Epidemiology of psychotic depression – systematic review and meta-analysis

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Large amount of data have been published on non-psychotic depression (NPD), schizophrenia (SZ), and bipolar disorder, while psychotic depression (PD) as an own entity has received much smaller attention. We performed a systematic review and meta-analyses on epidemiology, especially incidence and prevalence, risk factors, and outcomes of PD. A systematic search to identify potentially relevant studies was conducted using four electronic databases and a manual search. The search identified 1764 unique potentially relevant articles, the final study included 99 articles. We found that the lifetime prevalence of PD varies between 0.35% and 1%, with higher rates in older age. Onset age of PD was earlier than that of NPD in younger samples, but later in older samples. There were no differences in gender distribution in PD *v.* NPD, but higher proportion of females was found in PD than in SZ or in psychotic bipolar disorder (PBD). Risk factors have rarely been studied, the main finding being that family history of psychosis and bipolar disorder increases the risk of PD. Outcomes of PD were mostly worse when compared with NPD, but better compared with SZ and schizo-affective disorder. The outcome compared with PBD was relatively similar, and somewhat varied depending on the measure of the outcome. Based on this review, the amount of research on PD is far from that of NPD, SZ, and bipolar disorder. Based on our findings, PD seems distinguishable from related disorders and needs more scientific attention.

Introduction

Major depression with psychotic features (hereafter psychotic depression, PD) is a severe disorder with a high risk of recurrence and high mortality in both adult samples under 60 years (Lykouras & Gournellis, 2009) and older people samples (Gournellis *et al.* 2014). In spite of the severe course of illness, there seems to be some difficulty identifying the disorder in clinical settings (Rothschild *et al.* 2008).

Originally, Kraepelin (Goodwin & Jamison, 2007) considered PD as a type of manic-depressive illness. In the post-kraepelinian era, it has been classified among unipolar major depressive disorders. In International Classification of Diseases, 10th Edition (ICD-10) PD is considered the most severe subtype of major depressive disorder (WHO, 1992), whereas in

Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) psychotic features are not an indicator of severity of major depression (APA, 2013). Due to a number of differences between PD and non-psychotic depression (hereafter NPD), it has for long been proposed that PD should be considered a distinct disease entity (Schatzberg & Rothschild, 1992; Keller *et al.* 2007).

The point prevalence of PD is estimated to be approximately 0.4%, with older adults being in the highest risk (Kivelä & Pahkala, 1989; Perälä *et al.* 2007). The prevalence of psychotic features in the adolescent outpatient major depression sample was 18% (Ryan *et al.* 1987) while the same figure was 45% in a hospitalized adolescent patient sample (Haley *et al.* 1988). There is a lack of information concerning the risk factors for PD. Previous studies have often studied all affective psychosis, i.e. included bipolar disorder or studied PD as part of all major depressive disorders. Though there are marked similarities in PD and NPD risk factors, some differences are likely to exist. There is also considered a close link between PD and bipolar disorder (Keller *et al.* 2007; Østergaard *et al.* 2013).

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There are no previous systematic reviews on incidence, prevalence, or risk factors of PD.

Clinical course of illness in PD is more severe than in NPD. This applies especially in the short-term outcome, but it has been suggested that in a longer follow-up, the significance of psychotic features might fade (Keller *et al.* 2007; Lykouras & Gournellis, 2009). However, mortality is significantly higher in PD compared with NPD (Vythilingam *et al.* 2003), although there are conflicting findings (Suvisaari *et al.* 2013). The functional outcome has been suggested to be mostly better in PD compared with schizophrenia (SZ), and differences in outcomes between PD and psychotic bipolar disorder (PBD) have been unclear (Craig *et al.* 2000; Jarbin *et al.* 2003; Keller *et al.* 2007).

Huge amount of data and meta-analyses have been published on NPD, SZ, and bipolar disorder, while PD as an own entity has received much smaller attention (Crebbin *et al.* 2008). Meanwhile, there has been a concern over the validity of PD diagnosis mainly due to diagnostic instability (Ruggero *et al.* 2011). There are some meta-analyses and reviews on pharmacological treatments (Wijkstra *et al.* 2015), cognition (Fleming *et al.* 2004; Zaninotto *et al.* 2015), genetics (Domschke, 2013), neuroimaging studies (Busatto, 2013), cortisol non-suppression (Nelson & Davis, 1997), and PD in old age (Gournellis *et al.* 2014). Lykouras & Gournellis (2009) present a comprehensive review on neurobiology, treatments, epidemiology, course of illness, and outcomes of PD in comparison to NPD. However, they have not reported their results systematically, and some topics such as risk factors have not been studied. Earlier reviews presenting epidemiology of PD (Schatzberg & Rothschild, 1992; Gournellis & Lykouras, 2006; Lykouras & Gournellis, 2009) have not combined the data by meta-analytic means and they have compared their findings only to NPD.

Aims

Our aim was to perform a systematic review on epidemiology, especially incidence and prevalence, risk factors, and outcomes of PD. We also aimed to do a meta-analysis on sex differences, onset age, and outcome of PD in comparison to NPD, SZ, PBD, and schizoaffective disorder (SZAFF).

Methods

Data collection

We applied the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines for systematic reviews and meta-analyses (Moher *et al.* 2009).

In order to locate potentially suitable studies, we conducted database searches in May 2016 using four electronic databases: PubMed, Scopus, Web of Science, and CINAHL. The used search terms were the following: ('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 suicide OR physical OR somatic OR comorbidity OR 'early intervention' OR prevention). No publication date exclusions were used in the search. Articles were also searched manually from the reference lists of the previous reviews.

All abstracts were independently analyzed by two authors (HK and EJ). After the exclusion of irrelevant abstracts, all remaining articles were critically inspected by two authors (EJ or JM). For studies that met inclusion criteria, a third investigator (HL or TJ) independently extracted the data, and the collected data were checked by two authors (JM or EJ). When a disagreement occurred related to data extraction, this was resolved by consensus.

Study selection

Studies on prevalence and incidence were included if these were estimated from population surveys or used both inpatient and outpatient data to estimate prevalence or incidence.

Regarding studies on risk factors and outcomes in PD, to be included in the analyses, the studies had to be characterized by all of the following:

(1) Original study included a sample of PD. Also studies including only delusional depression were included, as the early studies on the topic often used only this definition. The sample had to include at least 80% of PD. Studies focusing on psychotic depressive episode of SZ or PBD, or studies with postpartum PD were not included.
(2) Diagnostic assessment and diagnostic criteria of PD were based on a commonly used diagnostic system or were otherwise adequately reported.
(3) The sample size of PD was at least 15.
(4) Studies presented risk or sociodemographic factors, or outcomes of PD.
(5) Studies of risk factors and outcomes had to include a comparison group of NPD, PBD, SZ, SZAFF, or healthy controls (HC) without mental disorder. The size of the comparison group had to be at least 15 and the comparison group had to include at least 80% of NPD, PBD, SZ, or SZAFF.
(6) The majority of subjects had onset age after 16 years.

Only observational (naturalistic) studies were included, whereas trials and intervention studies were excluded. While many intervention studies report clinical outcomes, the representativeness of these samples may vary widely according to the specific trial inclusion criteria. Thus, a large number of randomized controlled trials were excluded. To the current review, we finally included only studies published in English. In addition, studies analyzing neurobiological risk factors and correlates, treatments, mortality, suicides, and somatic comorbidities were excluded as being either out of the scope of this review (studies on treatments, neurobiology, somatic comorbidities) or being recently studied (mortality and suicides in PD; Lykouras & Gournellis, 2009; Rothschild, 2009; Zalpuri & Rothschild, 2016).

Incidence, prevalence, and risk factor studies

Studies on incidence and prevalence were reported with a systematic review. Regarding gender distribution and onset age, we pooled studies using meta-analytic methods. Other risk factors were reported only narratively and in a literature table. The included risk factors encompassed both early risk factors and sociodemographic factors, such as marital status and education, collected at study entry.

Outcome studies

Of studies analyzing outcomes of PD, studies analyzing the severity of psychotic symptoms (positive, negative, total symptoms), severity of depression symptoms, number of hospitalizations during prospective follow-up, symptomatic remission, global clinical outcome, global outcome, and occupational functioning were included. Global clinical outcome indicates outcome measured by the presence of clinical symptoms and severity of illness, without a specific instrument for the measurement. Global outcome indicates the outcome measured by Social and Occupational Functioning Assessment Scale (SOFAS), Global Assessment Scale (GAS), or Global Assessment of Functioning scale (GAF). Please see our earlier meta-analyses for the definitions of different outcome dimensions (Käkelä *et al.* 2014; Penttilä *et al.* 2014). Based on the number of studies (at least three studies from different samples per outcome), meta-analysis was performed on depression symptoms, total psychotic symptoms, positive and negative symptoms, global outcome, symptomatic remission, and poor global clinical outcome. For the meta-analysis, we selected symptoms measured at the baseline of studies, since this was the most common time of assessment of symptoms. In meta-analysis, outcomes were compared between PD and NPD, SZ, and PBD when data were available. Systematic review (without meta-analysis) was done for hospitalizations and occupational functioning.

Statistical analyses

Random-effects models were used in order to pool estimates of effect sizes between PD and comparison groups in the meta-analyses of gender, onset age, symptoms, symptomatic remission, global clinical outcome, and hospitalizations, based on the expected heterogeneity of the associations. Meta-analyses were done if at least three studies investigated same outcome. In the random-effects analysis, each study was weighted by the inverse of its variance and the between-studies variance. In continuous variables (onset age and symptoms), the effect size of the standardized mean difference between groups was described with Hedges' *g*. Hedges' *g* values is comparable with Cohen's *d* but recommended with small sample sizes. It can be interpreted as small 0.20, moderate 0.50, and large 0.80 effects (Cohen, 1992). In categorical variables, pooled effect size was estimated using Relative Risk (RR) with 95% confidence interval (CI). When the number of studies allowed, we checked the results of meta-analyses in the subgroups of studies based on publication year (1973–1991, 1993–2003, and 2004–2016), mean study age (below 45, 45–55, and above 55 years), or mean age of illness onset (below 45 *v.* 45 or above). In addition, as a sensitivity analyses, we performed analyses in strata by sample size (studies under 50 cases *v.* at least 50 cases with PD). In the current study, positive *g* values indicate that individuals with PD have more symptoms or later onset age than comparison group. Where multiple articles were available on the same or overlapping samples and presenting similar data, we selected one representative paper with the largest sample size or presenting outcomes measured by a more commonly used instrument for the meta-analysis. We assessed the heterogeneity of the studies using I^2 statistics, and the statistical significance in heterogeneity was tested using the χ^2 test. Values of I^2 range from 0% to 100%, reflecting the proportion of total variation across studies beyond chance. A value of 25% describes low, 50% moderate, and 75% high heterogeneity (Higgins *et al.* 2003). An α level of 0.05 was used for all statistical tests. The *metan* command of the Stata version 13 (Sterne, 2009; StataCorp, 2013) was used in all analyses.

Results

Characteristics of the studies

Database searches identified 2926 records, which reduced to 1764 after the removal of duplicates. After analyzing the abstracts, we were left with 279 articles
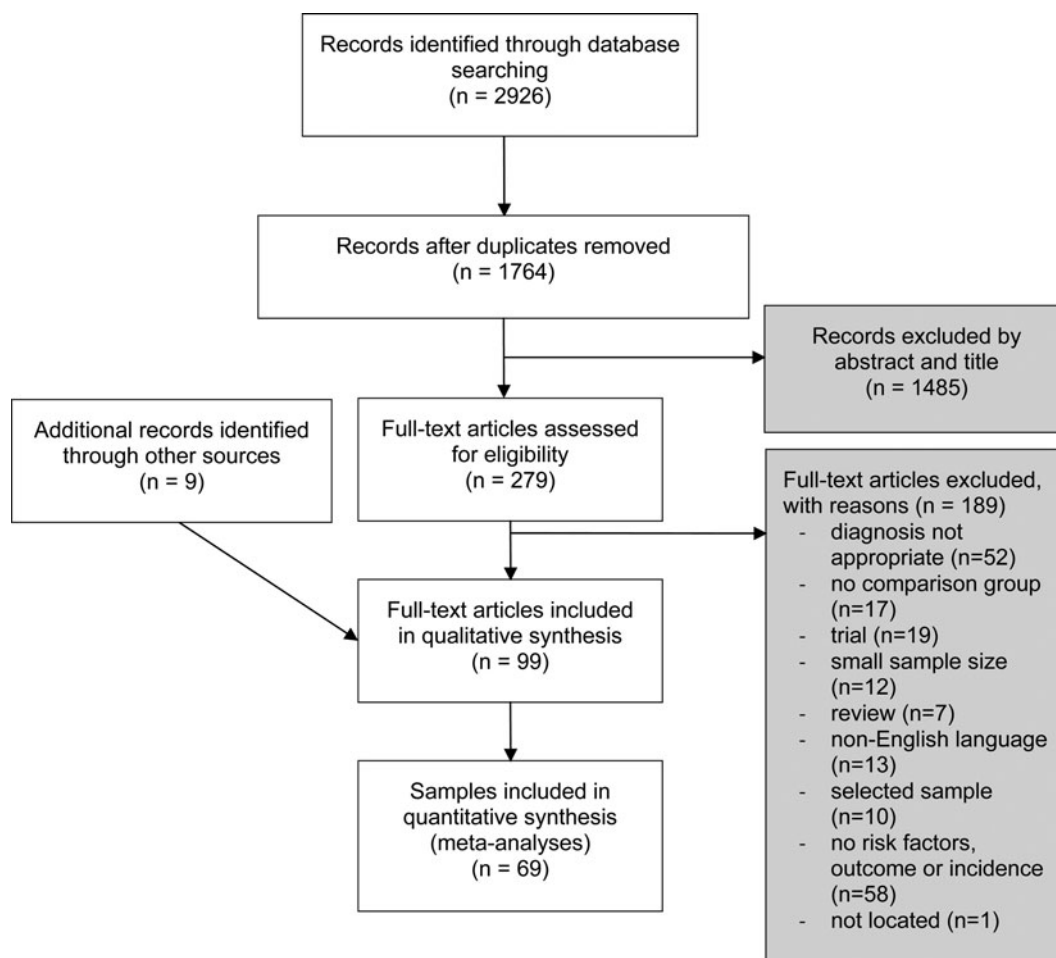
Fig. 1. Flow diagram of the selection of studies.

that potentially fulfilled our inclusion criteria. The most common reason for exclusion during abstract screening was that the article did not present results separately to PD. Figure 1 shows the flow diagram that details the exclusion criteria after abstract reading. In total, 99 studies met all of our criteria regarding incidence/prevalence, risk factors or outcome, and were included in the systematic review. The studies included nine studies from manual search.

Incidence and prevalence

Studies reporting prevalence or incidence estimates in community samples and using estimates based on inpatient and outpatient data have been collected into the online Supplementary Table S1.

Only four studies estimated *prevalence* in community samples, trying also to detect cases not in treatment using different screening methods. In the nationally representative Finnish Health 2000 sample, Perälä *et al.* (2007) found a lifetime prevalence of 0.35% for DSM-IV PD. The prevalence was higher among those

who were 65 years or more (0.43%) when compared with younger age groups; however, differences were not statistically significant. In the US Epidemiological Catchment Area (ECA) study, Johnson *et al.* (1991) reported a lifetime prevalence of DSM-III PD to be 0.6%. In an older community-based study of those with 60 years or more, the prevalence was 1.0% (0.6% for males, 1.2% for females) (Kivelä & Pahkala, 1989). In a large European telephone survey in five countries, an overall point prevalence for DSM-IV PD was 0.5%, and significantly higher rates were reported for females (0.6%) than males (0.3%) (Ohayon & Schatzberg, 2002).

Five studies used different in- and outpatient admission registers. Estimates for *annual incidence* (per 100 000 persons) were reported in three studies. In a British study, Farquhar *et al.* (2007) reported an incidence of 3.4 in the year 1875–1924 and 3.0 in 1995–1999. In an Irish study, Baldwin *et al.* (2005) found an incidence of 6.4 (males 5.4 and females 7.4), similar estimates (6.0 for those with 16 years and over) were also in a British study by Reay *et al.* (2010). A Finnish

study comparing two birth cohorts (from 1966 and 1986) found a substantial increase in cumulative incidence until age 27 years in the later cohort (0.02% *v.* 0.21%) (Filatova *et al.* 2017).

Gender differences have been reported in some incidence and prevalence studies. In three studies, females had higher estimates for incidence (Kivelä & Pahkala, 1989; Ohayon & Schatzberg, 2002; Baldwin *et al.* 2005); however, in one study, higher lifetime prevalence was reported for males (0.41%) than females (0.29%) (Perälä *et al.* 2007).

Proportion of psychosis in depression

In studies ($n = 43$) including both PD and NPD patients, the median proportion of PD patients was 28% of all depressive patients. Median proportion was lower in studies with mean age below 45 years (20%, $n = 16$) than in the middle age samples (27%, $n = 11$) or in older samples (34%, $n = 10$). The median proportion of PD in depression patients was 29% among females and 26% among males. In the studies including only depressive inpatients ($n = 22$), the median proportion of those with PD was 42%, whereas in the studies including both in- and outpatients or only outpatients ($n = 21$), corresponding proportion was 19%.

Gender differences in PD when compared with other patient samples

We compared gender distributions in the included studies on PD and patient control groups. In total, 57 studies compared PD with other included patients samples. The median number of PD patients was 45 in these studies, whereas the total number of PD patients was 28 370. In total, 43 studies compared gender distributions between PD and NPD, pooled RR being 1.03 (95% CI 0.97–1.08). Estimates of RR were relatively similar when studies were divided by mean study age or year of publication. The estimated RRs for PD for females are presented in Fig. 2, for the total sample and by mean study age. Studies comparing PD and SZ and PBD found a higher proportion of females in PD than in SZ (14 studies; RR 1.40, 95% CI 1.20–1.71) or in PBD (three studies; RR 1.36, 95% CI 1.01–1.83). The median percentage of females in PD was 65%, in NPD 65%, in SZ 37%, in SZAFF 57%, and in PBD 55%. Proportion of females in PD did not vary significantly when studies were divided by mean study age or year of publication. Proportions of females in different patient groups in the included studies are presented in the online Supplementary Table S2.

Onset age in PD when compared with other patient samples

Eighteen studies compared onset age between PD and NPD in different samples. Based on meta-analysis, there was no significant difference between the groups (Hedges' $g = 0.08$, $p = 0.44$). However, when we divided the studies into three categories based on mean study age, we found conflicting results. In the studies of the youngest subjects (below 45 years, $n = 6$), PD patients had earlier onset age ($g = -0.39$, $p < 0.001$), whereas in the studies among the oldest (above 55 years, $n = 7$) PD patients had later onset age ($g = 0.40$, $p < 0.001$) than NPD patients. The year of publication did not affect the results. A forest plot comparing onset age between PD and NPD by age groups and in the total sample is presented in Fig. 3. In the six studies comparing mean onset age between PD and SZ, five found earlier onset age in SZ, and pooled meta-analysis found significant difference ($g = 0.53$, $p = 0.013$). When we compared PD and PBD, PD patients had non-significantly later onset age ($g = 0.34$, $p = 0.069$). Mean onset ages in different groups in the included studies are presented in the online Supplementary Table S3.

Regarding comparison in onset age between PD and NPD, only six studies had sample size of at least 50. There were only two studies from each three age groups; however, all the statistically significant findings remained when compared with the original analyses.

Risk factors and sociodemographic factors

Studies on risk factors and sociodemographic factors in PD are summarized in the online Supplementary Table S4. In total, 36 studies were found.

Studies on *early risk factors* are rare. The only study analyzing risk factors from birth (place of birth, gestational age, birth weight, small for gestational age, maternal and paternal age at birth) was a large Danish register study that did not find any significant differences in these factors between PD and HC (Østergaard *et al.* 2013). Physical and sexual trauma was more likely in PD than in NPD in one study (84% *v.* 64%, $p = 0.017$) (Gaudiano & Zimmerman, 2010), but not in one (Gaudiano *et al.* 2016). Other premorbid factors linked with PD when compared with NPD were rural domicile (Ihezue, 1985), acute medical problems (Draper & Anstey, 1996), and poorer social competence score (Sands & Harrow, 1995). When compared with HC, PD patients differed in the number of physical anomalies (Čulav-Sumić & Jukić, 2010) and also a loss of mother because of an unnatural cause after age 15 years associated with PD (Østergaard *et al.* 2013). *Ethnicity* was studied in eight articles. Individuals with PD were less likely to be Caucasian in five different studies (Johnson *et al.* 1991; Goldberg

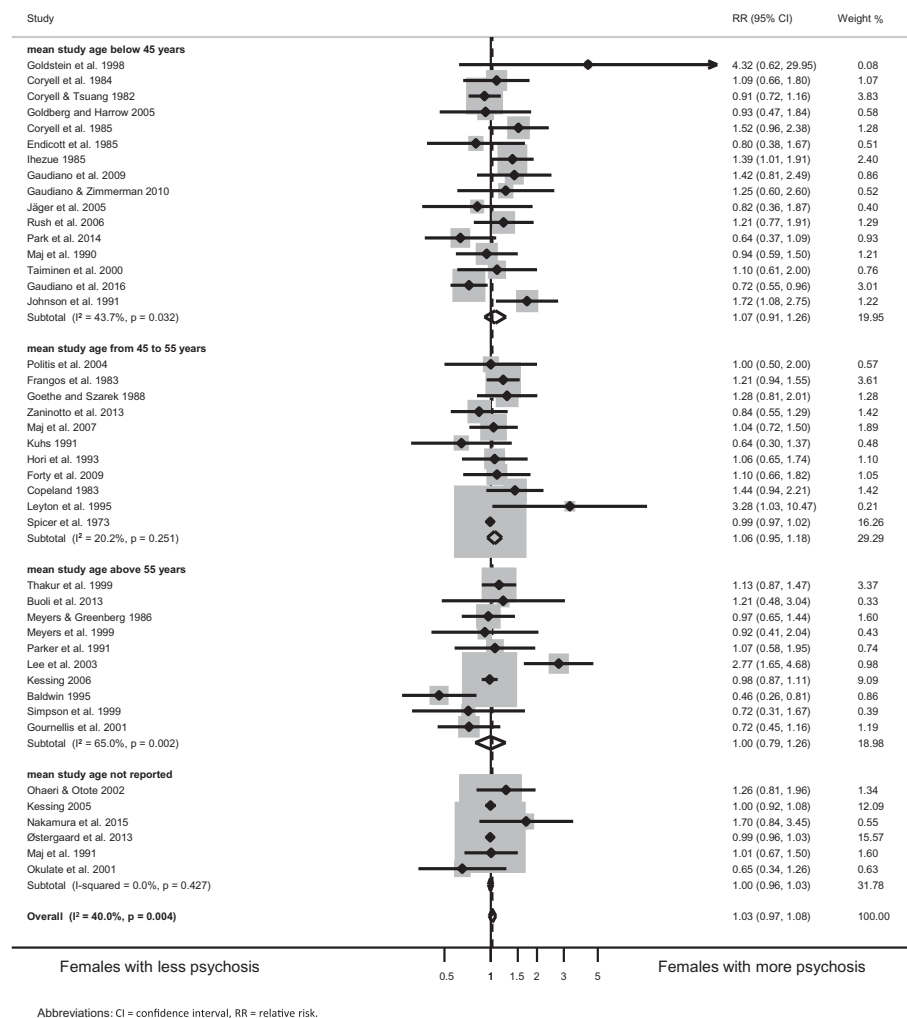# Risk of psychosis among females in depression

Fig. 2. Forest plot for estimated or relative rates (RR) psychotic depression among females in depression patients. Studies are grouped and analyzed separately by mean study age.
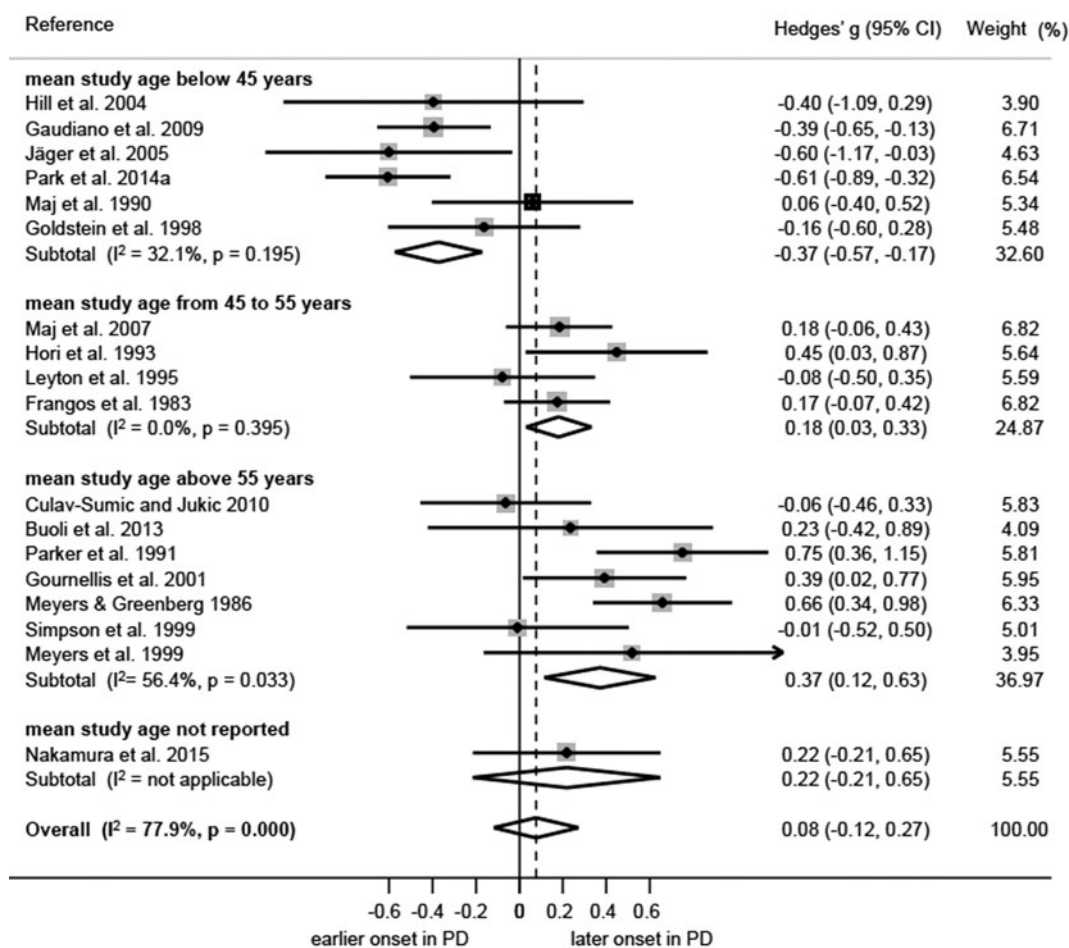
& Harrow, 2005; Gaudiano *et al.* 2009; Gaudiano & Zimmerman, 2010; Gaudiano *et al.* 2016). The British study by Heslin *et al.* (2016*a*) found that the PD patients had less contact with friends, and they were more likely to have childhood adversity of neurological soft signs when compared with HC.

The family history of different psychiatric illnesses and suicides was analyzed in 14 articles. Most of the associations were non-significant. When PD patients were compared with NPD, they more often had a family history of psychosis (Buoli *et al.* 2013) and bipolar I disorder (Maj *et al.* 2007). One study also found a higher likelihood of any mental illness in relatives (Okulate *et al.* 2001), whereas two other studies did not find differences (Frangos *et al.* 1983; Nakamura *et al.* 2015). Studies looking at the family history of affective or depressive disorders did not find

differences between PD and NPD (Frangos *et al.* 1983; Parker *et al.* 1991; Simpson *et al.* 1999; Park *et al.* 2014). The large Danish register study by Østergaard *et al.* (2013) found several maternal, paternal, and sibling psychiatric diagnoses to associate significantly with PD when compared with HC, the highest risk (incidence rate ratio of 2.2) being in any maternal mental disorder. A recent study in the UK also found the family history of any mental illness or psychosis to associate with PD (Heslin *et al.* 2016*a*).

Educational level or years of education between PD and other patient groups was compared in 18 studies. Differences were mainly non-significant. PD patients had less education when compared with PBD in one study (Breslau & Meltzer, 1988). When PD patients were compared with NPD, they had lower education in six studies (Ihezue, 1985; Karaaslan *et al.* 2003; Goldberg &

Mean difference in onset age between PD and NPD

Reference	Hedges' g (95% CI)	Weight (%)
mean study age below 45 years		
Hill et al. 2004	-0.40 (-1.09, 0.29)	3.90
Gaudiano et al. 2009	-0.39 (-0.65, -0.13)	6.71
Jäger et al. 2005	-0.60 (-1.17, -0.03)	4.63
Park et al. 2014a	-0.61 (-0.89, -0.32)	6.54
Maj et al. 1990	0.06 (-0.40, 0.52)	5.34
Goldstein et al. 1998	-0.16 (-0.60, 0.28)	5.48
Subtotal ($I^2 = 32.1\%$, $p = 0.195$)	-0.37 (-0.57, -0.17)	32.60
mean study age from 45 to 55 years		
Maj et al. 2007	0.18 (-0.06, 0.43)	6.82
Hori et al. 1993	0.45 (0.03, 0.87)	5.64
Leyton et al. 1995	-0.08 (-0.50, 0.35)	5.59
Frangos et al. 1983	0.17 (-0.07, 0.42)	6.82
Subtotal ($I^2 = 0.0\%$, $p = 0.395$)	0.18 (0.03, 0.33)	24.87
mean study age above 55 years		
Culav-Sumic and Jukic 2010	-0.06 (-0.46, 0.33)	5.83
Buoli et al. 2013	0.23 (-0.42, 0.89)	4.09
Parker et al. 1991	0.75 (0.36, 1.15)	5.81
Gournellis et al. 2001	0.39 (0.02, 0.77)	5.95
Meyers & Greenberg 1986	0.66 (0.34, 0.98)	6.33
Simpson et al. 1999	-0.01 (-0.52, 0.50)	5.01
Meyers et al. 1999		3.95
Subtotal ($I^2 = 56.4\%$, $p = 0.033$)	0.37 (0.12, 0.63)	36.97
mean study age not reported		
Nakamura et al. 2015	0.22 (-0.21, 0.65)	5.55
Subtotal (I^2 = not applicable)	0.22 (-0.21, 0.65)	5.55
Overall ($I^2 = 77.9\%$, $p = 0.000$)	0.08 (-0.12, 0.27)	100.00

-0.6 -0.4 -0.2 0 0.2 0.4 0.6
earlier onset in PD   later onset in PD

Abbreviations: PD = psychotic depression, NPD = non-psychotic depression, I^2 = heterogeneity, CI = confidence interval.

Fig. 3. Forest plot comparing mean onset age between psychotic depression and non-psychotic depression. Studies are grouped and analyzed separately by mean study age.

Harrow, 2005; Gaudiano *et al.* 2009; Gaudiano & Zimmerman, 2010; Heslin *et al.* 2016b) but more years of education in one study (Park *et al.* 2014). In the ECA study, PD patients had lower socioeconomic status when compared with NPD (Johnson *et al.* 1991). *Marital status* between PD and other patient groups was compared in 19 studies. Differences were mainly non-significant although two studies found PD patients to be more often single than NPD patients (Baldwin, 1995; Gaudiano *et al.* 2016) and in one study PD patients were less often single when compared with SZ patients (Heslin *et al.* 2016b).

Outcomes in PD

Study characteristic and quality

The studies included in outcome review are described in online Supplementary Table S5. We found

altogether 44 articles presenting results from 37 separate studies. Several studies did not report characteristics of PD group in detail (online Supplementary Table S5). The sample sizes of PD varied between 16 and 190. Fourteen of the studies had sample size of at least 50. In 25 of the studies, there were more females than males. Twenty-five studies included patients with onset age before 45 years of age (or if age of onset not reported, the sample was under 45 years at the study moment). Most of the studies ($n = 16$) were cross-sectional, and 13 studies had over 5 years follow-up. Study populations were mostly mixed samples ($n = 25$), with minority being first episode ($n = 10$) and consecutive samples ($n = 2$). Outcomes were most frequently defined using validated scales, but in some studies, the scale or its use was not clearly reported. Most commonly studied outcomes were different symptoms, remission, and global clinical outcome.

Outcome compared with NPD

Based on meta-analysis (online Supplementary Figs S1*a–f*), compared with NPD, the symptoms of depression were more severe in PD (Hedges' $g = 0.52$, $p < 0.001$). The difference in symptom severity was larger among three samples with onset age 45 years or older ($g = 0.84$, $p = 0.004$), but significant also in younger samples ($g = 0.40$, $p = 0.005$). Psychosis symptoms were more severe in PD ($g = 0.89$, $p = 0.037$). Symptomatic remission tended to be less common in PD though not statistically significantly (RR = 0.82, $p = 0.052$). There was no significant difference in the global clinical outcome or hospitalizations, though PD patients tended to have poorer outcomes. The global outcome (based on SOFAS, GAS, or GAF score) was somewhat worse in PD, but not statistically significant ($g = -0.43$, $p = 0.065$). Sensitivity analyses by sample size were performed for studies comparing depression symptoms, global outcome, symptomatic remission, and poor global clinical outcome in PD *v.* NPD. The results were mixed. Regarding depression symptoms, the difference in PD *v.* NPD was not statistically significant in larger samples (50 cases or more), and the results of global outcome remained nonsignificant. Regarding symptomatic remission and poor clinical outcome, the difference between PD and NPD was statistically significant in large samples (online Supplementary Figs S4*a–d*).

Based on systematic review (online Supplementary Table S5), the rate of relapses was higher in PD compared with NPD (Baldwin, 1988; Copeland, 1983). In most of the studies analyzing occupational outcomes, individuals with PD had a somewhat poorer outcome compared with NPD (Coryell *et al.* 1984; Coryell & Tsuang, 1985). However, there were also studies indicating similar occupational outcomes for PD and NPD (Jäger *et al.* 2005; Rush *et al.* 2006; Park *et al.* 2014). A good occupational outcome occurred in 60–79% of PD, and 68–78% on NPD (Coryell & Tsuang, 1985; Jäger *et al.* 2005; Park *et al.* 2014), and poor occupational outcome in 28% of PD and 19% of NPD (Coryell & Tsuang, 1985), and unemployment in 90% of PD and 81% of NPD (Rush *et al.* 2006). Based on only study analyzing full recovery (both symptomatic and functioning, Coryell *et al.* 1982), full recovery after 2–3 years of follow-up was more common in NPD (69%) than PD (40%).

Outcome compared with SZ

According to meta-analyses, when compared with SZ, there was no difference in severity of depression symptoms, but total psychosis symptoms ($g = -0.77$, $p = 0.000$) and positive ($g = -0.81$, $p = 0.000$) and negative symptoms ($g = -0.89$, $p < 0.001$) were significantly less severe in PD. Global outcome was better in PD ($g = 0.80$, $p = 0.001$) (online Supplementary Figs S2*a–e*). All but one of the samples in the meta-analyses included patients with mean onset age below 40 years. The rate of relapses was lower in PD (Craig *et al.* 2000). Occupational functioning was better in PD, 60–79% of PD and 36–47% of SZ having a good occupational outcome, and 28–29% and 57–88% having poor, respectively (Coryell & Tsuang, 1985; Jarbin *et al.* 2003; Jäger *et al.* 2005). Full recovery (both symptomatic and functioning, Coryell *et al.* 1982) after 2–3 years of follow-up was more common in PD (40%) than SZ (7%) (online Supplementary Table S5).

Outcome compared with PBD

Symptoms of depression did not differ. Negative symptoms ($g = 0.65$; $p = 0.001$) were more severe in PD. However, PD had less severe positive symptoms ($g = -0.44$; $p = 0.046$). There was no difference in global functioning between PD and PBD (online Supplementary Figs S3*a–d*). Rehospitalization rates were relatively similar in PD and PBD (Craig *et al.* 2000). The unemployment rate was similar in PD and PBD (63% *v.* 53–69%) (Dell'Osso *et al.* 2002), as was functional recovery (32% *v.* 37%, Tohen *et al.* 2000). Persons with PD were somewhat less often on a disability pension (29% *v.* 33%), and they were less often unemployed (7% *v.* 14%) (online Supplementary Table S5).

Outcome compared with SZAFF

Only a few studies comparing PD and SZAFF were found, and no meta-analysis could be performed. Symptomatic remission (Coryell *et al.* 1990; Opjordsmoen, 1991), and employment (Opjordsmoen, 1991) were more common in PD, but there was no difference in number of relapses at follow-up (Opjordsmoen, 1991). In one study, there was no marked difference in syndromatic recovery between PD and SZAFF, but PD subjects had more often functional recovery (Tohen *et al.* 2000).

Discussion

Main results

Based on this systematic review, though not as common as, e.g. SZ, it seems that PD is relatively common, especially in older populations. However, this conclusion is based on a relatively few studies with varying methodology. Within depression, the onset age of PD was earlier than that of NPD in younger samples, but later in older samples. This may be due to PD at first episode being a marker of later bipolar disorder in younger samples. It seems that the proportion of

Table 1. *Summary of the main results*

Topic	Main result
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 *v.* 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

Diagnoses: PD, psychotic depression; NPD, non-psychotic depression; PD, bipolar disorder; PBD, psychotic bipolar disorder; SZ, schizophrenia; SZAFF, schizoaffective disorder.

PD is higher in inpatient samples. Based on this review, the median proportion of those with PD was 42% in inpatients, and 19% in outpatients. There was no difference in gender distribution in PD *v.* NPD, but higher proportion of females was found in PD than in SZ or in PBD. Risk factors have rarely been studied, and most of the findings were statistically non-significant. Family history of psychosis and bipolar I seems to increase the risk of PD.

To our knowledge, this is a first systematic review and meta-analysis comparing the outcomes of PD not only to NPD, but also to SZ, SZAFF, and PBD. Several outcomes of PD were mostly worse when compared with NPD, but better compared with SZ and SZAFF. The outcomes compared with PBD were relatively similar, though there were more negative and less positive symptoms in PD. The number of studies comparing PD to SZ and PBD, and especially SZAFF are very few.

See Table 1 for the summary of main results.

Clinical and public health implications

The number of studies on the epidemiology of PD are far from the large amount of studies on SZ (Matheson *et al.* 2014) or on unipolar depression in general (Hirschfeld, 2012; Kessler & Bromet, 2013) and on bipolar disorder (Sherazi *et al.* 2006; Benazzi, 2007;

Esan & Esan, 2016). Many of the risk factors reviewed in reviews on NPD and SZ have not been studied on PD at all or only in a few small samples. Based on our review, there is lack of studies on epidemiology, especially risk factors, and longitudinal clinical and functional outcomes in PD. This is in line with the general notion of lack of clinical trials focusing on PD (Wijkstra et al. 2015). In addition, both treatment algorithms and clinical practice regarding PD are highly heterogeneous. This emphasizes the need for further studies also on the treatment of PD (Leadholm et al. 2013).

Our review supports the earlier conclusions about more severe depression symptoms in PD compared with NPD, especially in older samples (Lykouras & Gournellis, 2009). Most of the studies included in the meta-analysis included patients with relatively young age at the study moment, and thus the other results on symptoms and global outcome can be generalized only to this age group.

Our review summarizes the outcomes of PD in comparison to SZ and PBD. After our database searches, very recently, an AESOP study was published, where 10-year outcomes in PD compared with SZ and PBD patients were investigated. The study found only minimal differences in the outcome between PD and PBD. Differences in clinical, social, and service use outcomes between PD and SZ were more substantial with PD patients showing better outcomes on most variables (Heslin et al. 2016a). These results of AESOP seem relatively similar to ours.

The burden of disease of mood disorders to society among EU nations is higher than in any other brain disorders, most of the costs resulting from disability (Olesen et al. 2012). There are not many studies on the disability due to PD. In PD, disability was found to be increased even when compared with severe major depression in all functional dimensions of Short Form-36, there were, moreover, an increased number of absent days and days ill in bed (Kruijshaar et al. 2003). Severe forms of recurrent depressions, additionally, may have a scar effect in the form of an increase in disability (Ormel et al. 2004). Due to earlier age of onset and higher prevalence, the burden of disease on society is likely to be higher in SZ, although self-perceived suffering may be worse due to depression being a robust determinant of quality of life (Saarni et al. 2010).

Diagnostic instability has been a concern with PD (Bromet et al. 2011; Ruggero et al. 2011). In 10-year follow-up studies of relatively young patient samples, the diagnosis of PD has remained in less than half of the cases (Bromet et al. 2011; Ruggero et al. 2011; Heslin et al. 2015) and Ruggero et al. (2011) have even suggested that PD diagnosis should be

considered as a provisional diagnosis. However, in a 2-year follow-up of slightly more aged sample, the stability was 85% (Salvatore et al. 2011). The early onset of PD may well predict conversion to bipolar disorder (Østergaard et al. 2014). Additionally, changes in the symptom presentation seem to explain the instability (Bromet et al. 2011). A shift toward SZ has also been found during the course of a decade. Among these cases, poorer functioning and negative symptoms predicted the shift (Bromet et al. 2011). Altogether the stability of diagnosis in PD can be highly age-related as especially younger patients are more likely to develop PBD (Lykouras & Gournellis, 2009). The diagnosis might also be more stable in patients with medical comorbidity (Tohen et al. 2012). Still, among mood disorders, bipolar disorder has been found to best predict psychosis (Souery et al. 2011).

Considering the diagnostic validity of PD, it is interesting that gender distribution in PD is similar to NPD, while the proportion of females is lower in SZ and PBD. Meanwhile, the differences between PD and NPD are well documented (Keller et al. 2007) and our findings are in line with these. The increasing prevalence, though not statistically significant, and proportion of psychosis in depression in older patient samples also contradict with the concept of psychotic illness, e.g. SZ, starting usually at early adulthood. In this systematic review, onset age of PD was earlier than that of NPD in younger samples, but later in older samples. It remains possible that there are two forms of PD. PD in young adulthood may be an etiologically and prognostically different illness than PD in late adulthood and in geriatric populations. Early-onset form of PD may be more unstable, potentially an early expression for some patients of bipolar disorder, and for others perhaps other psychotic conditions. Among older onset cases, it is possible that medical and neurological conditions partly explain the occurrence of PD. Future studies should address these questions and include also late-onset PD patients.

Strengths and limitations

There are several limitations related to this review. We included only articles published in English, meaning that especially older relevant articles on the topic may be missing. It should be acknowledged that the oldest studies in this review were from 1980s. Although we consider our search criteria to be adequate, we may have missed some studies, especially older studies. Because of this, we have also done some manual work to locate these papers, e.g. using the reference lists of previous reviews. It should be noted that we excluded childhood onset samples. The included articles were quite mixed regarding methods, e.g. diagnostic

criteria or other inclusion criteria. The original studies on incidence and prevalence rates were few, and they had very heterogeneous methodology. There were four population studies with different design and methods of ascertaining the PD cases, and five registry studies. These two sets of studies produced considerably different estimates of PD. It may be that the available data are too heterogeneous to make precise estimate of incidence and prevalence of PD.

The sample sizes were relatively small, e.g. in risk factors median sample size being 45, and mainly not based on population samples, but comparing clinical samples. Minority of the studies based on first-episode samples. Most of the studies on outcomes had sample size of PD under 50. Due to the low number of studies, it is not possible to have a clear picture on the effect of study quality (e.g. sample size) on the results. However, based on the study characteristic summarized in Results section, many of the original studies have important limitations (e.g. small sample size, short follow-ups, lack of long-term follow-ups in older populations). In outcome analyses, some of the definitions of outcomes were heterogeneous, e.g. definitions of symptomatic remission, global clinical outcome, global outcome varied.

The strength of this review was the comprehensive search strategy, as we searched four electronic databases. We read in detail studies analyzing depression in general, and whenever possible, extracted the data concerning PD as separate group. There was a relatively good amount of data on gender differences, differences in onset age, and differences in some of the outcome measures to also allow new conclusion of the epidemiology of PD.

Conclusions

To our knowledge, this is the first systematic review on different aspects of epidemiology of PD. Based on this review, the amount of research on PD is far from that of NPD, SZ, and bipolar disorder. Based on differences in gender, onset age, and outcomes in PD in comparison to other disorders, PD seems distinguishable from related disorders and needs more scientific attention.

Supplementary material

The supplementary material for this article can be found at https://doi.org/10.1017/S0033291717002501.

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Declaration of Interest

None.

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