model, in which the endpoint was illness onset, death, moving abroad or the end of 2016. Hazard Ratios were first calculated separately for every risk factor and after that, a multivariate Cox regression model was performed. Multivariate model inclusion criteria for variables were as follows: A) p-value ($p < 0.1$) in the univariate analysis for minimum one category, B) in case of overlapping variables (parental mental illness variables, sports grade/physical activity), the one with the lowest p-value was picked.

A separate analysis to compare PD risk factors to all other disorder groups was conducted. For this, Pearson's Chi-Square test or Fisher's exact test were applied. SPSS version 25 was used in all the statistical analyses performed in the study (<https://www.ibm.com/analytics/spss-statistics-software>).

4.2.3 Clinical characteristics and outcomes (Study III)

In this Study III, the clinical course and characteristics of PD were examined. Information about sociodemography, educational background, onset age, comorbidity, mortality, hospitalization and the occupational outcome was collected. The time to readmission after the first hospitalization due to any psychiatric illness was also analyzed. Regarding these variables, a comparison to other disorder groups was made.

4.2.3.1 Data acquisition

All data concerning psychiatric diagnoses, including *comorbidity* and *onset age*, were obtained from national registers similarly as previously reported (4.2.1 Psychiatric Diagnoses). *Hospitalization* and *readmission* data were acquired from the Care Register of Finland until the end of 2015. The occupational outcome was studied using registers from the Finnish Center for Pensions. Data from 2014-2015 was applied to analyze the *proportion of working days* (0-100%) during that period and *disability pension* figures were available until the end of 2015. Statistics Finland registers until the end of 2015 were used to record the *educational status* of study subjects. *Mortality* was analyzed with the Population Register Center data, available until the end of 2015.

4.2.3.2 Statistical analyses

When comparing PD to other diagnostic groups, the Mann-Whitney U test was used for differences in median onset-ages, the median amount of hospitalizations, median cumulative hospitalization days and the relative proportion of hospitalization days from illness onset to death or end of the follow-up. For the differences in mortality, gender, comorbidity, the proportion of working days, disability pension rate, educational level and the number of subjects with at least one lifetime occurrence of hospitalization, Pearson's chi-square test or Fisher's exact test was applied. Survival curves, describing readmission rate after the first hospitalization due to any psychiatric illness, were analyzed using the log-rank test. R version 3.3.2 (<http://www.R-project.org>) was applied in all statistical analyses.

4.2.4 Effects of gender and psychiatric comorbidity on the outcomes (Study IV)

Study IV was designed to analyze how gender and psychiatric comorbidity affect the outcome of PD. Illness onset age, lifetime hospitalization days, disability pension rate and mortality were examined. A comparison was made between subgroups of

PD based on gender and comorbid personality or alcohol use disorder. Potential differences between genders in the prevalence of psychiatric comorbidities (personality or alcohol use disorder) were also studied.

4.2.4.1 Data acquisition

Psychiatric diagnoses for study group formation, *onset age* and *comorbidity* were acquired from several sources, as reported above (4.2.1 Psychiatric Diagnoses). Information about the total lifetime *hospitalization* days for each subject was obtained from The Care Register for Health Care, and this data was available until the end of 2015. For *mortality*, Population Register Center data until the end of 2015 was utilized. For disability pension rate, Statistics Finland data from 2014 was used.

4.2.4.2 Statistical analyses

Statistical comparisons were made on outcome variables between subgroups of PD (male vs. female, personality disorder vs. no personality disorder, alcohol use disorder vs. no alcohol use disorder). Lifetime hospitalization days and age of illness onset were analyzed using the Mann-Whitney U test, while for disability pension rate and mortality, Fisher's exact test was applied. Additionally, the gender differences in comorbidity were analyzed, and for that Fisher's exact test was used. SPSS version 25 was the statistical program used in all the analyses conducted in this study. (<https://www.ibm.com/analytics/spss-statistics-software>).

5 Results

5.1 Meta-analysis and systematic review of epidemiology (Study I)

The database search came up with 2926 records. After removing duplicates and excluding articles that did not fit the criteria based on title and abstract, there were 99 articles left plus 9 articles that were manually discovered. These 108 articles were analyzed in the study in total and 69 of these were included in the meta-analyses. The summary of the results is presented in Table 3.

5.1.1 Prevalence, incidence and proportion of psychosis in depression

The prevalence and incidence were analyzed qualitatively without a meta-analysis. The lifetime prevalence rate varied between 0.35-1.0% in different studies (Supplement table 1 in Study I) and was higher among females in most studies. Point prevalence was reported to be 0.5% and annual incidence 0.21-6.4/100000, while these both were also higher among females. There were 43 studies that included PD and NPD patients and a median 28% of patients in these studies had PD. The proportion of psychotic symptoms was greater among older patients and inpatients.

5.1.2 Risk and sociodemographic factors

No meta-analyses were able to be conducted on the risk factors and sociodemographic factors of PD. Therefore, these studies (n=36, Supplement table 4 in Study I) were analyzed narratively. Compared to NPD, PD patients more often had psychosis and BD in the family. Otherwise, the findings were scarce. According to some studies, PD patients had also more often than NPD patients experienced traumatic events, lived in rural surroundings and had both more acute medical problems and poorer social competence scores. They were also more likely to be non-Caucasian than NPD patients.

Otherwise, in comparison to HC, PD patients have been noted to have more physical anomalies, neurological soft signs and mental illness in the family. Also,

PD patients more often had less contact with friends and they more often had lost a mother because of an unnatural cause after the age of 15, compared to HC. Only one study (Østergaard et al. 2013) included early life risk factors and found no significant differences between PD and HC.

Table 3. Summary of essential results (Study I).

Occurrence	
Annual incidence	0.21–6.4/1 00 000 (higher in females)
Lifetime prevalence	0.35–1.0% (higher in older samples and females)
Point prevalence	0.5% (higher in females)
Proportion of all depressions	28% of all depressive patients, being higher in older samples and among inpatients
Gender	Approximately 65% of the PD patients were females; this was comparable to NPD but higher than especially in SZ
Onset age	No significant difference in onset age in PD <i>v.</i> NPD. Among youngest samples PD patients had earlier onset age, whereas in oldest samples PD patients had later onset age compared with NPD. SZ patients had younger age of illness onset than PD patients
Risk factors	Lack of studies on early risk factors Individuals with PD were less likely to be Caucasian and had more often family history of psychosis and bipolar I disorder when compared with NPD patients. Differences in educational level and marital status between PD and NPD were mostly non-significant
Outcomes	
Depression symptoms	More severe in PD compared with NPD No difference in PD compared with SZ and PBD
Psychosis symptoms	More severe in PD compared with NPD Less severe in PD compared with SZ
Positive symptoms	Less severe in PD compared with SZ and PBD
Negative symptoms	Less severe in PD compared with SZ More severe in PD compared with PBD
Symptomatic remission	Somewhat less common in PD than NPD More common in PD compared with SZAFF
Clinical global outcome	Somewhat poorer in PD than NPD
Relapses	Higher in PD compared with NPD Lower in PD compared with SZ Relatively similar in PD and PBD
Global outcome	Somewhat worse in PD compared with NPD Better in PD compared with SZ No difference between PD and PBD
Occupational outcomes	Somewhat poorer in PD, but in many studies also similar to NPD Better in PD compared with SZ and SZAFF Relatively similar in PD and PBD

Differences in gender distribution between PD and NPD were analyzed in 43 studies (Supplement table 2 in study I) and the meta-analysis showed no significant difference (RR 1.03 (0.97-1.08)). The median percentage of females was 65% in PD and 65% in NPD. However, a larger proportion of females was found in PD compared to SZ (37%; RR 1.40 (1.20-1.71)) or PBD (55%; RR 1.36 (1.01-1.83)). The age of the sample or the publication year did not significantly affect the gender distribution of PD.

5.1.3 Onset age

The onset age of PD was examined in 25 studies (Supplement table 3 in Study I). No significant difference was found in the onset age of PD patients compared to NPD in the meta-analysis of 18 studies (Hedges' $g = 0.08$, $p=0.44$). Splitting the studies into three categories based on subjects' age revealed interesting results. In studies conducted with patients under 45 years old ($n=6$), PD patients had an earlier onset age than NPD patients ($g = -0.39$, $p<0.001$). The opposite was found in the group of studies of over 55 years old patients ($n=7$). Among these latter studies PD patients were found to have a later onset age ($g = 0.40$, $p<0.001$). When comparing to SZ, PD patients had a later onset age (5 studies, $g = 0.53$, $p=0.013$). PBD and PD did not have a significantly different onset age.

5.1.4 Symptom severity, global outcome and hospitalization

The outcome of PD was reported in 44 articles (Supplement table 5 in Study I) from 37 different studies (sample size: $n=16-190$). Many of the studies ($n=16$) had a cross-sectional study design and only 10 had a first-episode sample. 13 of the studies included a follow-up period of over 5 years.

In comparison to NPD, PD was associated with more severe depressive ($g = 0.52$, $p<0.001$) and psychotic symptoms ($g = 0.89$, $p<0.037$). In other outcomes (symptomatic remission, hospitalization, global clinical outcome, global outcome) there was a trend of worse outcomes in PD, but the differences were not statistically significant. Sensitivity analyses (sample size) produced conflicting results. In large samples of 50 patients or more, the difference between depressive symptoms in PD and NPD was no longer significant. However, in these bigger samples, PD patients had less symptomatic remission and poorer clinical outcome. Some outcome variables between PD and NPD were only compared based on a systematic review. Occupational outcomes were mostly worse in PD and full recovery (symptomatic and functioning) more common in NPD.

Compared to SZ, PD patients had less positive ($g = -0.81$, $p=0.000$), negative ($g = -0.89$, $p<0.001$) and total psychotic symptoms ($g = -0.77$, $p=0.000$), whereas there was no significant difference in the depressive symptom severity. According to meta-analysis, the global outcome of PD patients was also better than in SZ ($g = 0.80$, $p=0.001$). The systematic review showed PD patients having a smaller rate of relapses, better occupational functioning and more often a full recovery.

PD patients had more negative ($g = 0.65$, $p=0.001$) symptoms but less positive ($g = -0.44$, $p=0.046$) symptoms than patients with PBD. Otherwise, no difference was found in global functioning. The systematic review showed mostly somewhat similar occupational outcomes for PD and PBD.

Few studies had compared PD to schizoaffective disorder and no meta-analysis was able to be conducted. Better symptomatic remission and occupational outcomes have been reported in PD, but relapse rates seem to be similar (Opjordsmoen 1991). In one study, functional recovery was more common in PD (Tohen et al. 2000).

5.2 Early life and adolescent risk factors (Study II)

In this second study, the potential risk factors of PD in early life and adolescence were focused on. Comparison groups of NPD, SZ, PBD, PNOS and HC were used. There were 58 subjects with the lifetime diagnosis of PD by the end of 2016 (lifetime prevalence 0.5%). There was a majority of females (60.3%). The group of HC was the largest comparison group (n=8200). Other groups had following sizes: NPD (n=746), SZ (n=195), PBD (n=27), PNOS (n=136). The summary of the results of all analyses is presented in Figure 3.

5.2.1 Univariate and multivariate analysis of PD risk factors compared to HC

Univariate analysis of PD risk factors in comparison to HC was first performed. Any psychiatric illness (HR 3.63 (1.99-6.62)) and psychosis (HR 3.89 (1.41-10.73)) of the parents were significant risk factors regarding the mental illness in the family of PD subjects. Affective disorders among parents did not independently increase the risk of PD in offspring.

Low physical activity at age 14 (at most once a fortnight: HR 2.03 (1.00-4.12)) increased the risk and high school sports grade in adolescence (HR 0.37 (0.16-0.82)) lowered the risk of PD. Also, in the univariate analysis not living in a two-parent household carried a higher risk for PD (HR 2.12 (1.11-4.08)). Other variables did not differ between PD and HC in the univariate analysis.

A multivariate cox regression analysis was performed into which those variables were selected that had $p < 0.1$ in the univariate analysis. Regarding those variable groups that had more than one suitable variable (parental mental illness, physical activity), the one with the lowest p-value was chosen. The multivariate model included the following variables: parent's any psychiatric illness (either parent or both), family type in 1980, the grade of physical education in 1982 and unwantedness of pregnancy. Following the multivariate analysis, and thereby adjusting for covariates, there were only two significant variables: high school sports grade (HR 0.29 (0.11-0.73)) was a protective factor and parental mental illness (HR 3.59 (1.84-7.04)) a risk factor for PD.

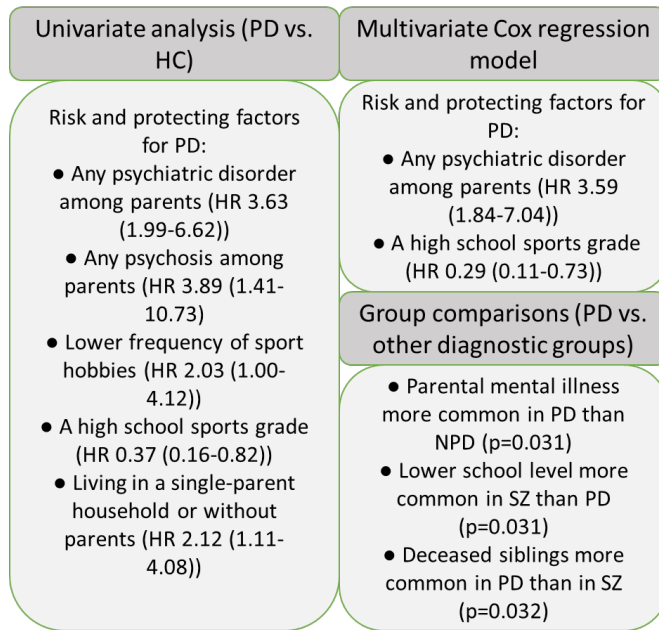


Figure 3. Summary of essential results of the risk factors and protecting factors in Psychotic Depression

5.2.2 Comparison between PD and other disorder groups

A comparison between PD and different disorder groups was also carried out. Most findings were non-significant. Parental mental illness was more common among parents of PD subjects compared to NPD subjects ($p=0.031$). PD subjects were less often at a lower school level than those with SZ (PD=5.4%, SZ=17.4%, $p=0.031$). Furthermore, subjects with PD more often had deceased siblings than SZ subjects (PD=14.6%, SZ=4.8%, $p=0.032$).

5.3 Clinical characteristics and outcomes (Study III)

In this study, PD was compared to other diagnostic groups (SZ, PBD, PNOS and NPD) regarding clinical characteristics and outcomes. The groups were formed based on a hierarchical lifetime diagnosis with information about the diagnoses until the end of 2013. There were 55 subjects in the PD group, which accounted for a lifetime prevalence of 0.5% in the Northern Finland Birth Cohort 1966. The mortality rate in the PD group was 10.9% and there were no significant differences between groups. There was a significantly larger proportion of females in the PD group compared to SZ (PD: 56.4%; SZ: 39.8%; $p=0.030$). The gender distribution in

PD resembled that of NPD (53.2%). The summary of the main results is presented in Figure 4.

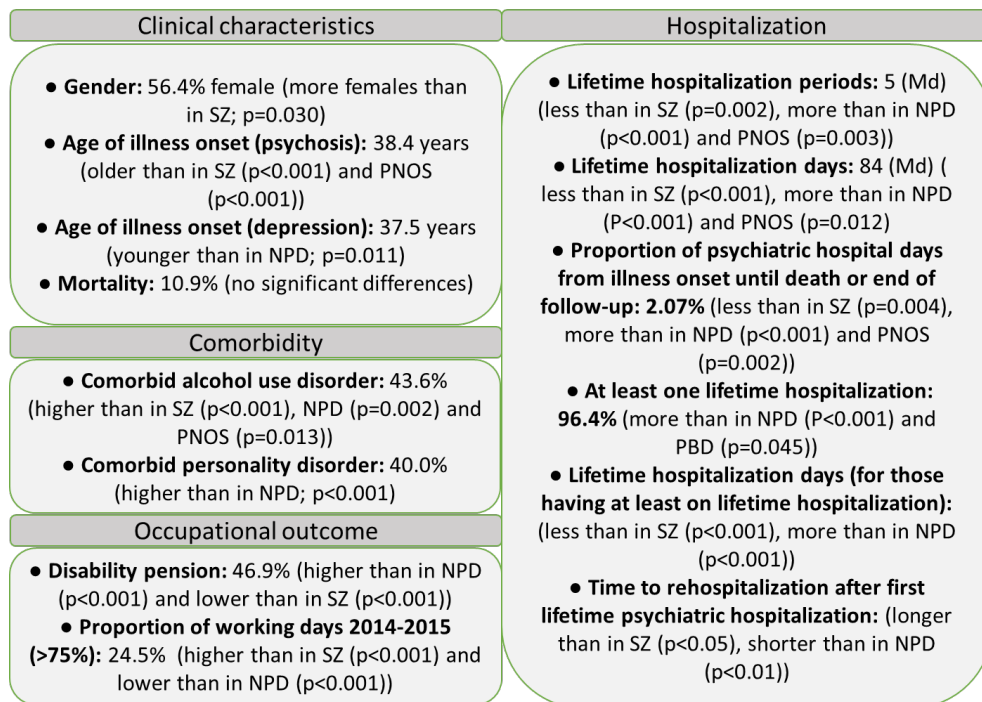


Figure 4. Summary of essential results on clinical characteristics, psychiatric comorbidity, occupational outcome and hospitalization in Psychotic Depression.

5.3.1 The clinical course of PD

The age of illness onset of the first psychotic episode and first depression episode were analyzed separately. PD subjects had a later onset of psychosis than those with SZ or PNOS ($p<0.001$ both) but an earlier onset of depression than those with NPD ($p<0.05$). A detailed analysis of lifetime hospitalization was also performed in all disorder groups. The hospitalization rate was intermediate among PD subjects. PD group subjects had a median of 5 lifetime hospitalization periods, which was significantly less than in SZ ($n=8$, $p=0.002$) but more than in NPD ($n=0$, $p<0.001$). Results concerning lifetime hospitalization days paralleled the hospitalization periods: PD was associated with more hospitalization days ($n=84$) than NPD ($n=0$, $p<0.001$) but less than in SZ ($n=254$, $p<0.001$). However, one can conclude that hospitalization periods were much longer in SZ on average.

Most PD patients had been hospitalized at least once during their lifetime (96.4%) and this was significantly more common than in NPD ($p<0.001$). In the PD

group, the proportion of psychiatric hospitalization days from illness onset until death or end of follow-up was 2.07%. This was, comparably to other results, more than in NPD ($p<0.001$) and less than in SZ ($p=0.004$). Since the NPD group in this study included mild and moderate depressions in addition to severe depression, the lifetime hospitalization days were separately looked into for those who had been hospitalized at least once. There was still a clear difference between PD ($n=84$) and NPD ($n=15$, $p<0.001$).

When comparing PD to PBD or PNOS, consistent differences were not found. However, the PD group was associated with more hospitalization on certain variables. PD subjects had more often been hospitalized at least once during their lifetime than PBD patients, while PNOS group subjects had less lifetime hospitalization periods ($n=2$, $p=0.003$) and smaller proportion of hospitalization days from illness onset until death or end of follow-up (0.86%, $p=0.002$).

Survival curve analysis of readmissions revealed a significantly shorter time to rehospitalization after first lifetime psychiatric hospitalization in the PD group than in the NPD group ($p<0.01$). SZ was oppositely associated with more rapid rehospitalization ($p<0.05$). There were no significant differences between PD and PBD or PNOS.

5.3.2 Comorbidity

Psychiatric comorbidity was found to be especially common in the PD group. Alcohol use disorder was found in 43.6% of PD subjects and 40.0% had been diagnosed with a personality disorder. The prevalence of both these disorders was higher than in any other diagnostic group in absolute numbers. There was a statistically significant difference in the frequency of comorbid alcohol use disorder when PD was compared to SZ ($p<0.001$), NPD ($p=0.002$) and PNOS ($p<0.05$). Personality disorders were significantly more common in PD than in NPD ($p<0.001$). There were no significant differences in the prevalence of comorbid anxiety disorders.

5.3.3 Educational background and occupational functioning

The educational level was examined in different study groups. There were no statistically significant differences between PD and any other group. However, in absolute numbers, PD subjects tended to have more often a high education than SZ subjects (32.7% in PD vs. 18.8% in SZ).

PD subjects were more often on a disability pension than subjects with NPD ($p<0.001$) but less often than SZ group subjects ($p<0.001$). Occupational functioning was also evaluated by analyzing the proportion of working days in the years 2013-

2014 in different disorder groups. The purpose was to examine how actively subjects were participating in working life (0-100% of working days). Active participation ($\geq 75\%$) was most common in the NPD group (44.3%), while low participation ($\leq 25\%$) was most infrequent (40.9%). Among PD subjects these proportions were 24.5% and 67.3%, which implicated significantly lower participation than in NPD ($p=0.006$) but more than in the SZ group (7.8% and 90.3%, $p<0.001$). There were no significant differences between PD and PBD or PNOS in disability pension rate or proportion of working days.

5.4 Effects of gender and psychiatric comorbidity on the outcomes (Study IV)

The fourth study was carried out to examine the effect of gender and psychiatric comorbidity on the outcomes of PD. Information about lifetime psychiatric diagnoses until the end of 2016 were utilized and there were 58 subjects in the PD group, comprising of 23 males and 35 females. The mortality rate was 10.3% ($n=6$, male=4, female=2). Regarding comorbidity, alcohol use disorders and personality disorders were focused on, since it was previously found (Study III) that they were especially prevalent in PD.

5.4.1 Gender differences in PD

While the average onset age of PD in the whole sample was 40.2 years, there was a 5.6 years difference in the median onset age of males and females (male: 37.3 years, female: 42.9 years). This difference between genders was however non-significant statistically. When observing lifetime hospitalization days, a significant gender difference was found with male sex being associated with more lifetime hospitalization ($p=0.03$). The disability pension rate was similar between both genders. Male and female subjects were found to have different comorbidity profiles (Figure 6). Comorbid alcohol use disorder was more common among men (male: 60.9%, female: 28.6%, $p=0.028$). Men also more often had been diagnosed with a personality disorder, the difference being statistically non-significant (male: 52.2%, female: 28.6%, $p=0.098$).

5.4.2 Effect of psychiatric comorbidity on the outcomes

Comorbid personality disorder had many negative effects on the outcome of PD subjects. It was associated with earlier median onset age (36.0 vs 42.4 years; $p<0.01$), more lifetime hospitalization ($p<0.001$) and higher mortality ($p=0.03$). The most common personality disorder diagnoses were emotionally unstable personality

disorder (n=7; B cluster: n=9) and unspecified personality disorder (n=7). Four subjects had an A cluster and two subjects a C cluster personality disorder diagnosis. Those who had a comorbid alcohol use disorder also had been hospitalized for a larger cumulative number of days ($p<0.01$) but other effects on the outcome were not statistically significant. To summarize (Figure 5), male gender, comorbid personality disorder and comorbid alcohol use disorder were all associated with increased lifetime hospitalization, while personality disorder also predicted higher mortality and earlier onset age.

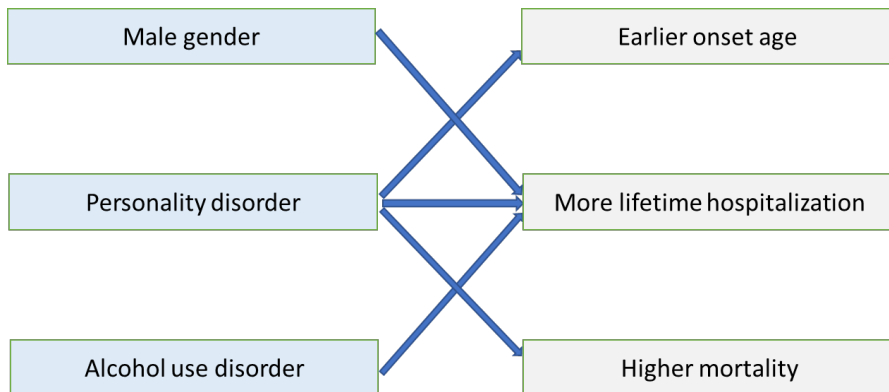


Figure 5. Summary of associative findings of the effects of gender and psychiatric comorbidity on the outcome of Psychotic Depression.

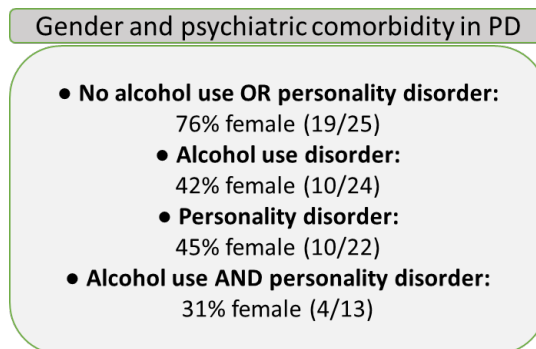


Figure 6. Gender variation in subgroups based on comorbidity.

6 Discussion

6.1 Main Findings

The systematic review and meta-analysis (Study I) revealed a lack of studies concerning risk factors of PD. Mental illness in the family was a risk factor for PD but otherwise, findings are mostly based on single studies or the results have been conflicting. The lifetime prevalence of PD was found to be 0.35-1.0%. The majority of PD patients were females and the onset age was younger than in NPD in young samples (under 45 years old) and older in old samples (over 55 years old). Onset age in PD was older than in SZ. In Study I, it was also found that PD patients have mostly better outcomes than in SZ, worse than in NPD and comparable to PBD.

In the NFBC 1966, familial mental illness was found to be a risk factor and high school sports grade in adolescence a protective factor for PD (Study II). Parental mental illness was also more common among PD than NPD subjects. PD subjects were less often on a lower school level and more often had deceased siblings than SZ subjects. Concerning clinical characteristics and outcome in the NFBC 1966 (Study III), the lifetime prevalence of PD was 0.5% (56.4% female). PD group had more hospitalizations and occupational deficits than NPD but less than SZ subjects. Psychiatric comorbidity was especially common in PD. Male gender and psychiatric comorbidity (alcohol use disorder and personality disorder) were associated with poor outcomes (Study IV).

6.2 Comparison to earlier studies

The results of the original study in the NFBC 1966 were quite much in line with the systematic review and meta-analysis presented in this thesis. In the NFBC 1966 the lifetime prevalence rate of PD was 0.5%, which was similar then the results of Study I that found lifetime prevalence in the previous studies to be 0.35-1.00%. Gender distribution in the cohort was similar to the meta-analysis: females formed a majority comparably to NPD but oppositely to SZ.

The finding in the NFBC 1966 of familial mental illness, especially psychosis, among the parents of PD subjects was in line with previous studies (Heslin et al. 2016b). In the study, a high school sports grade at the age of 16 acted as a protective

factor against PD. This is a novel finding in the case of PD, but physical activity is known to prevent the development of depression (Schuch et al. 2018) and low physical activity in adolescence is likely to increase the risk of non-affective psychosis in adulthood (Sormunen et al. 2017). The lack of significant early risk factors for PD was in line with the only other prospective study about early risk factors in PD by Østergaard et al. (2013), in which no significant risk factors were also found.

The onset age of psychosis and depression were analyzed separately in this birth cohort sample which made it harder to compare to previous studies. However, because a hierarchical lifetime diagnosis was used to form the study groups, it was more informative to examine the onset of psychosis and depression differently. SZ subjects were found to have an earlier onset age of psychosis than PD subjects and the onset age of depression was later for those with NPD when compared to PD. In the meta-analysis, PD was associated with a later onset age than SZ. Compared to NPD, the meta-analysis showed an age-dependent association in onset age: in young samples, PD patients' onset age was earlier but in old samples later than in NPD. Since the NFBC 1966 sample represents a young sample, the results concerning onset age were in line with the previous studies.

The high proportion of PD among all depressive patients (28%), discovered in our meta-analysis, is likely to reflect the severe symptom profiles within the sample populations. When only those studies, that included both in- and outpatients or only outpatients, were included, the proportion of PD was 19%. Even this number seems to be very high when comparing the lifetime prevalence rates of PD and NPD. One explanation is the use of mostly secondary care data in these studies: psychotic symptoms are more common in depression when investigating secondary care patients compared to primary care settings (Vuorilehto et al. 2007). Furthermore, a disproportionately large part of NPD patients in previous studies had been hospitalized, compared to epidemiological samples, which needs to be considered when interpreting the comparison between PD and NPD.

PD subjects had a better outcome than SZ subjects in the NFBC 1966 but worse than those with NPD. These differences were seen in the lifetime hospitalization rate, time to readmission after the first hospitalization and in the occupational outcome. These differences, that reflect the intermediate outcome of PD between NPD and SZ, are also seen in the meta-analysis. Two recent studies, published after the systematic search was conducted for the meta-analysis, with representative samples and 6-10-year follow-ups, reported similar results in the outcome of PD compared to SZ (Heslin et al. 2016a; Kingston et al. 2018) but did not include an NPD comparison group. A study by Coryell et al. (1996) with a 10-year follow-up did, similarly to our study, find worse outcomes in PD than in NPD. Another study in Germany did not find significant differences between PD and NPD in symptoms or

occupational functioning 15 years after the index episode (Jäger et al. 2005). In this study, PD was associated with more hospitalizations. The study included only patients who were hospitalized during the index episode, which may partly explain the results. Furthermore, an Italian study (Maj et al. 1990) with a 7-year follow-up was unable to show differences between PD and NPD, but in this study, all PD patients had mood-congruent symptoms, which is likely to affect the outcome of the sample. The systematic review and meta-analysis found also contradicting results regarding hospitalization and occupational outcome of PD compared to NPD, although the outcome in PD was generally poorer. Therefore, this study in the NFBC 1966 is an important contribution to this insufficient evidence base and shows PD to have a poorer prognosis.

Comparison analyses between PD and PBD or PNOS group in the NFBC 1966 sample did not show quite so uniform results as with NPD and SZ. In the NFBC 1966, there were still implications of a worse outcome in PD: PD was associated with more lifetime hospital days than the PNOS group. Also, there were fewer subjects without any hospitalizations in the PD than in the PBD group. Comparably to NFBC 1966, in the meta-analysis PD and PBD had comparable outcomes despite some differences in symptom profiles (more negative and less positive symptoms in PD). In the previous study most resemblant of our study design by Heslin et al. (2016a), PD and PBD also had mostly comparable results but PBD more often had an episodic course. Furthermore, a recent study, conducted in rural Ireland as part of the Cavan-Monaghan First Episode Psychosis Study, found no differences between PD and PBD at 6-year follow-up in the severity of symptoms or functional impairment (Kingston et al. 2018).

The mortality rate in PD ($n=6$, 10.3-10.9%) in the NFBC 1966 sample was not significantly different than in other disorder groups, which may have been due to a relatively small sample. In Study I mortality was not investigated but high mortality has previously been reported (Vythilingam et al. 2003).

In the NFBC 1966 sample, it is shown that male gender is associated with a poorer outcome and more comorbidity in PD. Gender differences in PD have not been extensively studied in the past. Only one previous study analyzed the effect of gender on the outcome of PD (Deligiannidis et al. 2013) and found no difference between genders in a 12-week pharmacotherapy trial. Our findings of poorer outcomes in the long term among males in PD are an important new result.

As for comorbidity, in the NFBC 1966 sample, alcohol use disorder and personality disorder were found to be more common in PD than in other groups. The meta-analysis did not focus on this issue, but previous studies have shown high levels of substance use disorders (Tohen et al. 2012) and personality disorders (Gaudiano et al. 2009) in PD. This was still the first study to do a comparison to many other disorder groups. Also, more B cluster personality disorders were found, oppositely

to a finding of more A cluster personality disorders in previous studies (Serretti et al. 1999, Gaudiano et al. 2009), which may result from the register study design (See Strengths and limitations). Alcohol use disorder was more common among males in PD which has also been found in previous studies (Fennig et al. 1993, Isometsä et al. 1994).

Psychiatric comorbidities (alcohol use and personality disorder) were associated with poor outcome in PD in the NFBC 1966. Especially comorbid personality disorder was associated with higher mortality, earlier onset age and more lifetime hospitalization. Personality disorders are known to be associated with poorer outcomes in depression (Kampman et al. 2013) and this seems to apply to PD. It is interesting that only two subjects had a C cluster personality disorder, which has also been associated with poor outcomes in depression previously (Viinamäki et al. 2003).

It is also noteworthy that all the deceased subjects had either comorbid alcohol use or personality disorder. Personality disorders are known to be a significant risk factor for suicide (Schneider et al. 2006), which may explain the elevated mortality rate. In this study, the causes of death were not analyzed. Potential reasons for higher mortality among those with alcohol use disorder include the effects of alcohol use on nutrition, physical activity and somatic health in general. Comorbid alcohol dependence is also a risk factor for suicide (Aaltonen et al. 2019). It is possible that treatment adherence in the comorbid groups has also been lower causing longer periods of severe symptoms that may have had an impact on physical health as well.

Alcohol use disorders have been found to be more common among males previously (Addington et al. 2007) and they are likely to contribute to poorer outcomes in psychotic illness (Cetty et al. 2019). Mood may be more strongly affected by alcohol compared to other symptoms (Barrowclough et al. 2014), and therefore alcohol use disorder is likely to associate more strongly with PD than with other psychotic disorders. It is also possible that mechanisms involved in depression are different among those with a comorbid alcohol use disorder (Paavonen et al. 2016).

To summarize, this thesis demonstrated that PD is not typically a one-episode illness but associated with several hospitalizations, grave symptoms, functional impairment and high psychiatric comorbidity. Sociodemographic characteristics such as gender (a female majority in PD) and onset age were also analyzed for the first time with meta-analytical methods. The understanding of subgroup differences within PD was also significantly increased by the evidence that male gender and psychiatric comorbidity are associated with poor outcomes. The small number of significant risk factors and internal heterogeneity indicate that multiple different etiologies may be present in PD, comparably to NPD.

6.3 Psychotic depression on the spectrum of mental disorders

Due to the dimensional nature of psychiatric illness, discussion on whether PD is a severe form of depression or a separate illness may be a relic from the past. The results of this thesis still emphasize the need to take a different stance on PD and NPD. PD resembles more other affective psychotic illness than NPD and is similarly a long-term psychotic illness than PBD. This can be seen in the number of hospitalizations and in the occupational outcome.

There were only a few significant risk factors of PD in the NFBC 1966 sample and no major differences in risk factor profiles between PD and other disorders. There may be many factors explaining this finding. First, depression is known to be a heterogeneous entity (Lieblich et al. 2015) and many different etiologies are present. Secondly, it is likely that affective and non-affective psychoses do not have completely distinct etiological factors (Craddock & Owen 2010).

When reflecting on the results of the whole study, the differences and similarities between PD and SZ depict an intriguing relationship between these two. As reported in the literature review, PD is associated with similar cognitive disturbances than SZ, in which cognitive problems are regarded as the core feature of illness (Green et al. 2019). Also, depressive symptoms are often present in SZ (Uptegrove et al. 2017) likely causing negative outcomes in the long term (Conley et al. 2007). Meanwhile, PD is associated with later onset age and better outcomes than SZ. In addition, opposite to SZ, PD has a female majority. Despite many similarities, it is clear, that PD represents a different illness profile than SZ. Furthermore, complicating the picture of co-existing depressive and psychotic symptoms, depressive symptoms during a first-episode psychosis have negative implications for at least short-term outcomes (Challis et al. 2013, Gardsjord et al. 2016).

Comparably to psychosis, depression is also a dimensional illness, and different patients have significant variation in the severity and number of symptoms. Historically, depression has been defined differently, and it is possible that certain important symptoms or signs are missed using only the current diagnostic criteria (Kendler 2016). Therefore, it is important to also look outside the diagnostic criteria of depression to understand how psychosis and depression are interconnected.

In order to improve the understanding of the place of PD on the psychosis spectrum, prospective long-term follow-up studies, including the whole scale of psychotic illness, should be conducted. Furthermore, efforts to predict the course of illness in first-episode psychosis (Suvisaari et al. 2018) are important, since psychosis and depression are a common symptom combination during the first episode, but the diagnosis often changes during follow-up.

6.4 Strengths and limitations of the studies

6.4.1 Meta-analysis and systematic review

The study and the accompanying data search were conducted in a systematic and comprehensive way, which is a major strength. Some areas of research (gender, onset age, certain areas of outcome) were also rather well represented in the literature and made possible the use of integrative quantitative analysis.

A significant limitation was the small number of original studies and the varying methodologies used in these studies. This applies especially to prevalence and incidence and resulted in the difficulty to make precise estimates. Also, the samples of the studies were relatively small and mostly did not focus on first-episode samples. In outcome studies, the used measurement methods were not completely homogenous.

Because of the abovementioned scarcity of studies regarding most studied variables, it was not possible to make an extensive analysis of the quality of original studies and base exclusion on these potential flaws. However, this can be considered a limitation of the study.

Another limitation is that childhood-onset samples were not included. In addition, it is possible that some studies have been missed due to changing terminology. For example, different names have been used to describe PD in the past. This concerns particularly older articles. The likelihood of this was minimized by selecting many search terms. In addition, a manual search was also conducted to minimize the effect of this problem.

6.4.2 The Northern Finland Birth Cohort 1966

The original study was conducted in the Northern Finland Birth Cohort 1966, where most of the diagnostic information was gathered from different national registers. Therefore, one clear limitation in this study was the lack of clinical diagnoses using validated instruments. However, the Care Register for Health Care, the primary source of diagnoses in the study, has been extensively used and studied in the past (Sund 2012).

Related to the former is the limitation concerning the use of changing diagnostic systems (ICD-8-10). In the ICD-8 and ICD-9, PD is not as unquestionably defined as it is in ICD-10. Into the PD group were chosen those diagnoses that included non-organic psychotic symptoms accompanied by significant depressive symptoms when there was not another disorder present. Also, possible changes in diagnostic practices (Korkeila et al. 1998) over the years cause a potential limitation. The significance of

these limitations is reduced by the use of hierarchical lifetime diagnoses using nationwide registers of psychiatric diagnoses.

However, it is known that the diagnoses of schizophrenia (Kampman et al. 2004) and bipolar disorder (Fritz et al. 2017) are delayed in clinical practice and the diagnostic validity of the PD group could potentially be reduced by this. The age of the sample (50 years at the end of follow-up) can be seen to minimize this risk but this limitation cannot be completely excluded.

In this study, we were not able to obtain information about those patients who never received treatment for their mental disorders. Since a significant proportion of patients with even severe depression do not seek treatment (Hämäläinen et al. 2004), this limitation needs to be considered when interpreting the results of this study. Due to a considerable number of untreated depression patients in the general population and the differences in patient profiles between primary and secondary care, studies focusing mostly on secondary care are likely not to reflect the complexity of the phenomena at a population level.

Also, the age of the NFBC 1966 sample means that this original study does not tell anything about late-onset PD but only about those PD subjects whose illness began latest in 2016. This is an important limitation given that PD is common in older samples as well (Kivelä & Pakkala 1989).

Another applicable concept compared to lifetime prevalence, which was mostly used in the study, would be cumulative incidence. Lifetime prevalence is often measured from a cross-sectional sample, in which the deceased subjects are missing. This limitation was able to be avoided because of the cohort study design, and it should be considered a significant strength.

Unfortunately, data about specialist outpatient diagnoses were able to be obtained starting as late as from 1998 when NFBC 1966 participants were over 30 years old. In the PD group, most (96.4%) subjects had been hospitalized, and it is unlikely that there would have been many PD patients who were treated only in outpatient care before 1998, although this is a possibility that cannot be completely excluded. However, since there has been a decrease in the number of psychiatric hospital beds and an increase in outpatient care after the 1980s and 1990s (Salokangas & Saarinen 1998), it would have been more likely for PD subjects to have been treated in outpatient care after 1998. Therefore, this lack of data should not be considered to be a major limitation to the validity of the PD group.

Nevertheless, lack of outpatient data prior to 1998 reduces the validity of the NPD group especially, because NPD is often treated in outpatient care. However, this bias in the NPD group is not likely to invalidate the results of group comparisons between PD and NPD because the potential subjects with NPD, that were not able to be detected, had never been hospitalized or treated in outpatient care after 1998. This means that they represent a part of NPD that has a very benign course. Oppositely,

the sample of NPD is biased to include those with a more severe outcome. Given that several important differences in outcome between PD and NPD were still able to be detected, this potential bias emphasizes the meaning of psychotic symptoms for the outcome of depression. As for risk factors, since many differences were not found when comparing to HC, it is unlikely that a less ill sample of NPD would have produced more group differences between PD and NPD.

The NPD group included diagnoses of also mild and moderate depressions, which can be seen to partly explain the differences observed in outcomes between PD and NPD groups. However, primary health care diagnostic information was available only from 2011, so most subjects had been treated in psychiatric clinics or hospitals. Also, as mentioned above, outpatient diagnoses were not available prior to 1998. Therefore, the NPD group comprises of subjects with significant symptoms and need for treatment.

Otherwise, concerning risk factors, early life and adolescent risk factors were only studied, whereas many factors later in life can function to increase the risk of PD. Also, data about potential risk factors such as cannabis use, migration or childhood traumas were not available. In addition, the PD sample size was not very large ($n=58$) to detect potentially smaller effects on the risk of PD. PBD group ($n=27$) was even smaller. Still, PD group size is considered large enough for analysis and PBD was important to be analyzed alongside it. Considering the results, since multiple different risk factors were studied and a big number of group comparisons were made, it is still possible that certain risk factors or between-group differences were significant due to chance. Especially the results of low school sports grades in adolescence should be considered preliminary.

No variable modification was carried out, and therefore the risk factors are comparable to previous studies conducted in the NFBC 1966, which is a considerable strength. However, it is possible that certain risk factors could have been significant if, for example, continuous variables would have been analyzed categorically.

As for mental illness among parents, BD or depression were not found to be more common in the families of PD subjects than HC, which is more likely to be explained by changing diagnostic practices (Korkeila et al. 1998, Filatova et al. 2017), than by the real absence of these disorders.

Outcome results in the different disorder groups were not adjusted for the duration of illness. However, this should not be considered a major limitation since the proportion of psychiatric hospital days from illness onset until death or end of follow-up was also analyzed, which did take illness onset into account. Results in this variable were comparable to other hospitalization variables. Also, all study participants were from the same age group and different disorders were studied in a naturalistic setting at the same points in life.

In this study, it was not possible to use data about specific treatments and rehabilitation that study subjects had received in the hospital or outpatient care. This would have been especially interesting regarding the outcomes because most studies about the treatment of PD have focused on the acute phase of the illness. Also, lack of this information means that PD outcomes in comparison to other disorder groups may have been partly explained by suboptimal or oppositely beneficial treatment practices in PD.

Regarding the effects of psychiatric comorbidity and gender on the outcomes, adjusting for potential confounding factors was not done due to the explorative study design. Therefore, the associative findings of worse outcomes among males and those with psychiatric comorbidities should not be considered causal. It is also possible that those PD subjects who had a worse prognosis received more comorbid diagnoses due to more contact with health care professionals. However, the threshold for diagnosing alcohol use and personality disorders is often high reducing the likelihood of this scenario. Furthermore, register data may underestimate the prevalence of comorbid personality disorders. Recently, it was reported in a Finnish study, that 47% of patients contacting psychiatric services for the first time fulfilled the criteria for a personality disorder (Karukivi et al. 2017).

6.5 Clinical implications

In everyday clinical practice, PD is often found to be a controversial disorder with foggy boundaries between it and other disorders. This is also affected by the insufficient evidence base guiding clinical decision-making. This has negative consequences for those suffering from this disorder. The blurry distinction between diagnostic entities is present in all psychiatry due to symptom-based descriptive nosology, and the sidelining of PD is not entitled from this perspective either.

Depression is a highly prevalent mental health problem in the world causing not only vast amounts of suffering but also significant costs for societies (Cuijpers et al. 2012). The results of this thesis emphasize that it is very important to assess the presence of potential psychotic symptoms in patients with depression since they have significant consequences for the clinical picture, treatment and outcomes. Furthermore, in this thesis, the lifetime prevalence rate of PD was found to be 0.35-1.0%, which means that PD is a rather common diagnosis in the clinic.

The findings of this dissertation that the majority of PD patients are females and that onset age in PD is likely to be younger than in NPD in patients under 45 years old but higher in patients over 55 years old, are important information for the evaluating clinician. All mental health professionals should also be aware that PD is associated with a more grave illness course than NPD.

Due to a scarcity of specific risk factors, possibilities to prevent PD remain uncertain. However, familial mental illness was found to be a significant risk factor for PD. This almost fourfold risk is important to keep in mind when evaluating and treating patients with depression, since psychotic symptoms may be concealed or otherwise hard to distinguish. Low sports grade at the age of 16 was also a significant risk factor in the NFBC 1966, which encourages investment in the physical activity of children.

When comparing to BD, a common invalid preconception in the clinic is that PD is more of a single-episode disorder with a good prognosis after remission, while BD lasts for a lifetime and needs to be handled accordingly. However, according to the results of this thesis, PD carries a similar, if not worse, prognosis than PBD. Therefore, the necessary action should be taken to ensure PD patients' treatment is planned with a focus also on the long-term outcome, in addition to acute-phase treatment. This conclusion is something that already Kraepelin would have agreed to since he recognized PD and PBD to be part of the same entity. Outcomes in PD seem to be better than in SZ, while previous findings show a similar cognitive disturbance in both disorders. PD should be considered an important differential diagnosis in first-episode psychosis, while it also has important repercussions for treatment.

The findings of the effects of gender and psychiatric comorbidity on the outcome showed that male gender, personality disorder and alcohol use disorder were associated with a more malign course in the long term. Personality disorders and alcohol use disorders were also especially common in PD. These results encourage clinicians to actively screen for comorbidities and initiate treatment for those disorders.

Currently, PD patients are likely to have a greater risk of suboptimal treatment than SZ and BD patients due to a lack of research. This is even more probable to happen in an overloaded public healthcare system that emphasizes the use of only evidence-based treatments. Hopefully, the findings of this thesis encourage clinicians to carefully plan and actively implement treatments for this patient group.

6.6 Implications for future research

The findings of this thesis encourage future studies to focus on PD, which has proven to be a common disorder with severe symptoms, high comorbidity, recurring hospitalizations and functional impairment. Special attention should be given to diagnostic instability and internal heterogeneity within the PD population. In order for studies on PD to be clinically useful, they should include naturalistic first-episode samples with a long follow-up. Different subgroups of PD have large variation in outcomes, as shown in this thesis, and it is likely that different treatment options

would prove most beneficial in the subgroups. Furthermore, a more detailed analysis of patient characteristics (including, for example, different profiles of psychotic and depressive symptoms) is important in the future. One possibility is to use dimensional models to investigate PD. Long-term follow-up studies utilizing data from multiple biological, psychological, functional and symptom dimensions, in addition to clinical characteristics and treatments, would have much to give to the understanding of PD. Inclusion into these studies should not be based on diagnostic criteria since individual symptom profiles change so much over time, but diagnostic groups should still be analyzed and their validity re-evaluated. Finally, it is crucial to explore new options to improve the long-term outcomes of PD. Effective treatments in the acute phase of PD already exist but very little is known about the long-term outcomes of different treatment options.

7 Conclusions

The research conducted on PD in the past is low in quantity and heterogeneous in methodology. Intermediate diagnostic stability further complicates the understanding of PD. However, both the systematic analysis of previous literature and naturalistic birth cohort study revealed a severe course of illness in PD. Several prognostic and symptomatic factors differentiate PD from SZ and NPD, positing it in between these two disorders. Clinical course in PD resembles that in PBD, which implicates that functional impairment is common and multiple recurring hospitalizations often take place. A combination of biological and cognitive changes is often present in PD, but few specific risk factors were found in this study. PD is characterized by a female majority similarly as in NPD, and male gender possibly indicates a more malign course of illness, as do psychiatric comorbidities, that are common in PD. For the clinician, these findings mean that PD needs to be treated with a long-term focus, while actively paying attention to comorbidities and acknowledging the heterogeneity of clinical pictures and outcome. To summarize research implications, major clinical significance and a severe scarcity of past research efforts underline the need for more prospective studies with a long follow-up on PD.

Acknowledgements

The studies that form this thesis were conducted as part of the Northern Finland Birth Cohort 1966 (NFBC 1966) during the years 2015-2020. I would like to thank the whole NFBC 1966 organization and the University of Oulu for enabling the use of their data in this study. It was a privilege to join a research group that had a long history of carrying out high-quality epidemiological studies in a world-renowned birth cohort.

A great number of people have helped and supported me in this project, and without their help, this thesis would have not been possible. Firstly, I wish to express gratitude to my supervisors, professor Jyrki Korkeila and Docent Erika Jääskeläinen, for their experienced and wise guidance. They have been very supportive and understanding during times when I have had to prioritize other issues over my thesis. I have been very fortunate to have both of them as my supervisors in this project. Furthermore, I owe my heartfelt thanks to professor Jouko Miettunen, Tanja Nordström, Anni Heiskala and Hanna Huovinen for their invaluable help in working with the data. In addition, all the abovementioned persons were my co-authors and offered very thoughtful comments that helped to improve the manuscripts.

I am grateful to my pre-examiners professor Jukka Hintikka from Tampere University and research professor Jaana Suvisaari from the National Institute for Health and Welfare, for their comprehensive examination of my thesis and constructive comments. I would also like to thank members of my follow-up committee, professor Jarmo Hietala and professor Erkki Isometsä, for their insightful comments and support.

These studies were supported financially by Turku University Foundation, Finnish Medical Foundation, the Doctoral Programme in Clinical Research and the Department of Psychiatry at the University of Turku. I would like to thank all these financiers for having trust in the research project and enabling periods of full-time research work for myself. Without these fundings, it is uncertain if I would have been able to finish this thesis.

I am very grateful to my parents Teijo and Vuokko, and to my sister Ella and her family, who have always been supportive and encouraging. Finally, I am most

grateful to my lovely wife Nikolina for her love and spirit. She has been my greatest support in finishing this thesis.

Turku, August 2020

Miika Nietola

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ISBN 978-951-29-8165-6 (PRINT)
ISBN 978-951-29-8166-3 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)