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Research paper

Effects of gender and psychiatric comorbidity on the age of illness onset and the outcome of psychotic depression—A birth cohort study

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ABSTRACT

Background: Psychotic depression (PD) is an under-researched disorder with severe symptoms and course of illness. Little is known about gender differences relating to this condition and possible variation of prognosis based on comorbid pathology. Our aim was to analyze the effects of gender and psychiatric comorbidities on the age of illness onset and on the outcome of psychotic depression.
Methods: The study was carried out in the Northern Finland Birth Cohort 1966. We utilized register data to acquire information about lifetime psychiatric diagnoses, hospitalization, age of illness onset, rate of disability pensions and mortality. The PD group ($n = 58$) was defined based on a lifetime register diagnosis. We compared outcome variables in sub-groups based on gender and comorbid alcohol use or personality disorder.
Results: The prevalence of comorbid personality disorders was 38% (22/58) and comorbid alcohol use disorders 41% (24/58). PD patients with a personality disorder diagnosis had an earlier onset age ($p<0.01$) and a higher mortality rate ($p = 0.03$). Male gender ($p = 0.03$), comorbid alcohol use disorder ($p<0.01$) and personality disorder ($p < 0.01$) were all associated with more psychiatric hospitalization. Comorbid alcohol use disorder was more common among men (males: 61%; females: 29%; $p = 0.03$).
Limitations: National registers were the main source of diagnostic information.
Conclusions: Gender and psychiatric comorbidity have significant implications for the course of illness in PD in naturalistic settings, which is an important message for all clinicians. More research into the heterogeneity of PD is needed in order to guide research and clinical practice.

Introduction

Psychotic depression (PD), i.e., unipolar depression with psychotic symptoms, is characterized by severe course of illness, distinct treatment options and high mortality compared to non-psychotic depression (Rothschild 2013). The lifetime prevalence of PD is 0.35–1.0% with higher rates among females and elderly, whereas the risk factors of PD are insufficiently researched and especially the early risk factors are mostly unknown (Jääskeläinen et al., 2018). Significant knowledge gaps about PD cause challenges for clinical decision-making and research (Heslin and Young 2018). Psychiatric comorbidities are common in PD (Tohen et al., 2012) and may have major implications for treatment and prognosis. Analyzing differences between potential PD sub-groups and their outcomes is central to understanding PD.

Approximately 65% of PD patients are female (Jääskeläinen et al., 2018) but otherwise the knowledge of gender differences in PD is scarce. Fennig et al. (1993) ($n = 30$) reported female PD patients to have more fatigue, psychomotor agitation and systematized and mood-incongruent delusions than male patients, whereas male patients had more frequent feelings of worthlessness. Male gender in PD has additionally been associated with more frequent suicide (Leadholm et al., 2014) and alcohol use disorders (Isometsä et al., 1994; Fennig et al., 1993). A

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higher mortality rate in males compared to women in old age PD has also been observed (Schoevers et al., 2000).

In a pharmacotherapy study of PD (STOP-PD) with a 12-week follow-up ($n = 259$), there was no gender difference in treatment outcome (Deligiannidis et al., 2013). Female gender was associated with more frequent life-time comorbid anxiety disorders and a divorced or widowed marital status. Hallucinations and delusions with disorganization were also more common among females. Conflictingly, in a cross-sectional assessment ($n = 53$), male patients had more hallucinatory behavior, anxiety and suicidal ideation than females (Park et al., 2015). They also had a poorer social and occupational functioning level. However, in this study, PD was diagnosed regardless of the severity of depressive symptoms, which means that the sample is not directly comparable.

Psychiatric comorbidity has been reported to be high in PD compared to non-psychotic depression (Gaudiano et al., 2009). In the Northern Finland Birth Cohort 1966 we previously reported high rates of lifetime alcohol use and personality disorders in PD patients (Nietola et al., 2018). Cluster A, but not cluster B or C, personality disorders have been reported to be more common in PD than in non-psychotic depression (Serretti et al., 1999; Gaudiano et al., 2009). These studies regarding comorbid personality disorders were conducted in inpatient and treatment-seeking outpatient samples. The high level of substance abuse is a significant concern. In the McLean-Harvard first episode project, 62.5% of PD subjects had comorbid alcohol use disorder at baseline. (Tohen et al., 2012)

Onset age in PD is younger than in non-psychotic depression, when analyzing patient groups under 45 years old, but older than in schizophrenia in general (Jääskeläinen et al., 2018). Early onset age is likely to predict a poorer outcome in other severe mental disorders such as in bipolar disorder (Joslyn et al., 2016) and in schizophrenia (Immonen et al., 2017). Different onset age may also be an indicator of differences in the aetiological mechanisms of psychosis (Golay et al., 2017). Little is known about potential sources of variation in onset age within PD and about how onset age affects the outcome.

Altogether, the knowledge base regarding the effects of gender and comorbidity on the outcome of PD is inconclusive and inadequate. Our aim in this study was to analyze how gender and comorbid alcohol use and personality disorders affect the course of illness in PD. The hypothesis was that male gender and comorbidities are associated with worse outcomes in PD. We chose age of illness onset, number of psychiatric hospital days, disability pension rate and mortality as indicators of illness course and outcome (Nietola et al., 2018), because these variables reflect severity of illness, functional impairment and need of treatment. PD is vastly under-researched, and, to our knowledge, this is the first prospective long-term follow-up study addressing the effects of gender and psychiatric comorbidity on PD.

Methods

Sample

The study was performed in the Northern Finland Birth Cohort 1966 (NFBC1966), comprising 12,058 subjects followed since mid-pregnancy. The Ethics Committees of the University of Oulu and of the Northern Ostrobothnia Hospital District both approved the study. Nationwide registers were utilized to acquire information about the study participants. The Care Register for Health Care provided the psychiatric diagnoses of each subject and included all somatic and psychiatric hospitalizations in Finland from birth until the end of 2016. Outpatient diagnoses were available from 1998 to 2016 for specialized care and from 2011 to 2016 for primary care. We used register information from Social Insurance Institute (medication reimbursement rights (1974–2005), sick days (until 1999) and disability pensions (1981–2000)) and from Finnish Center for Pensions (disability pensions until 2015) as supplementary information for psychiatric diagnoses. The PD group ($n = 58$) was formed using a lifetime diagnosis based on a hierarchical system (Nietola et al., 2018). Due to this hierarchical system, none of the PD group patients had ever during their lifetime been diagnosed with schizophrenia, schizoaffective disorder, delusional disorder or bipolar disorder. We previously reported in detail the clinical characteristics and outcomes of PD subjects (Nietola et al., 2018). In this previous study the PD group size was 55 subjects, but after the end of 2013 and before the end of 2016 five new subjects were diagnosed with PD and two subjects exited the group due to a schizophrenia spectrum or bipolar disorder diagnosis.

Data regarding age of illness onset, comorbidity and outcome

Information about the age of illness onset and comorbid alcohol use (ICD-8: 291, 303; ICD-9: 291, 303, 3050; ICD-10: F10) and personality disorders (ICD-8: 301; ICD-9: 301; ICD-10: F21, F60, F61) was gathered using register data analogously to the study sample acquirement (see above). For outcome variables (age of illness onset, life-time hospital days, mortality and disability pension rate), we utilized the Care Register for Health Care until the end of 2015 to acquire data about age of illness onset and psychiatric hospital days. Population Register Center data was used to analyze mortality and it was available until 2015. Statistics Finland data from 2014 was used to analyze the rate of disability pensions.

Statistical analyses

We compared age of illness onset, lifetime hospitalization days, mortality, disability pension rate and comorbidity between genders. Then we divided the sample into sub-groups based on whether the subject had a comorbid alcohol abuse or personality disorder and compared outcome variables in these sub-groups. Differences between genders and comorbidity groups in age of illness onset and life-time psychiatric hospital days were analyzed using the Mann-Whitney U test. Fisher's exact test was used to analyze sub-group differences in disability pension rates and mortality, and, also, in the amount of comorbidity between genders. IBM SPSS Statistics, version 25, was used for statistical analyses (https://www.ibm.com/analytics/spss-statistics-software). All p-values were two-tailed and values less than 0.05 were considered as statistically significant.

Results

Sample

58 subjects in the sample had a lifetime diagnosis of PD (male, $n = 23$; female, $n = 35$). The median age of illness onset for PD patients was 40.2 years. The lifetime prevalence of PD was 0.5%. There were 6 (10.3%) deceased study subjects by the end of 2015.

Gender differences in comorbidity

In our sample, alcohol use disorder was significantly more common among males than females ($p = 0.03$). 60.9% of men had a lifetime comorbid alcohol use disorder compared to 28.6% of women (Table 1). Personality disorders were also more often diagnosed in males, but this difference was not statistically significant (52.2% in males vs. 28.6% in females; $p = 0.10$). The distribution of comorbidity had a very different profile between genders (Fig. 1).

Age of illness onset

Gender difference in the age of illness onset was not statistically significant, although in absolute numbers the median onset among men was 5.6 years earlier than among women (37.3 vs 42.9 years) (Table 2). Dividing the PD sample into sub-groups by comorbid alcohol use or

Table 1
Gender differences in alcohol use disorder and personality disorder in Psychotic Depression.

Variables	Male ($n = 23$)	Female ($n = 35$)	Gender difference, Fisher's exact test, p-value		
	n	%	n	%	
Alcohol use disorder					0.028
No	9	39.1%	25	71.4%	
Yes	14	60.9%	10	28.6%	
Personality disorder					0.098
No	11	47.8%	25	71.4%	
Yes	12	52.2%	10	28.6%	

personality disorder revealed a significant difference between those with and without a personality disorder (Table 3). Comorbid personality disorder was associated with a younger illness onset age (median 36.0 vs 42.4 years; $p < 0.01$). Those with alcohol use as a comorbidity were also younger at illness onset, although the difference was not significant.

Outcome in sub-groups by gender and comorbidity

There were considerable differences between different PD sub-groups in the total amount of lifetime hospitalization (Tables 2 and 3). Male gender ($p = 0.03$), alcohol use disorder ($p < 0.01$) and personality disorder ($p < 0.01$) were associated with a greater amount of hospitalization. Group differences in the disability pension rate were smaller than in psychiatric hospital days. Male and female subjects had an almost identical percentage of disability pensions, whereas alcohol use

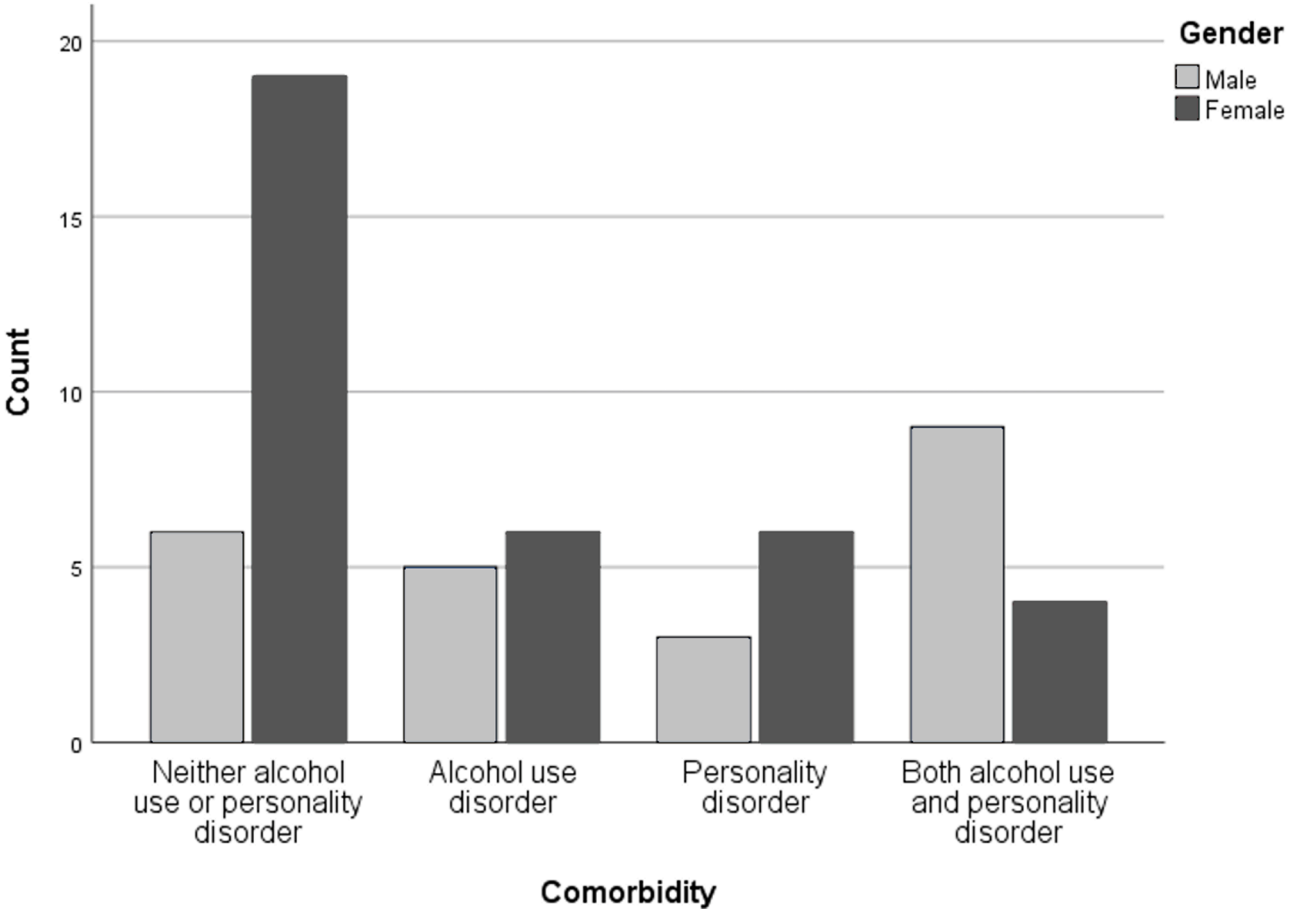

Fig. 1. Alcohol use and personality disorder comorbidity in Psychotic Depression.

Table 2
Gender differences in the age of illness onset and outcome in Psychotic Depression.

Variables	Male ($n = 23$)		Female ($n = 35$)		Gender difference, p-value
	median	IQR	median	IQR	
Age of illness onset	37.3	35.4–43.4	42.9	37.4–45.9	0.10[1]
Lifetime hospitalization days until the end of 2015	103.0	52.0–223.0	46.5	3.8–122.8	0.028[1]
	n	%	n	%	
Mortality					0.20[2]
Deceased	4	17.4%	2	5.7%	
Disability pension in 2014					1.00[2]
Yes	9	39.1%	14	40.0%	

[1] = Mann-Whitney U test;.
[2] = Fisher's exact test.

Table 3
Age of illness onset and outcome in Psychotic Depression subgroups formed by comorbidity.

Variables	Alcohol use disorder				*p*-value*	Personality disorder				*p*-value *
	Alcohol use disorder ($n = 24$)		No alcohol use disorder ($n = 34$)			Personality disorder ($n = 22$)		No personality disorder ($n = 36$)		
	median	IQR	median	IQR		median	IQR	median	IQR	
Age of illness onset	37.5	35.4–44.3	42.2	35.5–45.2	0.23	36.0	34.1–40.4	42.4	37.3–45.3	0.002
Lifetime hospitali-zation days until the end of 2015	98.0	60.0–176.5	36.0	2.0–132.5	0.009	113.5	35.3–235.0	53.0	3.0–113.0	0.007
	n	%	n	%		n	%	n	%	
Mortality					0.22					0.025
Deceased	4	16.7%	2	5.9%		5	22.7%	1	2.8%	
Disability pension					0.59					0.098
Yes	11	45.8%	12	35.3%		12	54.5%	11	30.6%	

* = Mann- Whitney U test for age of illness onset and lifetime hospitalization; Fisher's exact test for mortality and disability pension.

disorder and personality disorder were associated with a higher disability pension rate, the differences being however insignificant. In the PD sample, 6 subjects were deceased (4 males and 2 females) and mortality was strongly associated with comorbidity. All the deceased subjects had either comorbid alcohol use or personality disorder. 5 of the deceased subjects had been diagnosed with a personality disorder ($p = 0.03$) and 4 with alcohol use disorder ($p = 0.22$).

Distribution of personality disorders

There were 22 subjects with a personality disorder diagnosis. The most common diagnosis was emotionally unstable personality disorder ($n = 7$). Other B cluster disorders were dissocial personality disorder ($n = 1$) and histrionic personality disorder ($n = 1$). There were four subjects with an A cluster diagnosis (schizoid personality disorder, $n = 4$). C cluster was the most infrequent: one subject had been diagnosed with anankastic personality disorder and one with dependent personality disorder. Seven subjects had a NOS personality disorder diagnosis (F60.9 or F61.0).

Discussion

A central finding in our study was that comorbid personality disorder was associated with certain unfavorable outcomes in PD. Patients with this comorbidity had an earlier onset age, more psychiatric hospital days and higher mortality. Comorbid personality disorder was more common among males than females, but the difference was statistically insignificant. In our study, alcohol use disorder was more common among males and was associated with more psychiatric hospital days in PD. Male subjects also had more psychiatric hospital days than females.

Comorbid personality disorders are likely to increase the risk of poor outcome in non-psychotic depression (Newton-Howes et al., 2014). To our knowledge, the effects of comorbid personality disorder on PD outcome have not been studied before. The most common personality disorder in our birth cohort study was emotionally unstable personality disorder (borderline personality disorder in the DSM-V), which is not in line with previous studies that were conducted on inpatient (Serretti et al., 1999) and treatment-seeking outpatient samples (Gaudiano et al., 2009). High prevalence of B cluster disorders is an important finding, even though A and C cluster disorders may have gone partly unnoticed in our register-based study (See Limitations). Psychotic symptoms are common in borderline personality disorder (Puri et al., 2018), and patients with comorbid borderline personality disorder may receive different treatment during first-episode psychosis (Francey et al., 2018). Micropsychotic symptoms may also be considered a transdiagnostic marker for both borderline personality disorder and PD.

The effect of gender on the long-term outcome of PD is mostly unknown. Possibly due to a relatively small sample size, our results do not show a significant difference in onset age between genders in PD, even though the absolute difference in mean age of onset was 5.6 years. However, there was a clear indication of a more malign course of illness among men than women. These results are in line with literature focusing on first-episode psychosis in general, since there has been significant variation in the results of previous studies concerning the effect of gender on the onset age, but male patients are likely to have a more malign illness course at least during the first years of illness (Cotton et al., 2009). Female gender may be associated with a more benign course of illness in schizophrenia in the earlier phases of the illness (Leung and Chue 2000). However, no significant difference was found between genders in a meta-analysis focusing on recovery in schizophrenia (Jääskeläinen et al., 2013). Furthermore, the implications of gender for the long-term outcome of bipolar disorder are inconclusive (Tsai et al., 2001).

The interaction between male gender, alcohol abuse and PD is likely to be complex. Alcohol use disorders have previously been associated with male gender in general (Addington and Addington 2007) and multiple negative outcomes in psychotic illness (Cetty et al., 2019). Alcohol may also have a more significant effect on mood than on other symptom dimensions (Barrowclough et al., 2014), and therefore associate more strongly with PD than with other psychotic disorders, as previously reported in our data (Nietola et al., 2018).

Clinical implications of high alcohol use and personality disorder comorbidity in PD include rigorous assessment of these disorders in everyday practice and active implementation of effective treatments. There are potential possibilities to improve outcomes of PD by focusing more on those detrimental comorbidities that appear to associate with a malign course of illness.

It is important to consider how much the previously reported unfavorable course of illness in PD is actually due to comorbid pathology rather than to the PD itself. Significant mortality has been associated with PD in previous studies. We found either a comorbid alcohol use or personality disorder in all of the deceased subjects ($n = 6$) in our study. Vythilingam et al. (2003) found PD patients to have a twofold mortality rate compared to non-psychotic depression in their study. They utilized a sample consisting of 61 patients with PD (59% female) and 59 patients with non-psychotic depression (64% female). The follow-up period was up to 15 years long. The authors specified current substance abuse at the beginning of follow-up as an exclusion criterion in their study. Previous and subsequent substance abuse could still have contributed to increased mortality in PD. Furthermore, patients with comorbid personality disorders were not excluded and the prevalence was not reported.

Regarding the outcome of PD, it is interesting to consider why comorbidity and gender had a major effect on psychiatric hospital days but less on disability pension rate. Both of these variables are likely to reflect the long-term outcome. One possibility is that this could be caused by decreased contact with health care providers in outpatient care in the comorbid groups. In addition, the analyzed psychiatric comorbidities and gender may have had a more episodic effect, not causing full disability. Furthermore, a high number of psychiatric hospital days may

have independently increased the likelihood of comorbid diagnoses without indicating functional impairment.

Strengths and limitations

Our data comes from a well-known birth cohort with a 50-year follow-up and provides a comprehensive view on the long-term outcome of PD sub-groups. The use of a reliable and comprehensive register data and the application of lifetime diagnosis are further strengths of this study. Knowledge about comorbidity, age of illness onset, mortality and hospitalization was also acquired from these nationwide registers.

It is possible that those PD patients with a more severe course of illness were more likely to be diagnosed with additional disorders, because they had more contacts with health care providers and more hospitalizations. In our study, the diagnoses were gathered from registers, and it is very possible that milder cases of alcohol use or personality disorders were undetected. The threshold for diagnosing substance use disorders in everyday clinical work is high, not least due to the attached stigma. Therefore, our finding of a high level of comorbid alcohol use disorders might still underestimate the significance of this phenomenon.

Regarding other personality disorders than those with impulsive behavior and severe emotional dysregulation, the true prevalence may be higher than in our sample and our findings may even represent an underestimate of their effects on the course of PD. In a recent Finnish sample, 47% percent of patients contacting psychiatric services for the first time had a personality disorder on the basis of a SCID-II interview (Karukivi et al., 2017).

A limitation of the study is that outpatient register data begins as late as 1998, making it possible that some earlier alcohol use or personality disorder may have gone unnoticed. Due to the high hospitalization rate, this is not a relevant concern for PD diagnoses (Nietola et al., 2018). Our sample of 58 subjects was relatively small, but differences between genders and comorbidity sub-groups were high enough to show significance in many variables. However, these results need to be considered preliminary and should be confirmed in future studies. The sample size was determined by the size of the birth cohort and this led to relatively low statistical power. It is also possible that some findings, such as the difference in the age of illness onset between genders, remained insignificant only due to the small sample size. It is noteworthy that the sample size was comparable to previous research on PD (Jääskeläinen et al., 2018).

Conclusions

Our findings of strong internal heterogeneity in PD associated with gender and comorbidity emphasize the need for further studies to control them as confounding factors. Furthermore, comparably to non-psychotic depression, explorative studies on different naturalistic trajectories of PD are needed in order to increase understanding of this under-researched disorder.

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CRediT authorship contribution statement

Miika Nietola: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Tanja Nordström:** Methodology, Data curation, Writing – review & editing. **Jouko Miettunen:** Methodology, Writing – review & editing, Supervision. **Jyrki Korkeila:** Conceptualization, Writing – review & editing, Supervision. **Erika Jääskeläinen:** Conceptualization, Methodology, Writing – review & editing, Supervision.

Declaration of Competing Interest

None.

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